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META-ANALYSIS
Heart failure and cardiomyopathies

Bariatric surgery and cardiovascular disease: a systematic review and meta-analysis

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Aims Obesity is a global health problem, associated with significant morbidity and mortality, often due to cardiovascular (CV) diseases. While bariatric surgery is increasingly performed in patients with obesity and reduces CV risk factors, its effect on CV disease is not established. We conducted a systematic review and meta-analysis to evaluate the effect of bariatric surgery on CV outcomes, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline.

Methods and results PubMed and Embase were searched for literature until August 2021 which compared bariatric surgery patients to non-surgical controls. Outcomes of interest were all-cause and CV mortality, atrial fibrillation (AF), heart failure (HF), myocardial infarction, and stroke. We included 39 studies, all prospective or retrospective cohort studies, but randomized outcome trials were not available. Bariatric surgery was associated with a beneficial effect on all-cause mortality [pooled hazard ratio (HR) of 0.55; 95% confidence interval (CI) 0.49–0.62, $P < 0.001$ vs. controls], and CV mortality (HR 0.59, 95% CI 0.47–0.73, $P < 0.001$). In addition, bariatric surgery was also associated with a reduced incidence of HF (HR 0.50, 95% CI 0.38–0.66, $P < 0.001$), myocardial infarction (HR 0.58, 95% CI 0.43–0.76, $P < 0.001$), and stroke (HR 0.64, 95% CI 0.53–0.77, $P < 0.001$), while its association with AF was not statistically significant (HR 0.82, 95% CI 0.64–1.06, $P = 0.12$).

Conclusion The present systematic review and meta-analysis suggests that bariatric surgery is associated with reduced all-cause and CV mortality, and lowered incidence of several CV diseases in patients with obesity. Bariatric surgery should therefore be considered in these patients.

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Key question

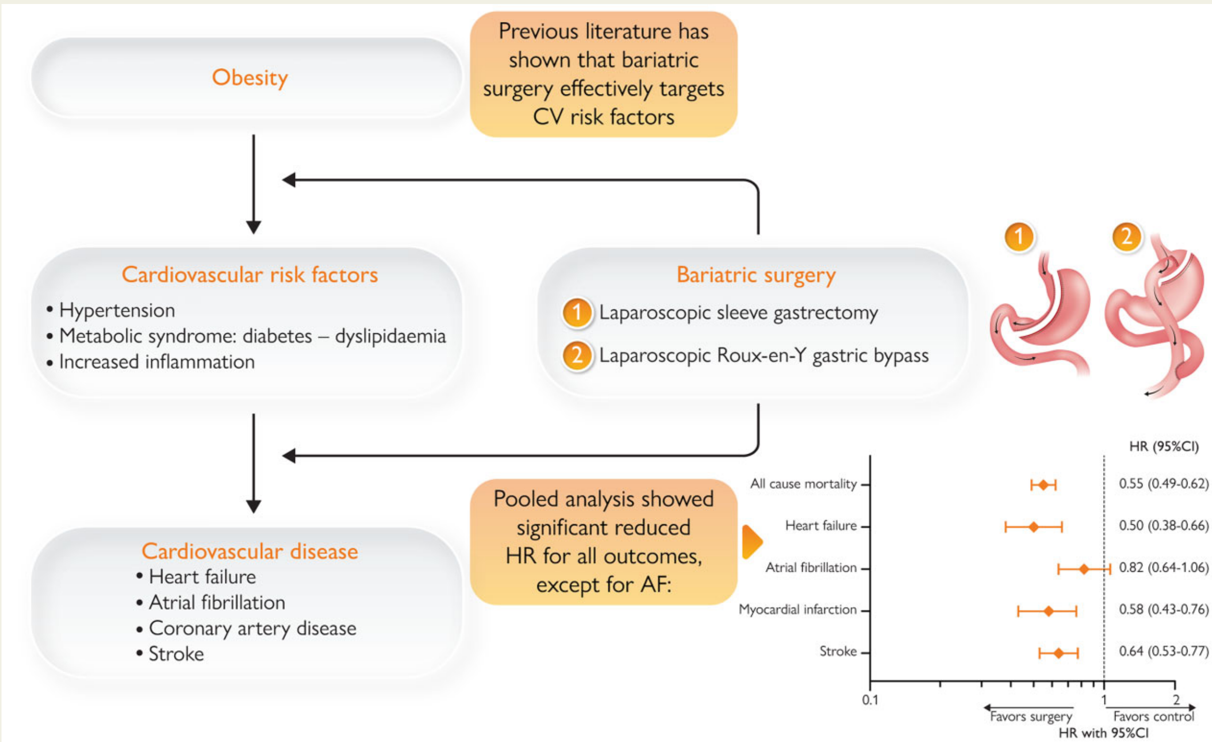
- What is the effect of bariatric surgery on mortality and cardiovascular (CV) disease?
- In this systematic review and meta-analysis, studies that compared bariatric surgery patients to non-surgical controls were evaluated.

Key finding(s)

- Pooled analysis showed a significant reduced hazard ratio for all-cause and CV mortality, heart failure, myocardial infarction, and stroke. Atrial fibrillation did not improve significantly.

Take-home message

- This current systematic review and meta-analysis of cohort studies illustrates that all-cause and CV mortality, as well as the incidence of CV diseases, are reduced by bariatric surgery. Bariatric surgery should therefore be considered in these patients.



Structured Graphical Abstract Obesity and cardiovascular disease: the effect of bariatric surgery.

Keywords Cardiovascular disease • Obesity • Heart failure • Atrial fibrillation • Myocardial infarction • Bariatric surgery • Metabolic surgery • Outcome

Introduction

Obesity is rapidly becoming one of the biggest healthcare problems in the western world, and is associated with significant morbidity and mortality.[1–4] In 2016, obesity was associated with four million deaths each year.[5] In the USA, the prevalence of obesity [defined as body mass index (BMI) ≥30 kg/m^2] was 40% in adults in 2015–16,[6] and this will rise to around 50% in 2030.[7]

Obesity is associated with increased adipose tissue, also referred to as adiposopathy,[8] and through several mechanisms this may be pathological to the cardiovascular (CV) system (*Structured Graphical Abstract*). First, CV disease can be the result of the systemic effects of adipose tissue, due to the development of risk factors. Second, adipose tissue may also directly or locally act by epicardial and perivascular effects into the myocardium and blood vessels.[8,9] And third, the accumulation of adipose tissue may cause (organ) compression,[1] leading to hypertension and renal dysfunction,[10] and obstructive sleep apnoea.[11]

Of the CV risk factors associated with obesity, hypertension is the most common, followed by diabetes. Their prevalences increase with the severity of obesity and are generally present in 30–40% of patients.[12] Dyslipidaemia and increased inflammation are also common in obesity (around 20–40%).

Cardiovascular diseases associated with obesity are atrial fibrillation (AF), heart failure (HF), coronary artery disease/myocardial infarction, and stroke. The hazard ratio (HR) to develop these CV diseases is at least 1.5–2.0, but this markedly increases to >6.0 in severe obesity, defined as BMI ≥40 kg/m^2.[13–15] Obesity is also a well-known risk factor for stroke,[16–18] and has also been associated with increased incidence of aortic valve stenosis, but much fewer data are available on this topic.[19]

Treatment of obesity is difficult, and initially based on lifestyle change, diet, and increased physical activity.[20] To achieve a sustained reduction of 5–10% of total body weight is difficult if not impossible in most patients.[21] Pharmacological treatment of obesity can be considered, but only a few drugs have been approved,[2,20] because of side-effects and safety concerns.[22,23]

Bariatric (or metabolic) surgery is an accepted treatment for patients with morbid obesity, i.e. BMI >40 kg/m^2, or severe obesity, i.e. ≥ 35 kg/m^2 in presence of obesity-associated comorbidities.[24] Since its introduction,[25] techniques have improved, particularly with laparoscopic procedures, which has resulted in a low incidence of serious complications, and a 30-day mortality rate $<0.5\%$.[20,26,27] A recent study of 9710 patients reported a mean total weight loss of around 25% after surgery.[28] Since obesity is increasingly common in patients with CV disease,[29] the use of bariatric surgery is expected to increase in this population.

The effect of bariatric surgery on CV diseases (or CV mortality) has been examined in four other systematic reviews and meta-analyses,[30–33] but since that time important, prospective studies have been published, or recent reviews did not include all important CV outcomes, and/or did not have substantial follow-up duration. Therefore, we aimed to perform a comprehensive systematic review and meta-analysis of the available literature on the effect of bariatric surgery on CV disease and outcome.

Methods

This systematic review and meta-analysis was performed according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[34] The PRISMA 2020 item checklist is detailed in Supplementary material online, *Figure S1*. We conducted a search in Pubmed and Embase databases from inception to 28 August 2021. The search strategy composed the PICO method: patients of interest were obese, adult (age $\geq$18 years old) patients, Intervention was bariatric surgery, Controls were obese patients who did not undergo bariatric surgery, and Outcomes were defined as all-cause mortality, CV mortality, and incidence of CV disease, i.e. incident AF, incident HF, incident myocardial infarction, incident stroke, and incident aortic stenosis. Further, for clarity reasons we investigated myocardial infarction, and not incident coronary artery disease, because it is very difficult if not impossible to define its onset, also this was not uniform across the studies. Somewhat similarly, we investigated stroke and not incident cerebrovascular disease. A few studies, however, further differentiated between ischaemic vs. haemorrhagic stroke, and thus we also separately investigated the effect on ischaemic stroke. The full search strategy is detailed in the Supplementary material online, *Figure S2*. The protocol for this systematic review and meta-analysis was registered to PROSPERO (identification number: CRD42021277135). Our search was limited to studies conducted in adults, published in peer-reviewed journals and written in English.

Study selection

Studies were considered eligible if they were designed to study outcomes in obese patients who underwent a weight-loss surgical intervention in comparison with an age, sex, and BMI matched control group who did not undergo a weight-loss surgical intervention. We searched for randomized controlled trials, prospective or retrospective longitudinal cohort studies, and case–control studies. For the control group, all non-surgical treatment options for obesity (e.g. intensive lifestyle intervention, standard of care, or no specific therapy) were accepted. Studies were excluded if (i) patients were not matched for age, sex, and BMI; (ii) the presence of one or more outcome parameters of interest (e.g. HF, AF, coronary artery disease) was required for inclusion; or (iii) if study groups were not representative in relation to the general population of patients with obesity (e.g. patients could only be included in the presence of a specific comorbidity, for instance, end-stage renal disease). The third criterium did not apply to Type 2 diabetes, thus studies that only included patients with Type 2 diabetes could be eligible for inclusion.

After removal of duplicates and non-English articles, conference abstracts, case reports, comments, review articles, and editorials, all records were independently reviewed by two observers (T.M.G. and G.v.W.), and studies were subsequently excluded at title, abstract, or full-text level. Disagreement was resolved by consensus. We also reviewed reference lists of included articles for relevant publications not identified by the initial search. Studies were specifically reviewed for potential overlap of study populations. If there was an overlap of the study population with identical outcome parameters of interest, the study with the longest follow-up duration for that endpoint was included. If one study population was described in various articles, these articles analysed different outcome parameters, both articles could be included. However, for each study population, the HR for that specific outcome parameter could only be extracted once, so no overlap in HR of the same outcome within the same study population could occur. The HR with the longest follow-up duration for a specific endpoint was chosen.

Data extraction

The following data were extracted: (i) study characteristics (i.e. publication year, type of bariatric surgery, number of patients, mean age and BMI and the percentage of patients diagnosed with Type 2 diabetes for both groups, study design, study cohort and recruitment period, major inclusion and exclusion criteria, primary and secondary outcome parameters and follow-up period); (ii) event rate per outcome parameter for each group; (iii) unadjusted and adjusted HRs with their 95% confidence intervals (CIs) for the association with outcome of interest; and (iv) adjustment variables.

Quality assessment

The risk of bias for each study was assessed by two independent reviewers (S.L.v.V. and G.v.W.) using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies. The length of follow-up was set at a minimum of 5 years to be evaluated as adequate. Agreement for the quality assessment between both observers was tested and disagreement was resolved by consensus. The quality of evidence was assessed for each outcome parameter using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework.[35] All study outcomes were assessed by two reviewers (S.L.v.V. and T.M.G.), and disagreement was resolved by consensus.

Statistical analyses

Continuous variables were reported as means $\pm$ standard deviation and categorical data as numbers or percentages. Hazard ratios were log transformed, and the CI was converted to standard error = (upper limit − lower limit)/3.92 for 95% CI. In random effect models (DerSimonian and Laird), we analysed adjusted HR to generate pooled HRs for the association between bariatric surgery for outcome in comparison with controls. The pooled HRs were calculated using inverse-variance weighted averaging and were depicted in forest plots. For the analyses that included <20 studies, the Hartung–Knapp–Sidik–Jonkman correction method of the DerSimonian and Laird random effect models was also applied, based on previous recommendation.[36] We performed a sensitivity analysis in which pooled HRs were primarily calculated in prospective and retrospective studies separately. We also performed a sensitivity analysis using only studies that were assessed to have good or fair quality, according to the Newcastle-Ottawa Quality Assessment Scale. Heterogeneity among effect sizes was assessed using the Q-statistic and magnitude of heterogeneity with I^2.[37] Publication bias was tested with funnel plot asymmetry and Egger's regression test if a minimum of 10 studies was included in the analysis.[38,39] Inter-rater agreement for the quality assessment was tested using Cohen's kappa coefficient. Statistical analyses were performed using RevMan 5.4 and SPSS (Version 26).

Results

Search results

The search strategy yielded 2965 articles. After removing duplicates and screening of articles, 39 studies were included in the systematic review. *Figure 1* shows the PRISMA flowchart for the literature search. There were no randomized, controlled trials that have examined the effect of bariatric surgery on mortality or CV disease. Our systemic search identified observational cohort studies that reported the effect of surgery. These were in mostly retrospective cohort studies,[40–66] but several prospectively defined (matched) cohort studies[67–78] were also found. The key characteristics of all included studies are presented in *Table 1*. All outcomes regarding mortality and incidence of AF, HF, myocardial infarction, and stroke of all included studies are available in Supplementary material online, *Table S1*. In our present search, we have not identified any reports which have examined the effect of bariatric surgery on incident valvular heart disease such as aortic stenosis.

In the quality assessment, 19 studies were assessed as 'good' quality, one study was assessed as 'fair' quality, and 19 studies were assessed as 'poor' quality (see Supplementary material online, *Table S2*). The inter-rater agreement on the quality assessment was good/excellent: overall agreement 91.4% (329/360); Cohen's kappa was substantial: 0.800. The quality of evidence for all outcome parameters was assessed as 'very low' quality. This was based on the observational design of all included studies and the substantial heterogeneity among studies per outcome parameter (see Supplementary material online, *Table S3*).

Heterogeneity among effect sizes was high for all outcome parameters. Publication bias could only be assessed for all-cause mortality (given the criterium of a minimum of 10 studies per outcome parameter for Egger's test and funnel plots), which showed possible publication bias (see Supplementary material online, *Table S4*).

Effect on all-cause and cardiovascular mortality

A total of 28 studies examined the effect of bariatric surgery on mortality, both all-cause and CV mortality. Following bariatric surgery, all-cause mortality varied from 0.0 to 23.7%, and 1.4 to 28.2% for controls, with follow-up duration ranging between 2 and 24 years (see Supplementary material online, *Table S1*). There were 21 studies that examined all-cause mortality, and reported adjusted HRs, and were therefore suited for the meta-analysis (*Figure 2*). These 21 studies included 133 524 patients after bariatric surgery, and 263 478 obese controls. The meta-analysis showed that patients who had undergone surgery had a pooled HR of all-cause mortality of 0.55 (95% CI 0.49–0.62, $P < 0.001$, $I^2 = 78\%$) compared with obese subjects in the control group. Three of these studies only reported adjusted HRs for separate subgroups [i.e. diabetic vs. non-diabetic, or Roux-en-Y gastric bypass (RYGB) vs. sleeve gastrectomy] and are thus mentioned twice in the forest plot.[49,54,65] Seven studies investigated CV mortality, with incidences of 0.2–8.3% in bariatric patients and 0.5–12.9% in controls. The results in the meta-analysis showed that bariatric surgery also reduced CV mortality (HR 0.59, 95% CI 0.47–0.73, $P < 0.001$, $I^2 = 71\%$; see Supplementary material online, *Figure S3*).

Effect on atrial fibrillation

A total of seven studies examined the effect of bariatric surgery on the incidence of AF (see Supplementary material online, *Table S1*), which ranged from 0.8–12.4% in patients after bariatric surgery to 1.3–16.8% in control subjects. Five of these studies were suitable for the meta-analysis, which accumulated to 24 015 patients following bariatric surgery and 80 394 controls (*Figure 3A*). The overall effect in the meta-analysis was a non-significant reduction after bariatric surgery vs. controls with regard to the incidence of AF (HR 0.82, 95% CI 0.64–1.06, $P = 0.12$, $I^2 = 76\%$).

Effect on heart failure

A total of 12 studies examined the effect of bariatric surgery on the incidence of HF (see Supplementary material online, *Table S1*). Incidence rates that were reported ranged from 0.4 to 9.9% in patients following bariatric surgery, as compared with 0.7–15.7% in controls. For the meta-analysis, eight studies fulfilled criteria and thus a total of 26 002 bariatric patients and 40 657 controls were examined. The pooled HR for incident HF following bariatric surgery vs. control subjects was 0.50 (95% CI 0.38–0.66, $P < 0.001$, $I^2 = 71\%$, *Figure 3B*).

It is important to mention that one large study that examined incident HF was not included in the current meta-analysis since the authors only provided unadjusted HR in their results. Sundstrom *et al.*[78] examined 25 804 patients who had undergone bariatric surgery, and compared them to 13 701 controls. During 4 years of follow-up, surgery led to a 46% reduction in HF incidence, but the overall incidence of events was very low, which may have been due to the design of the study (i.e. less stringent registration of events).

Effect on myocardial infarction

Nine studies reported on incident myocardial infarction after bariatric surgery and controls, and six on incident coronary artery disease. Incidence of coronary artery disease following bariatric surgery ranged from 1.5 to 13.7% vs. 2.7 to 44.7% in controls (see Supplementary material online, *Table S1*), but these were not analysed further. Myocardial infarction after bariatric surgery occurred in 0.1–9.9% of patients, compared with 0.5–10.0% in

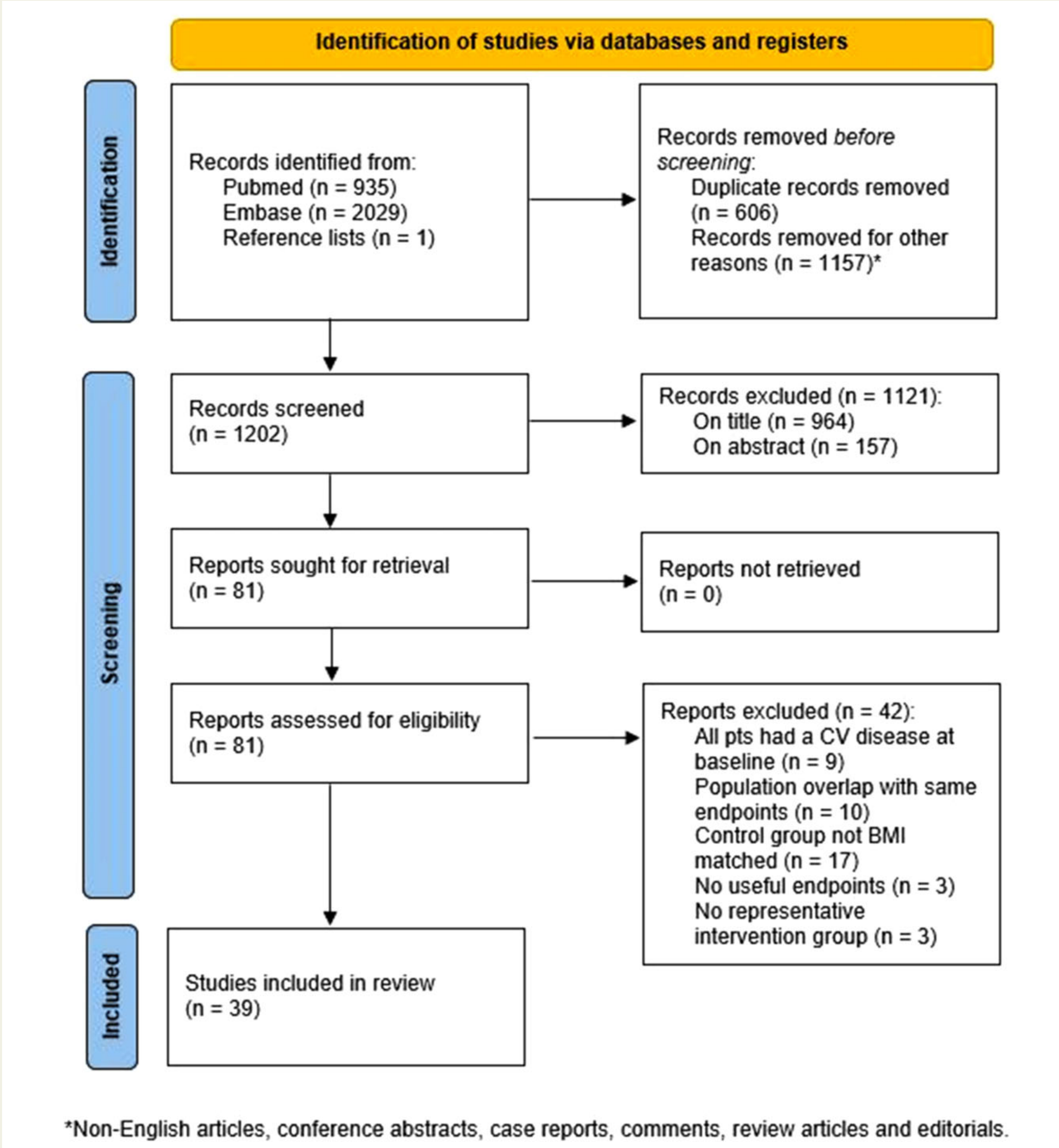


Figure 1 Flowchart of literature search according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. BMI, body mass index; CV, cardiovascular.

controls. For the meta-analysis of incident myocardial infarction after bariatric surgery, seven of the nine studies were suitable, involving 101 536 patients following bariatric surgery and 322 551 controls. Bariatric surgery was associated with a lower incidence of myocardial infarction when compared with controls (HR 0.58, 95% CI 0.43–0.76, $P < 0.001$, $I^2 = 82\%$, *Figure 3C*).

Effect on stroke

The incidence of stroke was investigated in 14 studies, and its incidence was much lower than other CV events (*Table 1*). Incidence of stroke ranged from 0.5 to 6.1% in bariatric patients, and 0.5 to 6.9% in controls. Nine studies were suitable for meta-analysis, involving 86 601 bariatric patients, and 318 599 controls. The pooled

Table 1 Key characteristics of included studies

First author/pub year	Intervention group					Control group				Study design	Cohort	Major inclusion criteria	Major exclusion criteria	Primary outcome	Secondary outcome	Follow-up period
	Surgery type	*N*	Age	BMI	% DM2	*N*	Age	BMI	% DM2							
Adams *et al.*[40]	RYGB (100%)	7925	39.5	45.3	NR	7925	39.3	46.7	NR	Retrospective cohort study	Single Utah surgical practice 1984–2002	Not specified other than BS	Not specified	All-cause mortality	CV mortality	7.1 years
Alkharaiji *et al.*[41]	RYGB or SG (% NR)	131	50.7	42.8	100%	579	52.0	40.6	100%	Retrospective cohort study	The Health Improvement Network (THIN) upon 2017	Age >18 years, insulin-treated DM2	DM1, or non-insulin-treated DM2	MI	Stroke, CAD, HF	10 years
Aminian *et al.*[42]	RYGB 63%, SG 32%, AGB 5%, duodenal switch 0.002%	2287	52.5	45.1	100%	11 435	54.8	42.6	100%	Retrospective cohort study	Cleveland Clinical Health System upon 2018	Age 18–80, BMI ≥30, HbA1c ≥6.5%, or ≥1 diabetic drug	Solid organ transplant, severe HF, active cancer, gastric cancer <1 year, ER admission <5 months, earlier gastric cancer surgery	6-Point-MACE[a]	All-cause mortality, CAD, HF, stroke, AF	3.9 years
Ardissino *et al.*[43]	NR	593	49.6	45.5	100%	593	49.5	45.1	100%	Retrospective cohort study	UK Clinical Practice Research Datalink	Age >18 years, BMI ≥30, DM2	CKD ≥ III, missing data: age, sex, BMI, DM2	ASCVD	All-cause mortality, CAD, stroke	42.7 months
Arterburn *et al.*[44]	RYGB (80.2%), AGB (4.4%), SG (2.4%), other (13.2%)	1395	48.2	47.4	100%	62 322	49.1	42.6	100%	Retrospective cohort study	US health plan and care delivery systems 2005–08	Uncontrolled or medication controlled DM2, BMI ≥35, age 18–80	Gestational diabetes, pregnancy, history of malignancy, prior GE surgery, peritoneal effusion/ascites	All-cause mortality	NA	2 years
Arterburn *et al.*[45]	RYGB (74%), SG (15%), AGB (10%), other (1%)	2500	52	47	NR	7462	53	46	NR	Retrospective cohort study	VA Surgical Quality Improvement Program data 2000–11	BMI ≥35	Missing BMI, BMI <35, no BS code, cancer, Crohn's disease, renal failure, pregnancy	All-cause mortality	NA	Max 14 years
Benotti *et al.*[46]	RYGB (100%)	1724	45.0	46.5	NR	1724	45.1	46.6	NR	Retrospective cohort study	Geisinger Health Center 2002–12	Age 20–80 years, BMI >35, no pre-existing CVD (ICD9 410–449)	Missing data to calculate Framingham Risk Score	Combined MI/HF/stroke	Stroke, MI, HF	6.3 years
Brown *et al.*[47]	RYGB (52.2%), SG (13.8%), AGB (34%)	60 445	42.7	NR	72.7%	268 362	43.3	NR	72.7%	Retrospective cohort study	Statewide Planning and Research Cooperative System database 2006–12	Age ≥18 years	In-hospital death in earliest records, duplicate records, missing data: sex	CV event	Stroke, MI	NR
Busetto *et al.*[48]	AGB (100%)	821	38.2	48.6	NR	821	42.8	48.1	NR	Retrospective cohort study	University of Padova 1994–2001	BMI ≥40, age >18 years	BMI <40	All-cause mortality	NA	Surg: 5.6 years, Con: 7.2 years
Carlsson *et al.*[67]	Vertical banded gastroplasty (68%), AGB	2007	47.2	42.4	17.2%	2040	48.7	40.1	12.9%	Prospective matched cohort study	Swedish Obesity Subjects 1987–2001	Age 37–60 years, BMI men ≥34, women ≥38	Earlier gastric/duodenal surgery, ongoing	All-cause mortality	CV mortality	Surg: 24 years, Con: 22 years

Continued

Table 1 Continued

First author/pub year	Intervention group: Surgery type	N	Age	BMI	% DM2	Control group: N	Age	BMI	% DM2	Study design	Cohort	Major inclusion criteria	Major exclusion criteria	Primary outcome	Secondary outcome	Follow-up period
	(19%), RYGB (13%)												malignancy, MI <6 months, drug/alcohol			
Ceriani et al.[60]	Biliopancreatic diversion/ biliointestinal bypass (100%)	472	43.1	47.3	23.5%	1405	43.5	46.8	27.4%	Retrospective cohort study	LAGB10 study group 1999–2008	BMI ≥40 or ≥35 with comorbidities	Not specified	All-cause mortality	CV mortality	12.1 years
Courcoulas et al.[49]	SG (45%), RYGB (55%)	31 158	44.6	43.6	26.1%	39 795	44.9	43.0	25.9%	Retrospective matched cohort study	Kaiser Permanente regions Washington and California 2005–15	Age 19–79 years, BMI ≥35	<1 year of enrolment, pregnancy, cancer	All-cause mortality	CV mortality	Up to 5 years
Douglas et al.[50]	ABG (47.1%), RYGB (36.6%), SG (15.8%), other (0.5%)	3882	45	44.7	34.0%	3882	45	42.1	33.4%	Retrospective cohort study	UK Clinical Practice Research Datalink upon 2014	>12 months prior registration in database	Reversal of bariatric surgery	MI	All-cause mortality, stroke	3.4 years
Doumouras et al.[51]	RYGB (87%), SG (13%)	13 679	45.2	47.2	26.7%	13 679	45.5	46.7	26.7%	Retrospective cohort study	Ontario Bariatric Network 2010–16	Not specified other than BS	Non-Ontario pts, age >70 years, BMI <35, cancer, substance abuse, palliative care, pregnancy, organ transplantation, liver/ heart disease	All-cause mortality	CV mortality	Surg: 4.9 years, Con: 4.8 years
Eliasson et al.[52]	RYGB (100%)	6132	48.5	42.0	95%	6132	50.5	41.4	92%	Retrospective cohort study	National Diabetes Register and Scandinavian Obesity Surgery Registry 2007–14	Complete socioeconomic data	Not specified	All-cause mortality	MI, CV mortality	3.5 years
Fisher et al.[53]	RYGB (76%), SG (17%), AGB (7%)	5301	49.5	44.7	100%	14 934	50.2	43.8	100%	Retrospective cohort study	US health plan and care delivery systems 2005–11	Age 19–79 years, BMI >35, DM2	<1 year of enrolment, cancer, pregnancy, gestational diabetes, CAD, or cerebrovascular disease, missing BMI	Macrovascular disease	All-cause mortality, CAD, stroke	Surg: 4.7 years, Con: 4.6 years
Höskuldsdóttir et al.[68]	RYGB (100%)	5321	49	42.0	100%	5321	47	41.0	100%	Prospective cohort study	National Diabetes Register and Scandinavian Obesity Surgery Registry 2007–13	Age 18–65 years, BMI >27.5, DM2	Other procedures than RYGB	Incident AF	HF	4.5 years
Jamaly et al.[70]	Vertical banded gastroplasty (68%), AGB (19%), RYGB (13%)	2000	47.2	42.4	17.2%	2021	48.6	40.1	12.7%	Prospective matched cohort study	Swedish Obesity Subjects 1987–2001	Age 37–60 years, BMI men ≥34, women ≥38	Earlier gastric/duodenal surgery, ongoing malignancy, MI <6 months, drug/alcohol abuse	Incident AF	NA	19 years
Jamaly et al.[69]	Vertial banded	2003	47.2	42.4	17.2%	2030	48.7	40.1	12.7%	Prospective	Swedish Obesity	Age 37–60 years,	Diagnosis of HF, <6	Incident HF	NA	22 years

Continued

Table 1 Continued

First author/pub year	Intervention group: Surgery type	N	Age	BMI	% DM2	Control group: N	Age	BMI	% DM2	Study design	Cohort	Major inclusion criteria	Major exclusion criteria	Primary outcome	Secondary outcome	Follow-up period
	gastroplasty (68%), AGB (19%), RYGB (13%)									matched cohort study	Subjects 1987–2001	BMI men ≥34, women ≥38	months MI, earlier gastric surgery			
Lent et al.[54]	RYGB (100%)	625 1803	52.5 43.8	44.9 47.4	100% 0%	625 1803	52.5 43.9	44.9 47.3	100% 0%	Retrospective cohort study	Geisinger Health Center 2004–15	BMI ≥40 or ≥35 with comorbidities	Not specified	All-cause mortality	NA	5.8 years 6.7 years
Liakopoulos et al.[71]	RYGB (100%)	5321	49	42.0	100%	5321	47	41.0	100%	Prospective cohort study	National Diabetes Register and Scandinavian Obesity Surgery Registry 2007–15	Age 18–65 years, BMI >27.5, DM2, primary RYGB	Other procedures than RYGB	All-cause mortality	MI, HF, AF, stroke	4.5 years
Liakopoulos et al.[72]	RYGB (100%)	5321	49	42.0	100%	5321	47	41.0	100%	Prospective cohort study	National Diabetes Register and Scandinavian Obesity Surgery Registry 2007–15	Age 18–65 years, DM2, primary RYGB	Other procedures than RYGB	Incident HF	All-cause mortality	Surg: 4.7 years, Con: 4.6 years
Lundberg et al.[73]	RYGB (100%)	28 204	40.8	NR	14.7%	40 827	43.1	NR	16.2%	Prospective cohort study	Swedish National Patient Registry 2001–13	Age 20–65 years, BMI ≥35	Other bariatric surgery or died <2 years after obesity diagnosis	Incident MI	Stroke, mortality, CV mortality	Surg: 4.1 years, Con: 4.8 years
Lynch et al.[55]	RYGB or SG (% NR)	3572	42	47.1	23.3%	45 750	42	47.7	23.8%	Retrospective cohort study	Single Virginia Academic Hospital 1985–2015	Age >18 years	Banded gastroplasty pts, pre-existing AF	Incident AF	NA	Surg: 6.2 years, Con: 8.0 years
MacDonald et al.[56]	RYGB (100%)	154	41.9	50.6	100%	78	43.5	48.8	100%	Retrospective cohort study	Obesity Research Program 1979–94	Non-insulin dependent DM2	No non-insulin dependent DM2, no morbid obesity, age >64 years	All-cause mortality	NA	Surg: 9 years, Con: 6.2 years
Michaels et al.[57]	RYGB (78.9%), AGB (11.7%), SG (7.7%), other (1.7%)	3242	43	47.7	27.1%	3242	43	48.0	27.4%	Retrospective cohort study	Single Virginia Academic Hospital 1985–2015	Not specified other than BS	Not specified	Incident MI	NA	NR
Moussa et al.[74]	RYGB (38%), AGB (35%), SG (15%), other (1%), undefined (11%)	3701	36	40.5	25.0%	3701	36	40.3	23.9%	Prospective cohort study	UK Clinical Practice Research Datalink upon 2020	Not specified other than BS	BMI <35, MACE before index date, lost to follow-up <12 months after index date, missing data: age, BMI, sex	Combined MI/stroke	All-cause mortality, MI, stroke, HF	140.7 months
Moussa et al.[75]	NR	4212	50	40.4	24.2%	4212	51	40.5	20.3%	Prospective cohort study	UK Clinical Practice Research Datalink upon 2021	Not specified other than BS	BMI <35, MACE before index date, lost to follow-up <12 months after index date,	Stroke	All-cause mortality, stroke	11.4 years

Continued

Table 1 ***Continued***

First author/pub year	Intervention group: Surgery type	*N*	Age	BMI	% DM2	Control group: *N*	Age	BMI	% DM2	Study design	Cohort	Major inclusion criteria	Major exclusion criteria	Primary outcome	Secondary outcome	Follow-up period
													missing data: age, BMI, sex			
Perry *et al.*[58]	Open RYGB (67%), (non-specified) laparoscopy procedure (28.5%), other (4.5%)	11 903	NR	NR	44.9%	NR	NR	NR	45.0%	Retrospective cohort study	Medicare claims 2022–2004	Not specified other than BS	Urgent BS code, active cancer, unstable angina, prior MI, inflammatory bowel disease	All-cause mortality	NA	2 years
Pontiroli *et al.*[59]	AGB (44.9%), biliopancreatic diversion/ biliointestinal bypass (55.1%)	857	42.6	44.7	19.0%	2086	43.2	44.1	24.5%	Retrospective cohort study	LAGB10 study group 1995–2008	BMI ≥40 or ≥35 with comorbidities	Not specified	All-cause mortality	NA	NR
Rassen *et al.*[61]	RYGB (50%), SG (44%), gastric resection (8%)	344	57.9	42.6	100%	551	59.0	42.1	100%	Retrospective cohort study	Electronic Health Records licenced from Optum 2007–18	Age 18–80 years, DM2, BMI ≥30	Solid organ transplant, severe HF, active cancer, ER admission 5 prior to index date, surgical procedures for GE cancer	6-Point-MACE[a]	All-cause mortality, CAD, CVA, HF, AF	2.5 years
Reges *et al.*[62]	AGB (55%), SG (40%)	8385	46	40.6	28.5%	25 155	46	40.5	28.5%	Retrospective cohort study	Clalit Health Service 2005–14	Age >24 years, membership Clalit health service	Missing BMI, BMI <30, pregnancy, severe comorbidities	All-cause mortality	NA	Surg: 4.3 years, Con: 4.0 years
Sampalis *et al.*[63]	RYGB (81.3%) vertical banded gastroplasty (18.7%)	1035	45	NR	0%	5746	47	NR	0%	Retrospective cohort study	McGill University Health Centre 1986–2002	Not specified other than BS	Cancer, haematological disease, CVD, digestive diseases, endocrinologic disease incl. diabetes, genitourinary, infectious, musculoskeletal, nervous system, psychiatric and mental, respiratory and skin diseases	Incident MI	NA	2.5 years
Singh *et al.*[64]	AGB, SG, RYGB, or duodenal switch (% NR)	5170	45.2	NR	22.7%	9995	45.3	NR	20.9%	Retrospective cohort study	The Health Improvement Network (THIN) 1990–2018	>1 year registered in general practice	BMI <30, age >75 years, gastric cancer, gastric balloon, endo-barrier, or revisional bariatric surgery	Stroke	All-cause mortality, CAD, HF, stroke, AF	3.9 years
Sjostrom *et al.*[76]	Vertical banded gastroplasty	2010	46.1	41.8	7.4%	2037	47.4	40.9	6.1%	Prospective	Swedish Obesity	Age 37–60 years,	Earlier gastric/duodenal surgery, ongoing	All-cause mortality	NA	14.7 years

Continued

Table 1 Continued

First author/pub year	Intervention group					Control group				Study design	Cohort	Major inclusion criteria	Major exclusion criteria	Primary outcome	Secondary outcome	Follow-up period
	Surgery type	N	Age	BMI	% DM2	N	Age	BMI	% DM2							
	(68%), (A)GB (19%), RYGB (13%)									matched cohort study	Subjects 1987–2001	BMI men ≥34, women ≥38	malignancy, MI <6 months, drug/alcohol			
Sjostrom et al.[77]	Vertical banded gastroplasty (68%), (A)GB (19%), RYGB (13%)	2010	46.1	41.8	7.4%	2037	47.4	40.9	6.1%	Prospective matched cohort study	Swedish Obesity Subjects 1987–2001	Age 37–60 years, BMI men ≥34, women ≥38	Earlier gastric/duodenal surgery, ongoing malignancy, MI <6 months, drug/alcohol	CV mortality	MI, stroke	14.7 years
Sundstrom et al.[78]	RYGB 100%	25 804	41.3	41.5	15%	13 701	41.5	41.4	9.4%	Prospective cohort study	Scandinavian Obesity Surgery Registry 2007–12 and Itrim Health Database 2006–13	BMI 30–50, ≥18 years	Cross-over, HF at baseline, missing data on education or marital status	Incident HF	MACE	4.1 years
Thereaux et al.[65]	RYGB (55%) and SG (45%)	8966	40.4	NR	13%	8966	40.9	NR	13%	Retrospective matched cohort study	French National Health Insurance database 2009	Not specified other than BS	Cancer, pregnancy, chronic infectious disease, contra-indication for bariatric surgery, earlier bariatric surgery	All-cause mortality	NA	6.8 years
Wong et al.[66]	Sleeve gastroplasty (80.5%), RYGB (16.2%), revision procedure (3%)	303	51.4	37.4	100%	1399	51.0	36.6	100%	Retrospective matched cohort study	Hospital Authority data base Hong Kong adult diabetes population 2006–17	DM2	BMI <27.5, non-DM2, history of CVD, eGFR <30	All-cause mortality	CV disease, MI, stroke, HF	32 months

[a]First occurrence of all-cause mortality, coronary artery events (unstable angina, myocardial infarction, or coronary intervention/surgery), cerebrovascular events (ischaemic stroke, haemorrhagic stroke, or carotid intervention/surgery), heart failure, nephropathy, and atrial fibrillation.

(A)GB, adjustable gastric band; AF, atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index (in kg/m^2); BS, bariatric surgery; CAD, coronary artery disease; CKD, chronic kidney disease; CV, cardiovascular; DM1, Type 1 diabetes mellitus; DM2, Type 2 diabetes mellitus; eGFR estimated glomerular filtration rate (in mL/min/1.73 m^2); ER, emergency room; GE, gastroenterological; HbA1c, glycated haemoglobin; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; NA, not applicable; NR, not reported; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Adams 2007	−0.5108	0.1015383	5.5%	0.60 [0.49, 0.73]
Aminian 2019	−0.5276	0.10343498	5.4%	0.59 [0.48, 0.72]
Ardissino 2020	−1.0217	0.33628594	2.3%	0.36 [0.19, 0.70]
Arterburn 2013	−0.6162	0.43906681	1.6%	0.54 [0.23, 1.28]
Arterburn 2015	−0.755	0.10124525	5.5%	0.47 [0.39, 0.57]
Busetto 2007	−1.0217	0.4105709	1.7%	0.36 [0.16, 0.80]
Carlsson 2020	−0.3567	0.07234064	5.9%	0.70 [0.61, 0.81]
Ceriani 2019	−0.6349	0.30801407	2.5%	0.53 [0.29, 0.97]
Courcoulas 2021 (RYGB)	−0.7985	0.13321158	5.0%	0.45 [0.35, 0.58]
Courcoulas 2021 (SG)	−1.273	0.37706681	2.0%	0.28 [0.13, 0.59]
Doumouras 2020	−0.3857	0.08964232	5.6%	0.68 [0.57, 0.81]
Fisher 2018	−1.0788	0.40714666	1.8%	0.34 [0.15, 0.76]
Lent 2017 (DM2)	−0.821	0.20978544	3.7%	0.44 [0.29, 0.66]
Lent 2017 (no DM2)	−0.1744	0.18968827	4.0%	0.84 [0.58, 1.22]
Liakopoulos 2018	−0.5447	0.10880574	5.3%	0.58 [0.47, 0.72]
Lundberg 2021	−0.0619	0.09456097	5.6%	0.94 [0.78, 1.13]
Moussa 2020	−1.3863	0.16963681	4.4%	0.25 [0.18, 0.35]
Pontiroli 2020	−0.7985	0.16087419	4.5%	0.45 [0.33, 0.62]
Rassen 2021	0.1222	0.35139891	2.2%	1.13 [0.57, 2.25]
Reges 2018	−0.6931	0.10765163	5.4%	0.50 [0.40, 0.62]
Singh 2020	−0.3567	0.12278142	5.1%	0.70 [0.55, 0.89]
Sjöström 2007	−0.3425	0.13591952	4.9%	0.71 [0.54, 0.93]
Thereaux 2019 (RYGB)	−0.4463	0.10343498	5.4%	0.64 [0.52, 0.78]
Thereaux 2019 (SG)	−0.9676	0.13896101	4.9%	0.38 [0.29, 0.50]
Total (95% CI)			**100.0%**	**0.55 [0.49, 0.62]**

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 105.14$, df = 23 ($P < 0.00001$); $I^2 = 78\%$
Test for overall effect: Z = 9.41 ($P < 0.00001$)

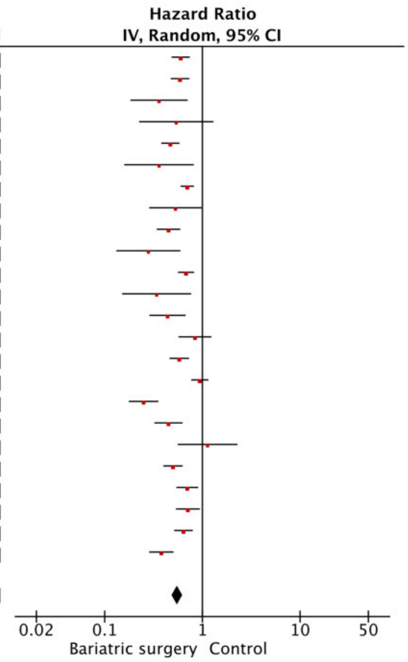


Figure 2 Forest plot of pooled hazard ratios of all-cause mortality. CI, confidence interval; DM2, Type 2 diabetes mellitus; RYGB, Roux-en-Y gastric bypass; SE, standard error; SG, sleeve gastrectomy.

analysis showed that bariatric surgery reduced the incidence of (all) strokes (HR 0.64, 95% CI 0.53–0.77, $P < 0.001$, $I^2 = 80\%$, *Figure 3D*).

A few studies further investigated the type of stroke, and so we performed additional analysis in studies that only reported on ischaemic stroke. Interestingly, we observed an even more outspoken protective effect of surgery on ischaemic stroke (HR 0.37, 95% CI 0.17–0.82, $P = 0.01$, $I^2 = 92\%$), compared with the effect on all strokes combined (see Supplementary material online, *Figure S4*).

Sensitivity analysis

As expected, small effect modification using the Hartung–Knapp–Sidik–Jonkman correction in the analyses with <20 studies changed the CIs but not the overall effect estimate: for CV mortality (HR 0.59, 95% CI 0.45–0.77, $P = 0.004$); for AF (HR 0.82, 95% CI 0.51–1.32, $P = 0.3$); for HF (HR 0.50, 95% CI 0.37–0.68, $P = 0.001$); for myocardial infarction (HR 0.58, 95% CI 0.42–0.80, $P = 0.006$); and for stroke (HR 0.64, 95% CI 0.50–0.82, $P = 0.003$).

In sensitivity analyses, we evaluated each outcome parameter for prospective and retrospective studies separately. The magnitude and direction of the pooled effect remained similar to all pooled HRs in comparison to prospective and retrospective studies for all-cause mortality (prospective studies: HR 0.60, 95% CI 0.43–0.83, $P = 0.002$, $I^2 = 92\%$, and retrospective studies: HR 0.54, 95% CI 0.48–0.60, $P < 0.001$, $I^2 = 59\%$). The same was observed in the analyses of CV-related mortality (single prospective study: HR 0.78, 95% CI 0.64–0.96, $P = 0.02$, and retrospective studies: HR 0.55, 95% CI 0.45–0.66, $P < 0.001$, $I^2 = 53\%$), incident HF (prospective studies: HR 0.45, 95% CI 0.26–0.78, $P = 0.004$, $I^2 = 84\%$, and retrospective studies: HR 0.54, 95% CI 0.38–0.77, $P < 0.001$, $I^2 = 65\%$), and all types of stroke (prospective studies: HR 0.56, 95% CI 0.35–0.90, $P = 0.02$, $I^2 = 92\%$, and retrospective studies: HR 0.02, 95% CI 0.00–0.31, $P = 0.005$, $I^2 = 66\%$).

Differences in outcomes between prospective and retrospective studies were seen in incident AF (prospective studies: HR 0.66, 95% CI 0.57–0.77, $P < 0.001$, $I^2 = 0\%$, and retrospective studies: HR 1.04, 95% CI 0.69–0.1.56, $P = 0.87$, $I^2 = 77\%$), as well as for incident myocardial infarction (prospective studies: HR 0.57, 95% CI 0.45–0.72, $P < 0.001$, $I^2 = 42\%$, and retrospective studies: HR 0.66, 95% CI 0.32–1.35, $P = 0.25$, $I^2 = 85\%$). For both outcomes, a protective effect following bariatric surgery was only found in prospective studies, and a non-significant (non-protective) outcome was seen in retrospective studies.

In sensitivity analysis that only assessed the studies of good or fair quality, outcomes were similarly beneficial following bariatric surgery for all-cause mortality (HR 0.50, 95% CI 0.43–0.59, $P < 0.001$, $I^2 = 80\%$), CV mortality (HR 0.59, 95% CI 0.47–0.73, $P = 0.002$, $I^2 = 63\%$), HF (HR 0.51, 95% CI 0.33–0.77, $P = 0.001$, $I^2 = 56\%$), all types of stroke (HR 0.55, 95% CI 0.34–0.88, $P = 0.01$, $I^2 = 90\%$), and ischaemic stroke (single study: HR 0.32, 95% CI 0.25–0.41, $P < 0.001$). For AF and myocardial infarction, outcomes of this sensitivity analyses (respectively; a single study on AF: HR 0.69, 95% CI 0.58–0.82, $P < 0.001$, and multiple studies on myocardial infarction: HR 0.61, 95% CI 0.39–0.94, $P = 0.02$, $I^2 = 67\%$) were in line with the pooled outcome of prospective studies, showing a lowered incidence of disease after bariatric surgery, but were different to the general pooled outcome.

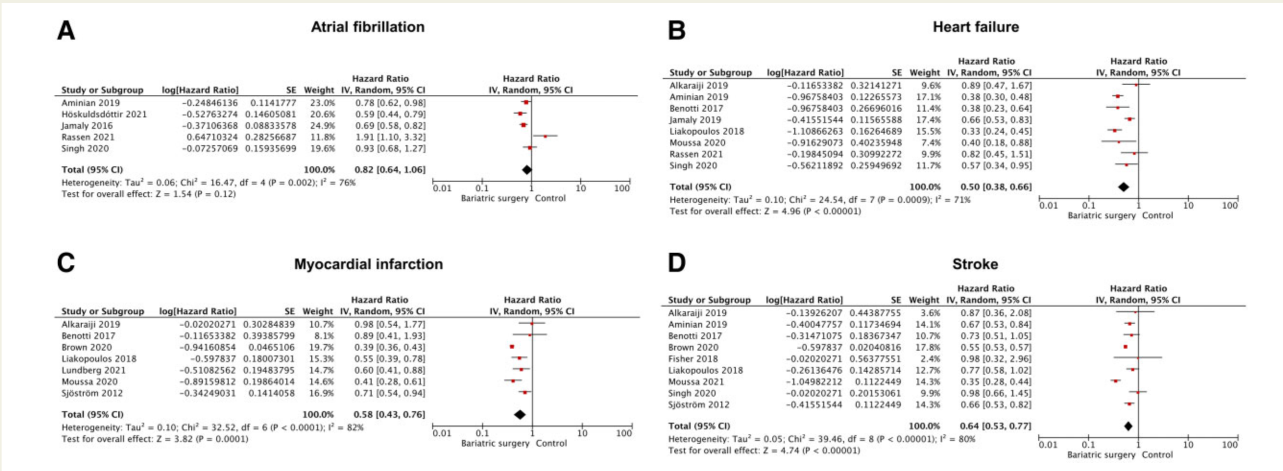


Figure 3 Forest plot of pooled hazard ratios of atrial fibrillation, heart failure, myocardial infarction, and stroke. CI, confidence interval; SE, standard error.

Discussion

Bariatric surgery is currently the only treatment option that achieves substantial and durable weight reduction in patients with obesity, in whom there is a markedly increased incidence of CV disease. The present systematic review and meta-analysis of 39 controlled cohort studies shows that bariatric surgery is significantly associated with reduction of not only mortality but also the incidence of CV disease, although it must be noted that no randomized outcome trials are available. Nevertheless, the data from the present systematic review and meta-analysis strongly suggest that bariatric surgery reduces the incidence of CV disease and lowers mortality during follow-up (*Structured Graphical Abstract*).

In recent years, four other systematic reviews have been published.[30–33] Zhou *et al.*[30] reviewed all studies until 2016 and reported all-cause mortality, cancer incidence, and CV outcomes after bariatric surgery compared with obese controls. Their findings are in line with the current results, but clearly, their data are older, and many recent studies were not part of the analysis, particularly since a number of important studies have been published in the last 2 years. In addition, for CV disease they only examined nine studies, and together these factors are the main limitation of their review. The meta-analysis by Wiggins *et al.*[31] published in 2020 focused on mortality and ischaemic heart disease, and CV risk factors such as diabetes, but they only included studies that drew their study population from nationwide registries as opposed to more precise hospital records, thereby missing many endpoints, and they only included 18 studies. Interestingly, using this approach, they observed a similar effect of bariatric surgery compared with controls as we did in the present analysis (i.e. a pooled odds ratio for all-cause mortality of 0.62 and 0.50 for CV mortality). In the third systematic review by Pontiroli *et al.*,[32] also published in 2020, the authors conducted a meta-analysis to evaluate outcome following bariatric surgery, and focused on the important issue of age at the time of surgery, and how that influences the effect of surgery on outcome. Using this approach the authors included nine studies, and observed that the beneficial effect of surgery on outcome was mainly found in patients above the median age (around 40). It should be noted, however, that the median follow-up duration in their meta-analysis was 8.7 years, and this may have been rather short, particularly in younger patients, since CV disease (and associated mortality) usually occurs later, even in obese patients. The review by Cardoso *et al.*[33] from 2017 misses recent studies due to the publication date, and it only uses eight studies for their outcome analysis. In addition, that study only examined short-term follow-up, and has very few endpoints.

Despite the potential favourable long-term effect of bariatric surgery, considering surgery for obesity, however, remains a significant step for patients. With the increasing safety and relatively low incidence of (long term) adverse outcomes, it can be an attractive alternative, however, for patients with morbid obesity.[79] Bariatric surgery has been shown to reduce CV risk factors, and arguably, this should be accompanied by a reduction in CV events, but there are no randomized controlled trials that have prospectively examined the incidence of CV disease. This is understandable, since the average age of patients undergoing bariatric surgery is 40 years, and the onset of CV disease in patients below the age of 50 is relatively low. In other words, despite a probably significant and clinically relevant patient benefit, randomized controlled trials that examined the effect of bariatric surgery on CV disease outcome would require long-term (e.g. 5–10 years or maybe even longer) follow-up. The present meta-analysis shows a 25–58% reduction of CV events and a 35–40% reduction in mortality. It would be nice if these findings were supported in large-scale randomized clinical outcome trials, with substantial follow-up duration. But it will be challenging, and maybe even unlikely, that such a randomized clinical trial will be conducted in the near future. The fact that bariatric surgery is already performed on a large scale (and that withholding bariatric surgery may sometimes seem unethical for patients with morbid obesity) will complicate matters further, and make an outcome trial very difficult. Hence, it will also be unlikely that a future systematic review and meta-analysis will render higher GRADE assessments for outcome parameters, even though this current review and future reviews consist of individual high-quality prospective studies.

An important factor in the beneficial effect of bariatric surgery is whether this is only due to the absolute weight reduction, or whether additional, ancillary effects also play a role. A recent small mechanistic study suggested that the benefits of bariatric surgery were all related to weight loss itself, with no other independent beneficial effects.[80] Many other studies, however, have suggested that ancillary factors associated with surgery are of influence, such as an altered profile in gut hormone expression, enhanced insulin sensitivity, and changed gut microbioma,[81] and the procedure is therefore increasingly referred to as metabolic surgery.[82] Nevertheless, there is no question that the magnitude of weight loss is very important, and in one study it was calculated that in non-surgical obese patients, a 20% decrease in weight was required (only rarely achieved) to reduce long-term major CV events, while in surgical patients at least 10% weight reduction was required, which is generally easily achieved,[81] and underlines the hypothesis that other metabolic mechanisms contribute to the beneficial effects of surgery.

As pointed out before, despite these potential benefits of bariatric surgery to prevent (and possibly treat) CV disease, no randomized controlled studies have primarily investigated the effect of surgery on CV events or outcome. At this moment, we are aware of only one ongoing randomized clinical trial in patients with morbid obesity and AF, who will undergo bariatric surgery 6 months prior to AF catheter ablation (Bariatric Atrial Restoration of Sinus Rhythm, ClinicalTrials.gov identifier NCT04050969). In terms of prevention, bariatric surgery could potentially be useful in any (morbidly) obese patient with an increased risk of CV disease. Regarding treating clinically present disease, surgery could possibly be useful to treat patients with HF, but also AF, as discussed above. The recently published guideline for CV disease prevention by the European Society of Cardiology[83] states that 'bariatric surgery for obese high-risk individuals should be considered when lifestyle change does not result in maintained weight loss', i.e. a 2A recommendation. This is a major change from the previous guideline of 2016,[84] in which diet and lifestyle are advocated as main-stay therapy options, and bariatric surgery did not receive a formal recommendation. In addition, prevention or treatment of CV disease has so far not affected the recommendations for surgery.[85] The strongest recommendation for metabolic surgery is for patients with obesity and Type 2 diabetes, and in this patient population, it is now considered a valid addition to existing standard therapy.[86]

There are some limitations that should be mentioned regarding the present systematic review and meta-analysis. First, all data regarding bariatric surgery that are discussed here stem from non-randomized studies, albeit many of them are prospective in design. Second, some of the studies in obese subjects only enrolled patients with (Type 2) diabetes, which may have affected the findings (see also Supplementary material online, *Table S1*). Indeed, it has been suggested that bariatric surgery may be more effective in reducing outcomes in patients with diabetes, as compared with those without diabetes.[54] However, this was not reported in another study[74] and the present meta-analysis does not provide an answer on this. Third, recent studies with new drugs like glucagon-like peptide 1 agonists or sodium–glucose cotransporter 2 inhibitors, have shown promising results in patients with diabetes and obesity, but no large studies are currently available on the (additive) effect of bariatric surgery in the population. But it is conceivable that these drugs may affect the outcome in this population. Fourth, we only examined the effect of surgical techniques combined, and did not investigate potential differences between techniques. Fifth, we did not specifically analyse HR of coronary artery disease in addition to myocardial infarction. This decision was based on the fact that the data on coronary artery disease were relatively scarce, and as coronary artery disease can occur silently, this may have been difficult to report in large (national) cohorts. We hypothesized that coronary artery disease is underreported to some extent, and therefore future studies could add valuable information regarding coronary artery disease following bariatric surgery. Last, some analyses should be interpreted with caution, as some sensitivity analyses consisted of single studies analysis, for example CV-related mortality in the analysis of prospective studies.[73] In addition, publication bias was not assessed for the majority of our outcome parameters, as the Egger's test and funnel plots are not appropriate in analysis containing $<$10 studies. For interpretation of funnel plots, it should be noted that asymmetry can also originate from other sources than publication bias.[39]

In summary, the results of this systematic review and meta-analysis of 39 studies suggest that bariatric surgery reduces mortality and incidence of CV disease in patients with obesity compared with non-surgical treatment. Bariatric surgery should therefore be considered in these patients.

Supplementary material

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

Conflict of interest: The authors declare no relevant conflicts of interest, and no funding or payment was obtained for this review. The Department of Cardiology, UMCG, has received research grants and/or fees from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals Gmbh, Ionis Pharmaceuticals, Inc., Novo Nordisk, and Roche. Some of the ongoing clinical trials are in the field of diabetes and CV disease, but none of them (specifically) in obesity, and none in bariatric surgery. At the Department of the Experimental Cardiology, UMCG (chair R.A.d.B.) some studies in obesity are ongoing, none of them related to bariatric surgery. R.A.d.B. is supported by a grant from the Netherlands Heart Foundation (CVON SHE-PREDICTS-HF, grant 2017–21 and CVON RED-CVD, grant 2017–11) and the European Research Council (ERC CoG 818715, SECRETE-HF). D.J.v.V. is an Established Investigator of the Netherlands Heart Foundation (Grant D97-017).

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