Accepted Article

Short- and long–term mortality after bariatric surgery: a systematic review and meta–analysis

Luís Cardoso[1,2]; Dírcea Rodrigues[1,2]; Leonor Gomes[1,2]; Francisco Carrilho[1]

[1] Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar e Universitário de Coimbra, Portugal

[2] Faculty of Medicine of the University of Coimbra, Portugal

Disclosure Statement: The authors declare that they have no conflicts of interest

Funding / Grant: None

Acknowledgements: None

Corresponding author and person to whom reprint requests should be addressed:

Luís Cardoso

Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar e Universitário de Coimbra

Praceta Prof. Mota Pinto

3000–075 Coimbra

Portuga

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/dom.12922

This article is protected by copyright. All rights reserved.

Accepted Article

Abstract

Aims: The objective of this study was to investigate short- (≤30 days) and long–term (≥2 years) all–cause mortality after bariatric surgery among adult patients with obesity.

Materials and Methods: For short–term mortality, eligible studies were randomized controlled trials (RCTs) reporting perioperative mortality. For long–term mortality, RCTs and observational studies comparing mortality between obese patients after bariatric surgery and non–operated controls were eligible. Random–effects models using a Bayesian or frequentist approach were used to pool the effect estimates of short- and long–term mortality, respectively.

Results: The short–term all–cause mortality based on 38 RCTs involving 4,030 patients was 0.18% (95% CI: 0.04%–0.38%) and was higher for open, 0.31% (95% CI: 0.03%–0.97%), and similar in mixed, 0.17% (95% CI: 0.03%–0.43%), and restrictive surgeries, 0.17% (95% CI: 0.03%–0.45%). For long–term mortality, 12 observational studies involving 27,258 operated patients and 97,154 non–operated obese controls were included. Of these, 8 studies were eligible for the meta–analysis, which showed a reduction of 41% in all–cause mortality (hazard ratio 0.59, 95% CI: 0.52–0.67, P<0.001); additionally, operated patients were 0.42 (95% CI: 0.25–0.72, P<0.001) and 0.47 (95% CI: 0.36–0.63, P<0.001) times as likely as non–operated obese controls to die from cardiovascular diseases and cancer, respectively.

Conclusions: Bariatric surgery is associated with low short–term mortality and may be associated with long–term reductions in all–cause, cardiovascular, and cancer–related mortality.

This article is protected by copyright. All rights reserved.

Accepted Article

Introduction

Obesity is a rapidly growing worldwide pandemic. In the past 30 years, the prevalence of overweight and obesity increased from 28.8% to 36.9% in men and from 29.8% to 38.0% in women.[1,2] In fact, the worldwide prevalence of overweight and obesity is 2.5 times higher than that of undernourishment (2.1 billion versus 0.842 billion, respectively).[2,3] In the United States, it is estimated that by 2030, the prevalence of obesity will reach 40–50% of the adult population; this prevalence will have a substantial impact on population morbi–mortality, as obesity accounted for ~3.4 million deaths, 3.9% of the years of life lost, and 3.8% of the disability–adjusted life–years worldwide in 2010.[4-6] The average life expectancy of individuals with obesity is 5–20 years lower than that of the non–obese population, depending on gender, age, and race.[7,8] In addition, obesity is an important risk factor for diabetes mellitus and cardiovascular, oncological, and musculoskeletal diseases.[9-12]

Bariatric surgery (BS) offers the most effective treatment option for obesity, and the number of weight loss surgeries increased dramatically in the past 15 years.[13,14] Since the publication of the first survey on metabolic/BS by Dr. Scopinaro in 1998, much has changed.[15] In that study, he reported that ~40,000 BSs were performed per year, but that number is currently much larger and has been progressively increasing; in 2013, the annual number of BS procedures performed was reported to be ~470,000.[16]

Despite the increasing experience with BS, there is still a lack of mortality data from randomized clinical trials (RCTs) and long–term observational studies. Previous systematic reviews included RCTs, observational studies, or even case series, and some studies imputed zero mortality for missing data if it was apparent that no deaths had occurred, assuming that the authors would have reported casualties if they had occurred.[17-19] Furthermore, the effects were often estimated using frequentist statistical approaches, which may be particularly problematic in the presence of rare events (i.e., zero deaths).[17-19] In most reviews, long–term

This article is protected by copyright. All rights reserved.

Accepted Article

mortality was evaluated as a secondary objective or in specific contexts (i.e., cardiovascular disease and mortality), and it was a primary objective in only a few reviews, which included studies with relatively short follow–up times; no reviews have reported time–to–event data, which may be valuable.[18-21] Consequently, reviews analysing mortality as a secondary objective may be affected by selection bias, while reviews that used frequentist approaches for rare events, imputed zero for missing data, or included studies with a short follow–up may have produced inaccurate estimates of both short- and long–term mortality.

Therefore, an up–to–date review specifically designed to pool the evidence on short–term mortality from RCTs whilst considering the rarity of events and to summarize the effect estimates of long–term mortality (i.e., time–to–event data) from studies with prolonged follow–up periods is needed. Thus, this systematic review and meta–analysis aimed to comprehensibly summarize and quantify short- (≤30 days) and long–term (≥2 years of follow–up) all–cause mortality among adult patients with obesity undergoing BS.

Methods

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta–Analyses (PRISMA) guidelines.[22] A detailed version of the study protocol can be found in Supplementary File 1.[23]

Eligibility Criteria

We screened all published RCTs and observational studies (OBS) reporting mortality data in adult patients (≥18 years) who underwent BS for obesity (body mass index [BMI] ≥35 kg/m^2). Only RCTs were included in the short-term mortality analysis. To analyse long–term mortality, RCTs and OBS studies were eligible. No comparisons were made when pooling the effect estimates of short–term or perioperative (≤30 days) mortality. However, for long–

This article is protected by copyright. All rights reserved.

Accepted Article

term mortality (≥2 years of follow–up), operated patients were compared to obese controls who underwent non–surgical interventions. Therefore, our outcomes were as follows: (1) death during the first 30 days after a bariatric procedure and (2) death after BS with a minimum follow–up of 2 years compared to death after non–surgical interventions.

BS procedures that aimed to promote weight loss and/or metabolic control were considered the interventions of interest and included (1) restrictive procedures (adjustable and nonadjustable gastric banding [AGB]/[NAGB], vertical banded gastroplasty [VBG], gastric plication [GP], and sleeve gastrectomy [SG]) and (2) both restrictive and malabsorptive techniques (gastric bypass [GB], which included Roux–en–Y gastric bypass [RYGB] and mini–gastric bypass, biliopancreatic diversion [BPD] with or without duodenal switch, and biliopancreatic diversion with RYGB).

Information Sources and Search Strategy

Literature search strategies were developed as described in Supplementary File 1 and were applied in MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (Wiley interface), and the National Institutes of Health clinical trials database (http://clinicaltrials.gov) from their inception until July 4, 2016. To ensure literature saturation, the reference lists of the included studies, relevant reviews, and authors' personal files were screened for further references. Only articles reported in English, French, Spanish, and Portuguese were eligible. The searches were re–conducted immediately prior to the final analyses.

Study Selection

Two authors (LC and DR) independently screened the titles and abstracts using the following exclusion criteria: duplicates, animal studies, publication type (conference abstracts, case

This article is protected by copyright. All rights reserved.

Accepted Article

reports, letters, comments, reviews, or meta–analyses), language other than those previously specified, not the population of interest (BMI <35 kg/m^2 or non–adults [age <18 years]), no surgical intervention or different surgical intervention, and lack of outcome of interest (lack of mortality data or unknown timing of death). Only clearly irrelevant citations were excluded at this stage. Full reports for all titles that were not excluded were obtained and rescreened again more thoroughly using the same exclusion criteria. Any disagreement regarding the eligibility of studies was resolved by discussion and consensus.

Data Extraction

Data collection was performed independently by two authors (LC and DR). The data abstracted included the following: (1) methodology and study characteristics (study design, country of origin, publication year, study population size, sample size, and follow–up length [mean ± standard deviation or median and interquartile range]); (2) demographic information (including age [mean ± standard deviation or median and interquartile range], race, gender, and BMI [mean ± standard deviation or median and interquartile range]); (3) intervention details (types of bariatric procedures and the interventions performed in the control group [for long–term mortality analysis only]); and (4) all important patient outcomes reported (number of deaths, adjusted and unadjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for death, and causes of death were collected when available). Risk of bias was assessed using the Cochrane Collaboration tool for RCTs and the Newcastle–Ottawa Scale for observational studies (Supplementary Table 1).[24,25]

Outcome measures

Studies reporting deaths occurring within 30 days of the surgery and studies reporting deaths with a follow–up ≥2 years were analysed separately. For short–term mortality, we extracted

This article is protected by copyright. All rights reserved.

Accepted Article

the number of patients who specifically did and did not die in each group. Studies reporting a timing of death that could not be attributed to the perioperative period (≤30 days) were excluded. The data were further stratified for subgroup analyses based on surgery type (GB, AGB, SG, and VBG), class (mixed or restrictive) and approach (open or laparoscopy). For long–term mortality, we calculated unadjusted HRs or extracted unadjusted and adjusted HRs with 95% CIs. When HR was partially or not reported[26-29] but time–to–event data were available, we calculated the HR, log(HR), SE log(HR), O–E, and V using the Excel® spreadsheet developed by Matthew Sydes (Cancer Division) in collaboration with the Meta–analysis Group of the MRC Clinical Trials Unit, London.[30] The crude odds ratio (OR) for the occurrence of specific causes of death after ≥2 years of follow–up were also calculated in a specific analysis of cardiovascular and cancer mortality.[31]

Statistical Analysis

A systematic narrative synthesis of the findings of the included studies was developed. Heterogeneity was clinically assessed by considering participant factors (e.g., age, gender, and BMI) and study factors (study design, loss to follow–up, and surgery type). Statistical heterogeneity was tested using the Q test (significance level: 0.1) and I^2 statistic.[32] Substantial heterogeneity was defined as I^2 ≥50% or P<0.1.[24] We explored the sources of heterogeneity by study design (prospective versus retrospective), last year of recruitment (before 2005 versus after 2005), extracted estimates (adjusted versus unadjusted estimates), and surgery type (AGB only versus GB only or versus composite data from various surgical techniques). We also performed sensitivity analyses using the leave–one–out method (i.e., analysing the consistency of the results by removing each individual study from the analysis). We used funnel plots to assess the risk of publication bias. Begg's and Mazumdar's correlation and

This article is protected by copyright. All rights reserved.

Accepted Article

Egger's regression intercept tests were initially considered but were not performed because of the number of included studies (Supplementary Figure 1).[33,34]

For short–term mortality, a Bayesian random–effects approach was chosen for the meta–analysis to avoid statistical problems caused by zero or rare events.[35-37] We pooled the results using Winbugs® software 1.4.3 (The BUGS Project, Cambridge, UK). To analyse long–term mortality, we opted for a frequentist approach (random–effects model) using Comprehensive Meta–Analysis® software 2.2.064 (Biostat, Englewood, USA).[38] Random–effects models assume that the effect sizes are sampled from a universe of effect sizes and were therefore more suitable for our sample than fixed–effect models, which assume a fixed population effect size. The means and 95% confidence/credible intervals associated with the frequentist/Bayesian estimates are reported in brackets.

Results

Data Retrieval

The flow diagram outlining the systematic review process is provided in Figure 1. The initial search identified 9,092 studies for screening. Of these, 2,869 were duplicates. After reviewing whether the titles and abstracts met the exclusion criteria, 5,702 articles were rejected. Full articles were retrieved for 521 reports, and of these, 460 did not meet the inclusion criteria.

Our search identified 38 RCTs (48 articles and 75 study arms) eligible for the qualitative and quantitative synthesis of short–term mortality (Supplementary Table 2). These RCTs involved a total of 4,030 patients. For long–term mortality, 13 publications, corresponding to 12 studies, were included in the qualitative analysis, but 4 were excluded from the meta–analysis of all–cause mortality: two[28,29] because they reported incomplete time–to–event data,

This article is protected by copyright. All rights reserved.

Accepted Article

one[39] because of potential selection bias, and one[40] because its entire sample was integrated into another study[26] that was also included in the dataset (Supplementary Table 1 and Supplementary Table 3). For the same reasons, the latter two studies were excluded from the subgroup analyses. Therefore, 12 studies were included in the qualitative synthesis, and 8 studies were considered in the meta–analysis of long–term mortality (Figure 1).

Study and Patient Characteristics

RCTs reporting on short–term mortality were performed between 1987 and 2013, but most RCTs (~70%) had been published in the last 10 years (Supplementary Table 2). Most studies were conducted in Europe (21 out of 38), and the second most common region was America (10 out of 38). The mean size of each arm and study was 53.7 (minimum–maximum [min–max]: 20–200) and 106.1 (min–max: 30–400) patients, respectively. The most frequent procedure was GB (52.3%), followed by AGB (24.4%), SG (15.2%) and VBG (4.8%). Only 3 RCTs reported mortality of BPD, corresponding to a total of 114 patients (2.8% of sample size).[41-45] Only 1 RCT, with a 20–patient arm, reported short–term mortality data for GP.[46] Most surgeries (85.0%) performed in RCTs used a laparoscopic approach (Supplementary Table 2).[41,42,47-58] Of the 605 patients whose operations used an open approach, most (68.8%) underwent GB, followed by VBG (17.2%), and BPD (14.0%). Of the study arms providing participant information, the mean age was 38.3 years (min–max: 29.2–56.0), the proportion of women was 77.2% (min–max: 43.3–100), and the average BMI was 46.9 kg/m^2 (min–max: 38.9–59.7). Most study arms (57.3%) did not report data on preoperative co–morbidities. Of those that did, the most frequent pre–operative complication was hypertension (37.5%), followed by arthritis (39.5%), dyslipidemia (32.0%), depression (27.4%), gastro–oesophageal reflux disease (26.4%), diabetes (21.9%), and obstructive sleep apnea (21.6%).

This article is protected by copyright. All rights reserved.

Accepted Article

The search did not retrieve any RCTs reporting time–to–event data for the long–term mortality analysis, and most (10 out of 12) observational studies were retrospective in design. The assessment of the methodological quality of observational studies is provided in detail in Supplementary Table 1. In the studies conducted by Maciejewski *et al.* and Arterburn *et al.*, most of the operated patients were men (74%); in another study by Eliasson *et al.*, most operated patients had diabetes (81%), whereas in a study by Sowemimo *et al.*, the number of non–operated obese controls was relatively low when compared to operated obese patients (112 versus 908, respectively), and there were differences in terms of age and BMI (Supplementary Table 1 and Supplementary Table 3).[26,39,40,59] In addition, two other studies by Flum *et al.* and Peeters *et al.* were not matched in design and could therefore have been a source of selection bias.[60,61] Most studies (10 out of 12) reported adjusted estimates.[13,26,28,39,40,59-63] Of these, 10 reported adjusted estimates for age, 9 for age and gender, and 5 for age, gender, and BMI (Supplementary Table 3). Furthermore, the study by Maciejewski *et al.* reported adjusted estimates for unmatched (e.g., age, gender, body mass index, race, marital status, and diagnostic cost group) and propensity–matched analyses (e.g., year of surgery), and Arterburn *et al.* reported estimates adjusted by time interval (i.e., <1 year, 1–5 years, and 5–14 years).[26,40] Most studies (8 out of 12) did not provide data on follow-up rates or reported unclear or low rates, and a high risk of attrition was therefore possible (Supplementary Table 1).[26,27,29,39,40,59,60,62] The extracted dataset (12 studies) had a BS:control group ratio of ~1:3 (27,258 and 97,154 participants, respectively). Of the operated patients, 21,637 underwent GB; 2,804, AGB/NAGB; 1,571, VBG; 381, SG; and 18, BPD (Supplementary Table 3). One study did not describe the types of BS performed.[40] Among the studies reporting preoperative patient characteristics, the proportion of women was 66.0% (min–max: 26.0–83.6) and 64.3% (min–max: 25.7–83.6) and the average age was 44.9 years (min–max: 38.2–52.0) and 47.5 years (min–max: 39.3–55.2) for the BS and control groups,

This article is protected by copyright. All rights reserved.

Accepted Article

respectively. BMI was 46.3 kg/m^2 (min–max: 41.4–54.0) and 44.4 kg/m^2 (min–max: 38.3–51.0) for the BS and control groups, respectively. The mean follow–up time was similar between the two groups and was 7.3 years (min–max: 2.5–13.9) and 7.4 years (min–max: 2.6–13.9) for the BS and control groups, respectively (Supplementary Table 3). The surgical and control arms had a prevalence of diabetes of 32.8% (min–max: 10.7–81.0) and 37.8% (min–max: 11.4–90.1) and a prevalence of hypertension of 50.9% (min–max: 23.9–80.5) and 49.1% (min–max: 23.9–80.5), respectively. However, patient characteristics were underreported, and only 8 of 12 studies reported the prevalence of diabetes, and 5 of 12 provided the prevalence of hypertension.

Short–term mortality

Among the 4,030 operated patients, 11 deaths occurred during the perioperative period (≤30 days). These deaths occurred in 9 out of 75 study arms (Supplementary Table 2). There were 3 deaths in 605 patients who underwent open surgery and 8 deaths in 3,425 patients operated by laparoscopy. Most patients underwent mixed surgical approaches (2,220 patients), with 6 casualties reported, and the remaining 5 deaths occurred in the restrictive surgery arms. Most deaths occurred in the GB study arms (n=6), followed by the VBG (n=2), SG (n=2), and AGB groups (n=1) (Supplementary Table 2). No casualties were reported in the BPD or GP study arms. Anticipating a null mortality in a large proportion of arms, we considered a Bayesian approach to summarizing the pooled effects to be the most suitable method (Supplementary File 1). The pooled estimate for perioperative mortality was 0.18% (95% CI: 0.04%–0.38%) (Figure 2). The all–cause mortality rate was higher for open (0.31%, 95% CI: 0.03%–0.97%) than for laparoscopic (0.16%, 95% CI: 0.03%–0.36%), and similar in mixed (0.17%, 95% CI: 0.03%–0.43%) and restrictive surgeries (0.17%, 95% CI: 0.03%–0.45%). The surgical procedure with the highest short–term mortality rate was VBG (0.78%, 95% CI:

This article is protected by copyright. All rights reserved.

Accepted Article

0.03%–3.03%), followed by SG (0.24%, 95% CI: 0.02%–0.80%), GB (0.18%, 95% CI: 0.03%–0.45%), and AGB (0.08%, 95% CI: 0.01%–0.32%). The number of studies and study arms that contributed to the pooled estimates is detailed in Figure 2.

Long–term Mortality

Eight studies, occurring between 1984 and 2014 and involving 23,647 operated patients and 89,628 non–operated obese controls, were included in the quantitative synthesis. All studies showed a decrease in long–term mortality of obese patients after BS. The pooled effect estimate showed a reduction in mortality of 41% (HR 0.59, 95% CI: 0.52–0.67, P<0.001; I^2=40.2%, P_Q=0.110) in mixed research synthesis (Figure 3a). Moreover, the adjusted pooled estimates (HR 0.57, 95% CI 0.47–0.69) were similar to the unadjusted pooled estimates (HR 0.60, 95% CI: 0.48–0.75) (Figure 3b and Figure 3c, respectively). The HR remained consistent when any one study was removed from the analysis (HR ranged from 0.56–0.62, P<0.001).

We found no significant difference (Q=0.453, P=0.501) in mortality reduction when the two prospective studies were compared to the six retrospective studies, although the HR was 0.65 (95% CI: 0.46–0.92, P=0.015) and 0.57 (95% CI: 0.492–0.66, P<0.001), respectively. Studies with a final recruitment year before 2005 (3 studies) were similar to those whose last recruitment year was in 2005 or after (5 studies) (HR 0.61, 95% CI: 0.51–0.74 and HR 0.53, 95% CI: 0.41–0.67, respectively, Q=0.87, P=0.352) (Supplementary Table 3). Subgroup analyses showed that for the four studies including only GB, the mean effect size (HR) was 0.56 (95% CI: 0.48–0.67, P<0.001); for the two studies including only AGB, the HR was 0.37 (95% CI: 0.21–0.66, P=0.001); and for the two studies including different operative procedures, the HR was 0.65 (95% CI: 0.54–0.78, P<0.001). However, there was no statistical evidence that the impact of BS varied by surgical technique, although the number

This article is protected by copyright. All rights reserved.

Accepted Article

of studies was low (Q=3.908, P=0.142). Although one study[61] included in the meta–analysis that assessed only AGB procedures did not report patient characteristics (for the BS or control groups), another[63] showed a lower prevalence of diabetes (16.8% versus median 31.9% [min–max: 10.7–90.1]) and hypertension (26.0% versus median 62.8% [min–max: 35.9–80.5]) than the rates reported in studies using GB or composite data from various surgical techniques (Supplementary Table 3). When this analysis was extended to the entire dataset, the results were similar, but the absence of patient characteristics in some studies limited the interpretation of the data.[29,39,40,61]

We found a reduction in cardiovascular–related mortality in the BS group compared to non–operated controls (OR 0.42, 95% CI: 0.25–0.72, P<0.001; I^2=76.5%, P_Q=0.001) (Figure 4a). Two studies were responsible for most of the heterogeneity observed.[13,59] Patients included in these studies, which were by Sjöström *et al.* and Eliasson *et al.*, were older (48.7 versus 42.7 years) than the patients in the other studies analysed (Supplementary Table 3).[13,28,59,62,63] Furthermore, the study by Eliasson *et al.* involved mostly patients with diabetes (81% in the BS group and 90% in controls). However, when any one study was removed, the effect size ranged from 0.37 to 0.57 (P<0.05), and therefore the exclusion did not change the tendency of the summary effect. Cancer data were reported in four studies, and the unadjusted pooled estimates showed that mortality was also lower in the BS group than in the non–operated obese control group (OR 0.47, 95% CI: 0.36–0.63, P<0.001; I^2=0%, P_Q=0.461) (Figure 4b).[13,28,62,63] Again, when any one study was removed from the analysis, the OR remained consistent (OR ranged from 0.40–0.52, P<0.05). Other causes of death reported in the studies are summarized in Supplementary Table 4.

This article is protected by copyright. All rights reserved.

Accepted Article

Discussion

This systematic review and meta–analysis demonstrated that BS is associated with a low perioperative mortality rate (0.18%) and a long–term reduction in all–cause mortality of 41% in patients receiving BS compared to non–operated obese controls.

The two observational studies, i.e., the Bariatric Outcomes Longitudinal Database and the Longitudinal Assessment of Bariatric Surgery, showed a perioperative mortality risk of 0.1% and 0.3%, respectively.[64,65] These findings are supported by those of previous meta–analyses.[17-20] Maggard *et al.* reported pooled mortality rates that ranged from 0.02% for AGB, in case series, to 1.0% for RYGB, in controlled trials; however, the inclusion of RCTs, observational and case studies is a potential source of publication bias.[19] Furthermore, the imputation of zero for missing data and the inclusion of deaths described without a clear time point but described as "early" in the original publication may affect the accuracy of the estimate. Buchwald *et al.* reported a perioperative mortality rate of 0.28% in 475 treatment arms involving 84,931 patients using a frequentist approach (i.e., random–effects model), and the included studies were published between 1990 and 2006 and analysed RCTs, observational and case–control studies.[18] Recently, Chang *et al.* reported a pooled perioperative mortality rate of 0.08% using a Bayesian approach based on 1,803 patients and 30 RCT study arms published between 2003 and 2012.[20] Our analysis substantially updated that review, including 38 RCTs and 75 study arms with 4,030 patients, as well as 10 new RCTs (19 study arms) that were published after the timeframe defined by Chang *et al.*. In concordance with this study, we found a higher short–term mortality rate in the SG arms than in the GB and AGB arms. The surgical technique with the highest mortality in our review was VBG (~0.8%), but only four studies, conducted between 1987 and 2002, contributed to the VBG mortality analysis; additionally, most of the patients were operated on using an open approach, which contrasts with the much lower use of an open approach (15%) identified in

This article is protected by copyright. All rights reserved.

Accepted Article

the remaining study arms included in our meta–analysis. We summarized all effect estimates using a Bayesian hierarchical method, which addressed the problem presented by zero–events and added additional consistency to our findings. Therefore, our results summarized the best evidence available (i.e., RCTs) and validated the observational findings of low perioperative mortality after BS.

Several studies have evaluated the long–term mortality rates of patients with obesity after BS. Data from registries have shown long–term mortality rates after BS ranging from 1.5–6.1% during a mean follow–up of 8–10.9 years, and one of these studies by Telem *et al.* reported a significantly lower mortality in patients receiving BS than in the general population (1.5% versus 2.1%, respectively).[66-68] Furthermore, one study summarizing the estimate effects of 140 treatment arms, which involved 19,928 patients from RCTs and observational studies, reported a total mortality at 30 days to 2 years of 0.35%.[18] Other meta–analyses have reported a global mortality reduction (OR 0.48–0.55) in patients receiving BS compared to non–operated obese controls.[21,69,70] However, were not evaluated by any of these studies, and the wide range (1–14.7 years) of follow–up times of the included studies in those reviews must be taken in consideration when interpreting the pooled point estimations, as their effect measure (i.e., odds ratio) does not reflect the time factor. Furthermore, despite time–to–event data can sometimes be analyzed as dichotomous data (i.e., odds ratio or relative risk), the most appropriate way of summarizing survival data is to express the intervention effect as a hazard ratio, and if the total number of events reported for each study is used to calculate an odds ratio or relative risk, this can encompass combining studies with different follow–up times, resulting in an estimate that is difficult to interpret.[24,30] In addition, one review included a large study that compared BS with obese orthopaedic and gastrointestinal surgical controls, who were exposed to a different mortality risk than the non–operated obese controls in the other studies, and this difference may have affected the pooled effect estimate.[21]

This article is protected by copyright. All rights reserved.

Accepted Article

Previous reviews have focused on summarizing the effect of BS on cardiovascular and cancer events but not mortality.[21,70-72] We showed that operated patients were 0.42 and 0.47 times as likely as non–operated obese controls to die from cardiovascular disease and cancer, respectively. However, these estimates should be interpreted with caution because underreporting of causes of death, adjusted estimates and time to cause–specific mortality was frequent, and the estimate effects were pooled from observational studies, which may include errors in the classification of the causes of death.

This is the most up–to–date and comprehensive systematic review of the effects of BS for the treatment of obesity on short- and long–term mortality in adults. Furthermore, to our knowledge, this is the first meta–analysis evaluating time–to–event data after a pre–specified minimum follow–up of 2 years, and our estimates were robust across the sensitivity and subgroup analyses. There is great demand for information on the safety of BS, as suggested by the recent American Society for Metabolic and Bariatric Surgery position statement on the long–term survival benefits after metabolic and bariatric surgery, which were issued in response to inquiries made by patients, physicians, health payers, and others.[73] Therefore, in light of the growing obesity prevalence and the expanding indications for metabolic and BS, our results provide important additional information to support physician and patient decision making regarding which treatment for obesity to propose and to choose, respectively, as well as healthcare payers' decision to provide access to BS.[74]

Our study has several limitations that, as for all reviews, originated from the quantity and quality of the identified studies and limited the strength of our conclusions. There was a high level of clinical and methodological heterogeneity. The effects of BS may vary according to patient characteristics (e.g., age, gender, preoperative BMI, and co–morbidities), procedures (trends in which change over time), and setting (unexperienced centres or surgeons versus highly specialized centres or surgeons). Therefore, the perioperative conditions in some

This article is protected by copyright. All rights reserved.

Accepted Article

studies may not be applied to others. Furthermore, patient characteristics and specific causes of death were often incompletely reported, which may have affected the pooled estimations and limited the subgroup analyses. For the short–term mortality analyses, the number of patients included in each RCT was generally low. For the long–term mortality studies, the absence of data from RCTs, the low number of available studies, the underreporting of subgroup and adjusted estimates, and the different methods of selecting the non–operated obese controls, which might influence the time–to–event estimations, were the observed limitations. In addition, the inadequate reporting of follow–up rates in the observational studies may have resulted in attrition bias, since the pooled estimate could have been different if there was no data loss or if all studies had evaluated mortality at similar time points, and this should be addressed in the design of future long–term studies. The protocol of the review was designed and applied prospectively; however, it was not registered in an online database for systematic reviews (Supplementary File 1).

Conclusions

Our study suggests that BS is a safe therapeutic option for weight loss. The current body of evidence from RCTs estimates a short–term all–cause mortality after BS of 0.18% (95% CI: 0.04%–0.38%). We found a reduction in long–term mortality of 41% (HR 0.59, 95% CI: 0.52–0.67) among patients receiving BS compared to non–operated obese controls. Thus, the evidence suggests that BS may improve the long–term survival of obese patients and possibly decrease cardiovascular and cancer–related mortality, but these effect estimates were pooled from lower quality studies (i.e., observational studies). Therefore, prospective studies are needed to firmly establish whether benefits on cardiovascular and cancer mortality can be observed. In addition, future studies should address the predictors of long–term mortality, as

This article is protected by copyright. All rights reserved.

Accepted Article

some patients (e.g., patients with diabetes) appear to benefit more in terms of survival than others.[63]

Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

LC had the idea for the study. LC and DR led the study design, performed all data analysis, and checked for statistical consistency. LC, DR, LG, and FC interpreted and discussed the results, and critically revised all versions of the manuscript.

References

1. Finucane MM, Stevens GA, Cowan MJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet.* 2011;377(9765):557-567.

2. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2014;384(9945):766-781.

3. FAO, IFAD, WFP. *The State of Food Insecurity in the World 2013. The multiple dimensions of food security.* Rome: FAO; 2013.

4. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380(9859):2224-2260.

This article is protected by copyright. All rights reserved.

Accepted Article

5. Finkelstein EA, Khavjou OA, Thompson H, et al. Obesity and Severe Obesity Forecasts Through 2030. *Am J Prev Med.* 2012;42(6):563-570.

6. Wang Y, Beydoun MA, Liang L, Caballero B, Kumanyika SK. Will all Americans become overweight or obese? estimating the progression and cost of the US obesity epidemic. *Obesity (Silver Spring).* 2008;16(10):2323-2330.

7. Prospective Studies Collaboration, Whitlock G, Lewington S, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet.* 2009;373(9669):1083-1096.

8. Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB. Years of life lost due to obesity. *JAMA.* 2003;289(2):187-193.

9. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA.* 2003;289(1):76-79.

10. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation.* 1983;67(5):968-977.

11. Moller H, Mellemgaard A, Lindvig K, Olsen JH. Obesity and cancer risk: a Danish record-linkage study. *Eur J Cancer.* 1994;30A(3):344-350.

12. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer.* 2004;4(8):579-591.

13. Sjostrom L, Narbro K, Sjostrom CD, et al. Effects of bariatric surgery on mortality in Swedish Obese Subjects. *N Engl J Med.* 2007;357(8):741-752.

14. Padwal R, Klarenbach S, Wiebe N, et al. Bariatric surgery: a systematic review and network meta-analysis of randomized trials. *Obes Rev.* 2011;12(8):602-621.

15. Scopinaro N. The IFSO and obesity surgery throughout the world. International Federation for the Surgery of Obesity. *Obes Surg.* 1998;8(1):3-8.

This article is protected by copyright. All rights reserved.

Accepted Article

16. Angrisani L, Santonicola A, Iovino P, Formisano G, Buchwald H, Scopinaro N. Bariatric Surgery Worldwide 2013. *Obes Surg.* 2015;25(10):1822-1832.

17. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA.* 2004;292(14):1724-1737.

18. Buchwald H, Estok R, Fahrbach K, Banel D, Sledge I. Trends in mortality in bariatric surgery: a systematic review and meta-analysis. *Surgery.* 2007;142(4):621-632; discussion 632-625.

19. Maggard MA, Shugarman LR, Suttorp M, et al. Meta-analysis: surgical treatment of obesity. *Ann Intern Med.* 2005;142(7):547-559.

20. Chang SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003-2012. *JAMA Surg.* 2014;149(3):275-287.

21. Kwok CS, Pradhan A, Khan MA, et al. Bariatric surgery and its impact on cardiovascular disease and mortality: a systematic review and meta-analysis. *Int J Cardiol.* 2014;173(1):20-28.

22. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med.* 2009;151(4):264-269, W264.

23. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ.* 2015;349:g7647.

24. Higgins JPT, Green S, Cochrane Collaboration. *Cochrane handbook for systematic reviews of interventions (updated March 2011).* Chichester: John Wiley & Sons; 2011.

25. Wells GA, Shea B, O'connell D, et al. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.* 2000.

This article is protected by copyright. All rights reserved.

Accepted Article

26. Arterburn DE, Olsen MK, Smith VA, et al. Association between bariatric surgery and long-term survival. *JAMA.* 2015;313(1):62-70.

27. Guidry CA, Davies SW, Sawyer RG, Schirmer BD, Hallowell PT. Gastric bypass improves survival compared with propensity-matched controls: a cohort study with over 10-year follow-up. *Am J Surg.* 2015;209(3):463-467.

28. Busetto L, Mirabelli D, Petroni ML, et al. Comparative long-term mortality after laparoscopic adjustable gastric banding versus nonsurgical controls. *Surg Obes Relat Dis.* 2007;3(5):496-502.

29. Christou NV, Sampalis JS, Liberman M, et al. Surgery decreases long-term mortality, morbidity, and health care use in morbidly obese patients. *Ann Surg.* 2004;240(3):416-423.

30. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials.* 2007;8:16.

31. Deeks JJ. Issues in the selection of a summary statistic for meta-analysis of clinical trials with binary outcomes. *Stat Med.* 2002;21(11):1575-1600.

32. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327(7414):557-560.

33. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315(7109):629-634.

34. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics.* 1994;50(4):1088-1101.

35. Smith TC, Spiegelhalter DJ, Thomas A. Bayesian approaches to random-effects meta-analysis: a comparative study. *Stat Med.* 1995;14(24):2685-2699.

36. Sutton AJ, Cooper NJ, Lambert PC, Jones DR, Abrams KR, Sweeting MJ. Meta-analysis of rare and adverse event data. *Expert Rev Pharmacoecon Outcomes Res.* 2002;2(4):367-379.

This article is protected by copyright. All rights reserved.

Accepted Article

37. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med.* 2004;23(9):1351-1375.

38. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods.* 2010;1(2):97-111.

39. Sowemimo OA, Yood SM, Courtney J, et al. Natural history of morbid obesity without surgical intervention. *Surg Obes Relat Dis.* 2007;3(1):73-77.

40. Maciejewski ML, Livingston EH, Smith VA, et al. Survival among high-risk patients after bariatric surgery. *JAMA.* 2011;305(23):2419-2426.

41. Skroubis G, Anesidis S, Kehagias I, Mead N, Vagenas K, Kalfarentzos F. Roux-en-Y gastric bypass versus a variant of biliopancreatic diversion in a non-superobese population: prospective comparison of the efficacy and the incidence of metabolic deficiencies. *Obes Surg.* 2006;16(4):488-495.

42. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med.* 2012;366(17):1577-1585.

43. Risstad H, Sovik TT, Engstrom M, et al. Five-year outcomes after laparoscopic gastric bypass and laparoscopic duodenal switch in patients with body mass index of 50 to 60: a randomized clinical trial. *JAMA Surg.* 2015;150(4):352-361.

44. Sovik TT, Aasheim ET, Taha O, et al. Weight loss, cardiovascular risk factors, and quality of life after gastric bypass and duodenal switch: a randomized trial. *Ann Intern Med.* 2011;155(5):281-291.

45. Sovik TT, Taha O, Aasheim ET, et al. Randomized clinical trial of laparoscopic gastric bypass versus laparoscopic duodenal switch for superobesity. *Br J Surg.* 2010;97(2):160-166.

46. Darabi S, Talebpour M, Zeinoddini A, Heidari R. Laparoscopic gastric plication versus mini-gastric bypass surgery in the treatment of morbid obesity: a randomized clinical trial. *Surg Obes Relat Dis.* 2013;9(6):914-919.

This article is protected by copyright. All rights reserved.

Accepted Article

47. Bessler M, Daud A, Kim T, DiGiorgi M. Prospective randomized trial of banded versus nonbanded gastric bypass for the super obese: early results. *Surg Obes Relat Dis.* 2007;3(4):480-484.

48. Lujan JA, Frutos MD, Hernandez Q, et al. Laparoscopic versus open gastric bypass in the treatment of morbid obesity: a randomized prospective study. *Ann Surg.* 2004;239(4):433-437.

49. MacLean LD, Rhode BM, Forse RA, Nohr R. Surgery for obesity - an update of a randomized trial. *Obes Surg.* 1995;5(2):145-150.

50. MacLean LD, Rhode BM, Sampalis J, Forse RA. Results of the surgical treatment of obesity. *Am J Surg.* 1993;165(1):155-160.

51. Nguyen NT, Braley S, Fleming NW, Lambourne L, Rivers R, Wolfe BM. Comparison of postoperative hepatic function after laparoscopic versus open gastric bypass. *Am J Surg.* 2003;186(1):40-44.

52. Nguyen NT, Goldman C, Rosenquist CJ, et al. Laparoscopic versus open gastric bypass: a randomized study of outcomes, quality of life, and costs. *Ann Surg.* 2001;234(3):279-289.

53. Paluszkiewicz R, Kalinowski P, Wroblewski T, et al. Prospective randomized clinical trial of laparoscopic sleeve gastrectomy versus open Roux-en-Y gastric bypass for the management of patients with morbid obesity. *Videosurgery Miniinv.* 2012;7(4):225-232.

54. Puzziferri N, Austrheim-Smith IT, Wolfe BM, Wilson SE, Nguyen NT. Three-year follow-up of a prospective randomized trial comparing laparoscopic versus open gastric bypass. *Ann Surg.* 2006;243(2):181-188.

55. Sundbom M, Gustavsson S. Randomized clinical trial of hand-assisted laparoscopic versus open Roux-en-Y gastric bypass for the treatment of morbid obesity. *Br J Surg.* 2004;91(4):418-423.

This article is protected by copyright. All rights reserved.

Accepted Article

56. van Dielen FM, Soeters PB, de Brauw LM, Greve JW. Laparoscopic adjustable gastric banding versus open vertical banded gastroplasty: a prospective randomized trial. *Obes Surg.* 2005;15(9):1292-1298.

57. van Mastrigt GA, van Dielen FM, Severens JL, Voss GB, Greve JW. One-year cost-effectiveness of surgical treatment of morbid obesity: vertical banded gastroplasty versus Lap-Band. *Obes Surg.* 2006;16(1):75-84.

58. Westling A, Gustavsson S. Laparoscopic vs open Roux-en-Y gastric bypass: a prospective, randomized trial. *Obes Surg.* 2001;11(3):284-292.

59. Eliasson B, Liakopoulos V, Franzen S, et al. Cardiovascular disease and mortality in patients with type 2 diabetes after bariatric surgery in Sweden: a nationwide, matched, observational cohort study. *Lancet Diabetes Endocrinol.* 2015;3(11):847-854.

60. Flum DR, Dellinger EP. Impact of gastric bypass operation on survival: a population-based analysis. *J Am Coll Surg.* 2004;199(4):543-551.

61. Peeters A, O'Brien PE, Laurie C, et al. Substantial intentional weight loss and mortality in the severely obese. *Ann Surg.* 2007;246(6):1028-1033.

62. Davidson LE, Adams TD, Kim J, et al. Association of patient age at gastric bypass surgery with long-term all-cause and cause-specific mortality. *JAMA Surg.* 2016.

63. Pontiroli AE, Zakaria AS, Mantegazza E, et al. Long-term mortality and incidence of cardiovascular diseases and type 2 diabetes in diabetic and nondiabetic obese patients undergoing gastric banding: a controlled study. *Cardiovasc Diabetol.* 2016;15(1):39.

64. Benotti P, Wood GC, Winegar DA, et al. Risk factors associated with mortality after Roux-en-Y gastric bypass surgery. *Ann Surg.* 2014;259(1):123-130.

65. Smith MD, Patterson E, Wahed AS, et al. Thirty-day mortality after bariatric surgery: independently adjudicated causes of death in the longitudinal assessment of bariatric surgery. *Obes Surg.* 2011;21(11):1687-1692.

This article is protected by copyright. All rights reserved.

Accepted Article

66. Zhang W, Mason EE, Renquist KE, Zimmerman MB, Contributors I. Factors influencing survival following surgical treatment of obesity. *Obes Surg.* 2005;15(1):43-50.

67. Marsk R, Freedman J, Tynelius P, Rasmussen F, Naslund E. Antiobesity surgery in Sweden from 1980 to 2005: a population-based study with a focus on mortality. *Ann Surg.* 2008;248(5):777-781.

68. Telem DA, Talamini M, Shroyer AL, et al. Long-term mortality rates (>8-year) improve as compared to the general and obese population following bariatric surgery. *Surg Endosc.* 2015;29(3):529-536.

69. Pontiroli AE, Morabito A. Long-term prevention of mortality in morbid obesity through bariatric surgery. a systematic review and meta-analysis of trials performed with gastric banding and gastric bypass. *Ann Surg.* 2011;253(3):484-487.

70. Zhou X, Yu J, Li L, et al. Effects of Bariatric Surgery on Mortality, Cardiovascular Events, and Cancer Outcomes in Obese Patients: Systematic Review and Meta-analysis. *Obes Surg.* 2016;26(11):2590-2601.

71. Casagrande DS, Rosa DD, Umpierre D, Sarmento RA, Rodrigues CG, Schaan BD. Incidence of cancer following bariatric surgery: systematic review and meta-analysis. *Obes Surg.* 2014;24(9):1499-1509.

72. Tee MC, Cao Y, Warnock GL, Hu FB, Chavarro JE. Effect of bariatric surgery on oncologic outcomes: a systematic review and meta-analysis. *Surg Endosc.* 2013;27(12):4449-4456.

73. Kim J, Eisenberg D, Azagury D, Rogers A, Campos GM. American Society for Metabolic and Bariatric Surgery position statement on long-term survival benefit after metabolic and bariatric surgery. *Surg Obes Relat Dis.* 2016;12(3):453-459.

74. Rubino F, Nathan DM, Eckel RH, et al. Metabolic Surgery in the Treatment Algorithm for Type 2 Diabetes: A Joint Statement by International Diabetes Organizations. *Diabetes Care.* 2016;39(6):861-877.

This article is protected by copyright. All rights reserved.

Accepted Article

75. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. *N Engl J Med.* 2007;357(8):753-761.

76. Morino M, Toppino M, Bonnet G, del Genio G. Laparoscopic adjustable silicone gastric banding versus vertical banded gastroplasty in morbidly obese patients: a prospective randomized controlled clinical trial. *Ann Surg.* 2003;238(6):835-841.

77. Scozzari G, Farinella E, Bonnet G, Toppino M, Morino M. Laparoscopic adjustable silicone gastric banding vs laparoscopic vertical banded gastroplasty in morbidly obese patients: long-term results of a prospective randomized controlled clinical trial. *Obes Surg.* 2009;19(8):1108-1115.

78. Lee WJ, Huang MT, Yu PJ, Wang W, Chen TC. Laparoscopic vertical banded gastroplasty and laparoscopic gastric bypass: a comparison. *Obes Surg.* 2004;14(5):626-634.

79. Inabnet WB, Quinn T, Gagner M, Urban M, Pomp A. Laparoscopic Roux-en-Y gastric bypass in patients with BMI <50: a prospective randomized trial comparing short and long limb lengths. *Obes Surg.* 2005;15(1):51-57.

80. Suter M, Giusti V, Worreth M, Heraief E, Calmes JM. Laparoscopic gastric banding: a prospective, randomized study comparing the Lapband and the SAGB: early results. *Ann Surg.* 2005;241(1):55-62.

81. Lee WJ, Yu PJ, Wang W, Chen TC, Wei PL, Huang MT. Laparoscopic Roux-en-Y versus mini-gastric bypass for the treatment of morbid obesity: a prospective randomized controlled clinical trial. *Ann Surg.* 2005;242(1):20-28.

82. Alami RS, Morton JM, Schuster R, et al. Is there a benefit to preoperative weight loss in gastric bypass patients? A prospective randomized trial. *Surg Obes Relat Dis.* 2007;3(2):141-145.

83. Angrisani L, Lorenzo M, Borrelli V. Laparoscopic adjustable gastric banding versus Roux-en-Y gastric bypass: 5-year results of a prospective randomized trial. *Surg Obes Relat Dis.* 2007;3(2):127-132.

This article is protected by copyright. All rights reserved.

Accepted Article

84. Angrisani L, Cutolo PP, Formisano G, Nosso G, Vitolo G. Laparoscopic adjustable gastric banding versus Roux-en-Y gastric bypass: 10-year results of a prospective, randomized trial. *Surg Obes Relat Dis.* 2013;9(3):405-413.

85. Dapri G, Vaz C, Cadiere GB, Himpens J. A prospective randomized study comparing two different techniques for laparoscopic sleeve gastrectomy. *Obes Surg.* 2007;17(11):1435-1441.

86. Gravante G, Araco A, Araco F, Delogu D, De Lorenzo A, Cervelli V. Laparoscopic adjustable gastric bandings: a prospective randomized study of 400 operations performed with 2 different devices. *Arch Surg.* 2007;142(10):958-961.

87. Miller KA, Pump A. Use of bioabsorbable staple reinforcement material in gastric bypass: a prospective randomized clinical trial. *Surg Obes Relat Dis.* 2007;3(4):417-421.

88. Arceo-Olaiz R, Espana-Gomez MN, Montalvo-Hernandez J, Velazquez-Fernandez D, Pantoja JP, Herrera MF. Maximal weight loss after banded and unbanded laparoscopic Roux-en-Y gastric bypass: a randomized controlled trial. *Surg Obes Relat Dis.* 2008;4(4):507-511.

89. Zarate X, Arceo-Olaiz R, Montalvo Hernandez J, Garcia-Garcia E, Pablo Pantoja J, Herrera MF. Long-term results of a randomized trial comparing banded versus standard laparoscopic Roux-en-Y gastric bypass. *Surg Obes Relat Dis.* 2013;9(3):395-397.

90. Leyba JL, Llopis SN, Isaac J, Aulestia SN, Bravo C, Obregon F. Laparoscopic gastric bypass for morbid obesity-a randomized controlled trial comparing two gastrojejunal anastomosis techniques. *JSLS.* 2008;12(4):385-388.

91. Pinheiro JS, Schiavon CA, Pereira PB, Correa JL, Noujaim P, Cohen R. Long-long limb Roux-en-Y gastric bypass is more efficacious in treatment of type 2 diabetes and lipid disorders in super-obese patients. *Surg Obes Relat Dis.* 2008;4(4):521-525.

92. Angrisani L, Cutolo PP, Ciciriello MB, et al. Laparoscopic adjustable gastric banding with truncal vagotomy versus laparoscopic adjustable gastric banding alone: interim results of a prospective randomized trial. *Surg Obes Relat Dis.* 2009;5(4):435-438.

This article is protected by copyright. All rights reserved.

Accepted Article

93. Nguyen NT, Slone JA, Nguyen XM, Hartman JS, Hoyt DB. A prospective randomized trial of laparoscopic gastric bypass versus laparoscopic adjustable gastric banding for the treatment of morbid obesity: outcomes, quality of life, and costs. *Ann Surg.* 2009;250(4):631-641.

94. Lazzati A, Polliand C, Porta M, et al. Is fixation during gastric banding necessary? A randomised clinical study. *Obes Surg.* 2011;21(12):1859-1863.

95. Nguyen NT, Dakin G, Needleman B, et al. Effect of staple height on gastrojejunostomy during laparoscopic gastric bypass: a multicenter prospective randomized trial. *Surg Obes Relat Dis.* 2010;6(5):477-482.

96. Kehagias I, Karamanakos SN, Argentou M, Kalfarentzos F. Randomized clinical trial of laparoscopic Roux-en-Y gastric bypass versus laparoscopic sleeve gastrectomy for the management of patients with BMI < 50 kg/m2. *Obes Surg.* 2011;21(11):1650-1656.

97. Avsar FM, Sakcak I, Yildiz BD, Cosgun E, Hamamci EO. Is gastro-gastric fixation suture necessary in laparoscopic adjustable gastric banding? A prospective randomized study. *J Laparoendosc Adv Surg Tech A.* 2011;21(10):953-956.

98. Dixon JB, Schachter LM, O'Brien PE, et al. Surgical vs conventional therapy for weight loss treatment of obstructive sleep apnea: a randomized controlled trial. *JAMA.* 2012;308(11):1142-1149.

99. Helmio M, Victorzon M, Ovaska J, et al. SLEEVEPASS: a randomized prospective multicenter study comparing laparoscopic sleeve gastrectomy and gastric bypass in the treatment of morbid obesity: preliminary results. *Surg Endosc.* 2012;26(9):2521-2526.

100. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. *Lancet.* 2015;386(9997):964-973.

101. Aggarwal S, Sharma AP, Ramaswamy N. Outcome of laparoscopic sleeve gastrectomy with and without staple line oversewing in morbidly obese patients: a randomized study. *J Laparoendosc Adv Surg Tech A.* 2013;23(11):895-899.

This article is protected by copyright. All rights reserved.

Accepted Article

102. Peterli R, Borbely Y, Kern B, et al. Early results of the Swiss Multicentre Bypass or Sleeve Study (SM-BOSS): a prospective randomized trial comparing laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass. *Ann Surg.* 2013;258(5):690-694.

103. Abdallah E, El Nakeeb A, Youssef T, et al. Impact of extent of antral resection on surgical outcomes of sleeve gastrectomy for morbid obesity (a prospective randomized study). *Obes Surg.* 2014;24(10):1587-1594.

104. ElGeidie A, ElHemaly M, Hamdy E, El Sorogy M, AbdelGawad M, GadElHak N. The effect of residual gastric antrum size on the outcome of laparoscopic sleeve gastrectomy: a prospective randomized trial. *Surg Obes Relat Dis.* 2015;11(5):997-1003.

105. Svanevik M, Risstad H, Hofso D, et al. Perioperative outcomes of proximal and distal gastric bypass in patients with BMI ranged 50-60 kg/m^2 - a double-blind, randomized controlled trial. *Obes Surg.* 2015;25(10):1788-1795.

Captions / Legends

Figure 1. Flow diagram summarizing the search results. RCTs, randomized controlled trials; BMI, body mass index.

This article is protected by copyright. All rights reserved.

Accepted Article

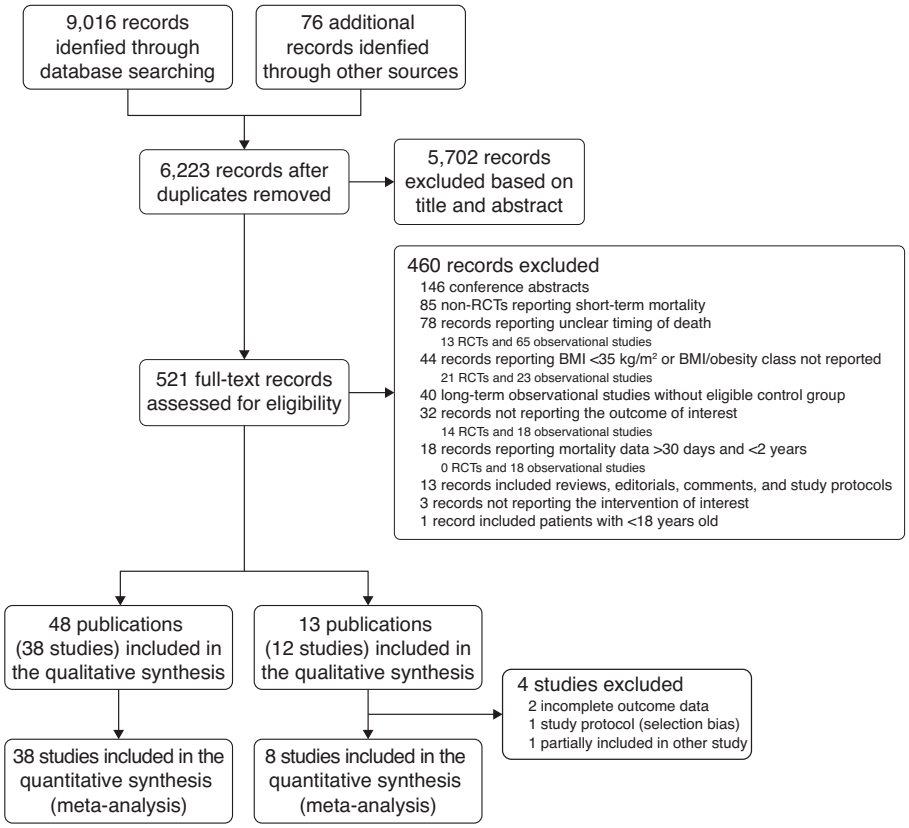


Figure 2. Meta–analysis of short–term all–cause mortality after bariatric surgery. The pooled effect estimates of all–cause mortality were calculated from 38 randomized controlled trials (RCTs) and 74 study arms (of the initial 75 arms, one gastric bypass study[95] reported the number of events for both arms together, and they were thus analysed as a single arm, Supplementary Table 2). For the subgroup analyses, the pooled effect estimates were calculated from 27 RCTs (41 study arms) for gastric bypass, 9 RCTs (13 study arms) for adjustable gastric banding, 8 RCTs (12 study arms) for sleeve gastrectomy, 4 RCTs (4 study arms) for vertical banded gastroplasty, 20 RCTs (30 study arms) for restrictive surgeries, 27 RCTs (44 study arms) for mixed surgeries, 35 RCTs (61 study arms) for laparoscopic surgeries, and 10 RCTs (13 study arms) for open surgeries. The horizontal lines show the 95% credible interval (CI) for each study. The diamond represents the pooled mortality rate from the Bayesian random–effects model.

This article is protected by copyright. All rights reserved.

Accepted Article

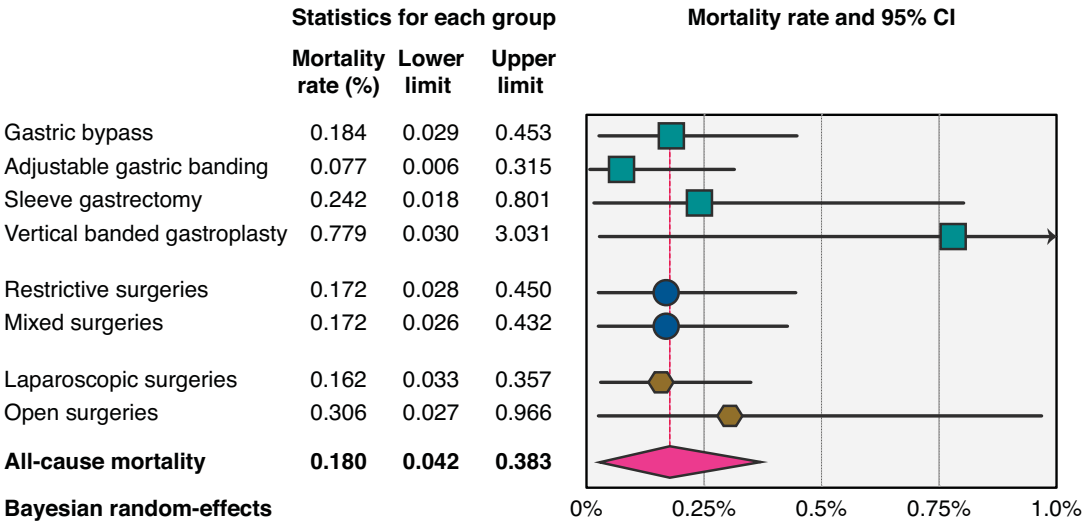


Figure 3. Meta–analysis of long–term mortality of patients after bariatric surgery (BS) compared to that of non–operated obese controls (CON) pooled from (a) mixed research synthesis and (b) adjusted and (c) unadjusted estimates. Each square denotes the hazard ratio (HR) for that study comparison with the horizontal lines showing the 95% confidence interval (CI). The size of the square is directly proportional to the amount of information contributed by the study to the random–effects model. The diamond represents the pooled HR from the random–effects model.

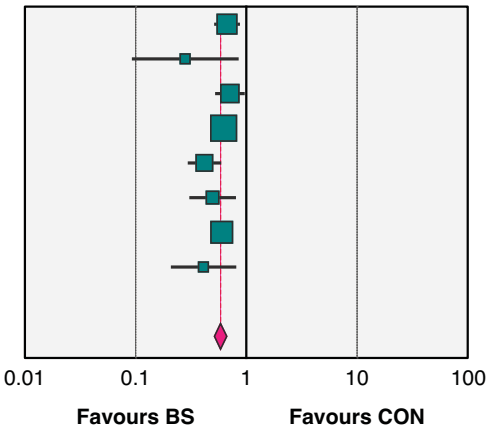
This article is protected by copyright. All rights reserved.

Accepted Article

a)

	Hazard ratio	Lower limit	Upper limit	Z-Value	P-Value
Flum *et al.* 2004	0.670	0.530	0.848	-3.333	0.001
Peeters *et al.* 2007	0.281	0.096	0.825	-2.309	0.021
Sjöström *et al.* 2007	0.712	0.541	0.937	-2.429	0.015
Arterburn *et al.* 2015	0.625	0.556	0.703	-7.833	0.000
Eliasson *et al.* 2015	0.419	0.306	0.573	-5.438	0.000
Guidry *et al.* 2015	0.497	0.316	0.779	-3.043	0.002
Davidson *et al.* 2016	0.600	0.494	0.731	-5.100	0.000
Pontiroli *et al.* 2016	0.411	0.215	0.784	-2.697	0.007
Random-effects	**0.586**	**0.515**	**0.665**	**-8.193**	**0.000**

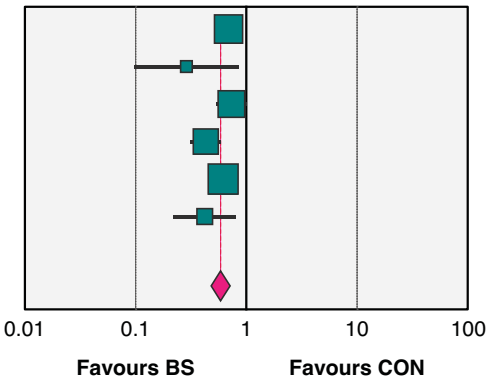
Heterogeneity: Q = 11.7, df=7, P=0.110, I^2=40.2%



b)

	Hazard ratio	Lower limit	Upper limit	Z-Value	P-Value
Flum *et al.* 2004	0.670	0.530	0.848	-3.333	0.001
Peeters *et al.* 2007	0.281	0.096	0.825	-2.309	0.021
Sjöström *et al.* 2007	0.712	0.541	0.937	-2.429	0.015
Eliasson *et al.* 2015	0.419	0.306	0.573	-5.438	0.000
Davidson *et al.* 2016	0.600	0.494	0.731	-5.100	0.000
Pontiroli *et al.* 2016	0.411	0.215	0.784	-2.697	0.007
Random-effects	**0.568**	**0.467**	**0.690**	**-5.684**	**0.000**

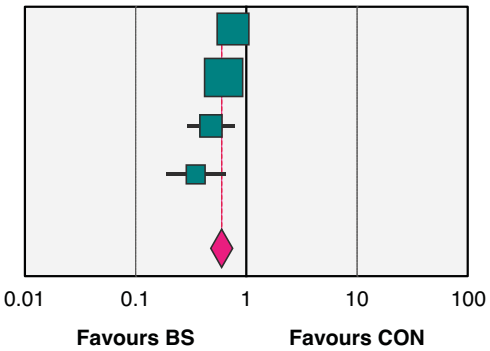
Heterogeneity: Q = 10.6, df=5, P=0.061, I^2=52.7%



c)

	Hazard ratio	Lower limit	Upper limit	Z-Value	P-Value
Sjöström *et al.* 2007	0.760	0.587	0.984	-2.078	0.038
Arterburn *et al.* 2015	0.625	0.556	0.703	-7.833	0.000
Guidry *et al.* 2015	0.480	0.293	0.787	-2.908	0.004
Pontiroli *et al.* 2016	0.350	0.189	0.647	-3.346	0.001
Random-effects	**0.599**	**0.477**	**0.752**	**-4.413**	**0.000**

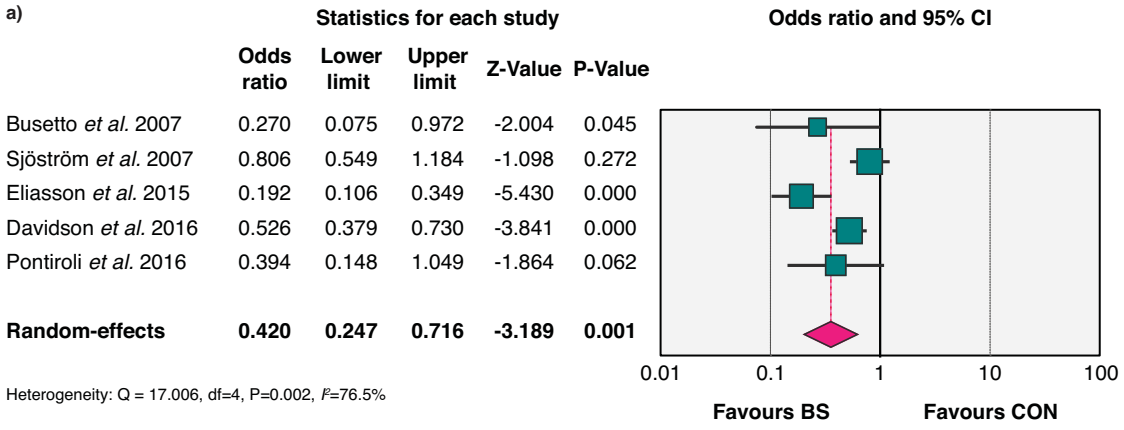
Heterogeneity: Q = 6.7, df=3, P=0.061, I^2=55.2%

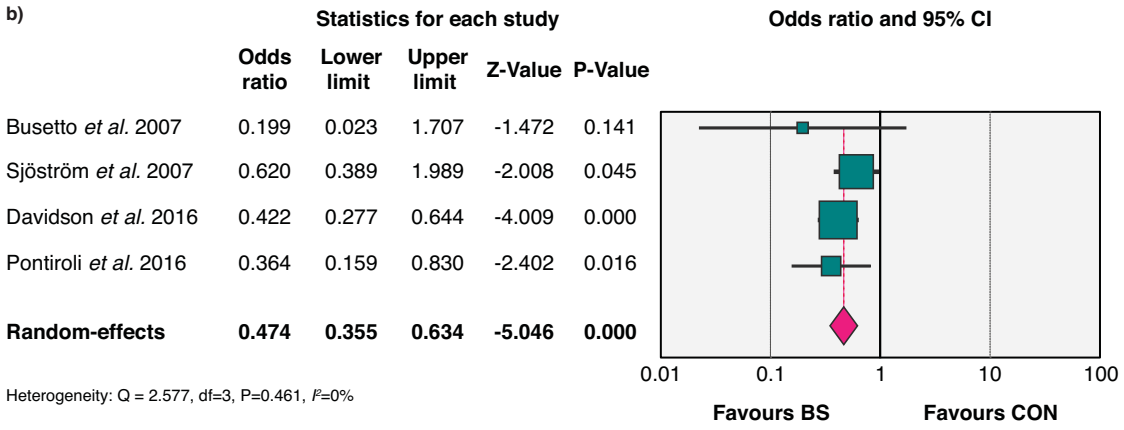


This article is protected by copyright. All rights reserved.

Accepted Article

Figure 4. Meta–analysis of (a) cardiovascular and (b) cancer–related mortality in patients after bariatric surgery (BS) compared to that of non–operated obese controls (CON). Each square denotes the unadjusted odds ratio (OR) for that study comparison, with the horizontal lines showing the 95% confidence interval (CI). The size of the square is directly proportional to the amount of information contributed by the study to the random–effects model. The diamond represents the pooled OR from the random–effects model.





Supplementary Figure 1. Funnel plot for studies included in the meta–analysis of long–term mortality of patients after bariatric surgery compared to that of non–operated obese controls.

This article is protected by copyright. All rights reserved.

Accepted Article

Supplementary Table 1. Methodological quality assessment of the observational studies included in the long–term mortality analysis.

Supplementary Table 2. Randomized controlled trials reporting perioperative (≤ 30 days) mortality after bariatric surgery.

Supplementary Table 3. Observational studies comparing long–term mortality between patients after bariatric surgery and non–operated obese controls.

Supplementary Table 4. Causes of death reported in long–term mortality studies.

This article is protected by copyright. All rights reserved.