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

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Background: Bariatric surgery has been reported to reduce long-term mortality in operated participants in comparison with nonoperated participants.
Methods: We performed a systematic review and meta-analysis of clinical trials published as full articles dealing with cardiovascular (CV) mortality, all-cause mortality (noncardiovascular), and global mortality (sum of CV and all-cause mortality). Pooled-fixed effects of estimates of the risk of mortality in participants undergoing surgery were calculated compared with controls.
Results: Of 44,022 participants from 8 trials (14,052 undergoing surgery and 29,970 controls), death occurred in 3317 participants (400 in surgery, 2917 in controls); when the kind of death was specified, 321 CV deaths (118 in surgery, 203 in controls), and 523 all-cause deaths (218 in surgery, 305 in controls) occurred. Compared with controls, surgery was associated with a reduced risk of global mortality (OR = 0.55, CI, 0.49–0.63), of CV mortality (OR = 0.58, CI, 0.46–0.73), and of all-cause mortality (OR = 0.70, CI, 0.59–0.84).
Data of all-cause mortality were not heterogeneous; heterogeneity of data of CV mortality decreased when studies were grouped according to size (large vs small studies). The reduction of risk was smaller in large than in small studies (OR = 0.61 vs 0.21, 0.63 vs 0.16, 0.74 vs 0.35 for global, CV, and all-cause mortality, respectively). The effect of gastric banding and gastric by-pass (3797 vs 10,255 interventions) was similar for global and all-cause mortality (OR = 0.57 vs 0.55, and 0.66 vs 0.70, respectively), different for CV mortality (OR = 0.71 vs 0.48). At meta-regression analysis, a trend for a decrease of global mortality (Log OR) linked to increasing BMI appeared.
Conclusion: This meta-analysis indicates that (1) bariatric surgery reduces long-term mortality; (2) risk reduction is smaller in large than in small studies; and (3) both gastric banding and gastric by-pass reduce mortality with a greater effect of the latter on CV mortality.

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Morbid obesity is expanding worldwide,[1] and increasing levels of obesity are associated with increasing risk of comorbidities and of death.[2] Also the use of bariatric surgery continues to increase worldwide, and the trends of increase of different surgical techniques vary between different countries.[3] The metabolic effects of bariatric surgery have been the object of 2 meta-analyses that clearly state the relative efficacy of different approaches, such as adjustable gastric banding, roux-en-y gastric bypass, biliopancreatic diversion, and sleeve gastrectomy.[4,5]

To make a decision of what kind of surgery to suggest to their own patients remains a significant issue, based also on comorbidities, and recent studies clearly show the relative risk of minor and major complications of the perioperative period for different surgical techniques.[6,7]

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Bariatric surgery has been reported to reduce long-term mortality in morbid obesity, but available data come only from studies performed with gastric banding/vertical-banded gastroplasty and gastric by-pass.[8–16] We, therefore, performed a systematic review and meta-analysis of clinical trials published as full articles dealing with all-cause mortality, cardiovascular (CV) mortality, and global mortality (sum of all-cause and CV mortality) in patients undergoing gastric banding and gastric by-pass.

MATERIALS AND METHODS

Eligible controlled clinical trials (CCT) were those comparing bariatric surgery versus no-surgery in patients with morbid obesity, irrespective of publication status or language. Measures of treatment efficacy were as follows: (1) all (noncardiovascular-related)-cause mortality; (2) cardiovascular (CV) cause-related mortality; (3) global mortality, that is, sum of the preceding 2.

Retrieval of CCTs was based on the Cochrane Library, MEDLINE, and EMBASE (until December 2009) using the terms obesity, bariatric surgery, mortality, and limiting the search to controlled clinical trials and human studies. A manual search was also performed using the reference lists from articles, reviews, editorials, and the proceedings of international congresses. When the results of a single study were reported in more than 1 publication, only the most recent and complete data were included in the meta-analysis. Decisions on which trials to include were taken unblindly by the 2 authors (AEP and AM). Disagreements were resolved by discussion. Excluded trials were identified with the reason for exclusion. Eight CCTs fulfilled the inclusion criteria, all published as full reports.[9–16] The methodologic quality of the trials was assessed by 4 major criteria previously validated.[17–23] Each quality component was rated as yes, unclear, or no. Data concerning trials, patient characteristics, and treatment outcome (Table 1) were abstracted by the 2 authors (AEP, AM) and discrepancies were resolved by discussion. Data concerning deaths were derived as such from all studies, except for study,[11] where deaths were extrapolated by participants at risk at 10 years and odds ratio (OR) for global mortality.

STATISTICAL METHODS

Treatment outcomes were expressed as (ORs) and pooled odds ratios (PORs), with 95% confidence intervals (CIs) estimated by a fixed-effects model according to Normand,[24] and are shown in Figure 1, and Figure 2. In an additional analysis, treatment outcomes were expressed by a random-effects model according to Der Simonian and Laird.[25] A χ^2 test for heterogeneity was performed for each assessed outcome and potential sources of heterogeneity were discussed where appropriate.[26–28] A P of less than 0.05 was considered indicative of statistically significant heterogeneity.

To explore the potential effect of several patients or trial characteristics on the pooled estimates, a meta-regression analysis was performed for the outcomes showing a statistically significant heterogeneity. The dependent variable was the observed mortality rate from each trial for the outcome of interest. The role of each covariate in heterogeneity was expressed by Wald test estimated by

TABLE 1. Details of the Eight Studies Considered*

Study n (start year)	Interv	Number (Men/Women)	Follow Up (Years)	Age (Years)	BMI (kg/m^2)	All Cause Mortality	Cardiovascular Mortality	Global Mortality	Weight lost (BMI)	Surgery	% DM	Dead Men/Women
9 (1988)	Surgery	154 (36/118)	9	48	48	12	2	14	17	rygb	100	NA
9	Controls	78 (21/57)	6.2	48	48	10	12	22	0		100	NA
10 (1986)	Surgery	1035 (356/679)	2.5	47	50	NA	NA	7	17	rygb	NA	NA
10	Controls	5746 (2068/3678)	2.5	45	50	NA	NA	354	NA		NA	NA
11 (1987)	Surgery	233 (46/187)	10	43	NA	NA	NA	28	NA	rygb	NA	NA
11	Controls	11132 (3975/7157)	10	47	NA	NA	NA	1814	NA		NA	NA
12 (1990)	Surgery	2010 (590/1420)	10	47	42	43	58	101	7	lagb/vbg	10.7	49/52
12	Controls	2037(590/1447)	10	47	42	53	76	129	0		11.4	59/70
13 (1994)	Surgery	821 (203/618)	6.2	40	48	5	3	8	8	lagb	NA	2/6
13	Controls	821 (203/618)	6.2	40	48	25	11	36	0		NA	22/14
14 (1984)	Surgery	7925 (1268/6657)	7	39	47	158	55	213	NA	rygb	NA	29/63
14	Controls	7925 (1268/6657)	7	39	47	217	104	321	NA		NA	63/258
15 (1997)	Surgery	908 (241/667)	9	43	54	NA	NA	25	NA	rygb	NA	NA
15	Controls	112 (33/79)	9	48	51	NA	NA	16	NA		NA	NA
16 (1994)	Surgery	966 (222/744)	4	47	45	3	1	4	8	lagb	NA	1/3
16	Controls	2119 (485/1634)	12	55	38	NA	NA	225	0		NA	95/130

*For each study and for each arm, starting year, kind of intervention, number of patients (men/women), duration of follow-up (years), age (years), body mass index (BMI), actual deaths, weight lost, kind of surgery, comorbidities and dead men/women are indicated.

%DM, percentage of patients with diabetes mellitus; lagb, banding; NA, not available; rygb indicates by-pass; vbg, vertical-banded gastroplasty.

the meta-regression. The following covariates were included in the meta-regression analysis, including covariates previously shown to be associated with survival in patients; age, sex, presence of diabetes, BMI of each study (weighted means of surgery and control participants), amount of weight lost, year of starting of study (as a proxy for technical improvement with time), number of patients enrolled, kind of controls (clinics vs community patients), duration of follow-up, and efficacy of treatment (vs controls) in each trial. A sensitivity analysis using a fixed-effects model also was performed to assess the consistency of results. All statistical analyses were performed by STATA 9 (Stata Corporation, College Station, Texas).

RESULTS

Table 1 shows details of 8 trials considered for this meta-analysis. Of 44,022 participants from 8 trials [11,605 men and 32,417 women; 14,052 undergoing surgery and 29,970 controls; age 45.1 ± 1.07 years; body mass index (BMI 47.0 ± 1.10 kg/m^2); duration of studies 7.5 ± 0.71 years], death occurred in 3317 participants (400 in surgery, 2917 in controls); when the kind of death was specified, 321 CV deaths (118 in surgery, 203 in controls), and 523 all-cause deaths (218 in surgery, 305 in controls) occurred.

Figure 1 shows that, compared with controls, surgery was associated with a reduced risk of global mortality (OR = 0.55, CI, 0.49–0.63), of CV mortality (OR = 0.58, CI, 0.46–0.73), and of all-cause mortality (OR 0.70, CI, 0.59–0.84).

Data of global mortality (I-squared = 91.4%, $P = 0.000$) and of CV mortality (I-squared = 73.6%, $P = 0.010$) were heterogeneous, at difference from all-cause mortality (I-squared = 60.4%, NS). Therefore, studies were arbitrarily divided according to size, that is, smaller or greater than 3000 patients; as a result, heterogeneity of data decreased (*small studies*: global mortality: I-squared 0.0%, NS; CV mortality: I-squared 40.5%, NS; all-cause mortality: I-squared 61.6% NS; *large studies*: global mortality: I-squared 93.0%, $P = 0.000$; CV mortality: I-squared 58.8%, NS; all-cause mortality: I-squared 0.0%, NS). The effect was, however, significantly different between small and large studies [OR 0.21 (0.14–0.31) vs 0.61 (0.54–0.70), 0.16 (0.06–0.42) vs 0.63 0.49–0.80), 0.35 (0.18–0.67) vs 0.74 (0.62–0.89) for global, CV, and all-cause mortality, respectively).

The studies were also divided according to the surgical technique employed; it seems from Figure 2 that the effect of gastric banding (3797 interventions) versus gastric by-pass (10,255 interventions) was similar for global [OR 0.57 (0.44–0.73) versus 0.55 (0.47–0.64)], and for all-cause mortality [OR 0.66 (0.45–0.96) vs 0.71 (0.58–0.87)], less evident for CV mortality [OR 0.71 (0.51–1.00) vs 0.48 (0.35–0.66)]. However, except for CV mortality in participants undergoing gastric banding, and for all-cause mortality in participants undergoing gastric by-pass, data were heterogeneous.

Finally, studies were divided according to kind of controls (clinics vs community participants), and OR were not different (not shown).

Supplementary file shows that ORs were not greatly different, though in general more conservative, when using a fixed-effects model or a random-effects model (supplementary file A).

At meta-regression analysis, sex, and age, year of start of study, duration of follow-up, amount of weight lost, and kind of controls were not associated with a different Log OR. Decrease of global mortality (Log OR) was not significantly associated with increasing BMI when all studies were considered (coefficient = 0.0051513, SE = 0.1030994, $t = 0.05$, $P = 0.962$, 95% CI, −0.2471238 to 0.2574263; when study 16 was excluded, (Log OR) was significantly associated with increasing BMI (coefficient = −0.2044346, SE = 0.0720125, $t = -2.84$, $P = 0.047$, 95% CI, −0.4043734 to −0.0044959; supplementary file B shows the difference in global mortality LogOR as a function of BMI.

The role of BMI was not significant for all-causes mortality (coefficient = 0.1105201, SE = 0.1165778, $t = 0.95$, $P = 0.443$, 95% CI, −0.3910738 to 0.6121139), and CV mortality (coefficient = 0.2110385, SE = 0.1567263, $t = 1.35$, $P = 0.310$, 95% CI, −0.4633005 to 0.8853774), despite a clear trend, probably because of the reduced number of observations; supplementary file C describes results of this meta-regression.

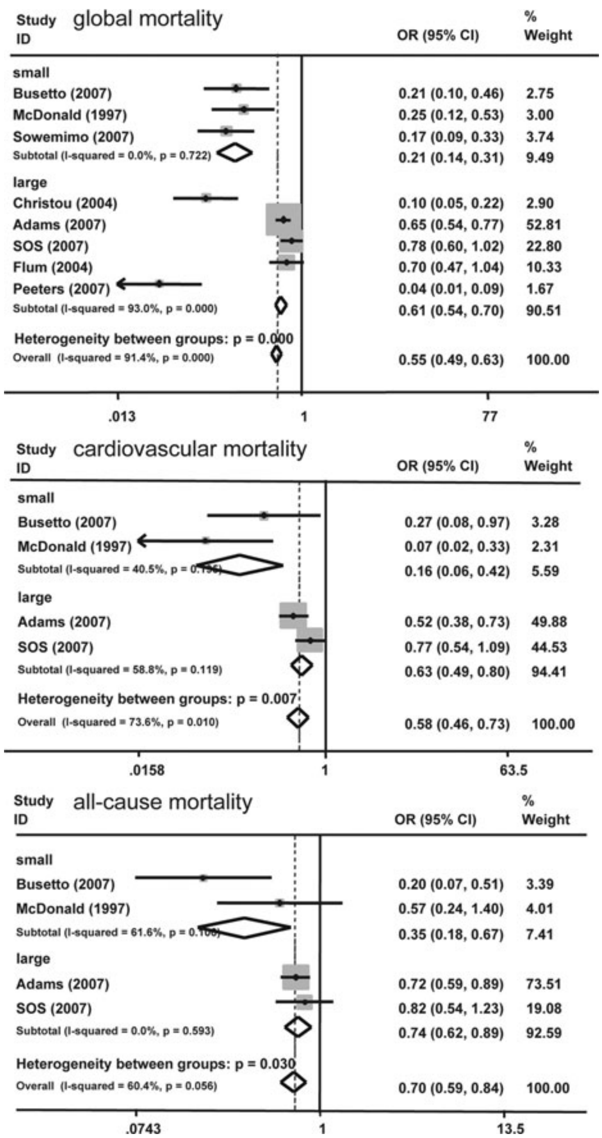

FIGURE 1. Forrest plot of meta-analysis of all studies (global mortality, cardiovascular mortality, all-cause mortality) divided according to study size (small and large). OR indicates odds ratio (with 95% CI).

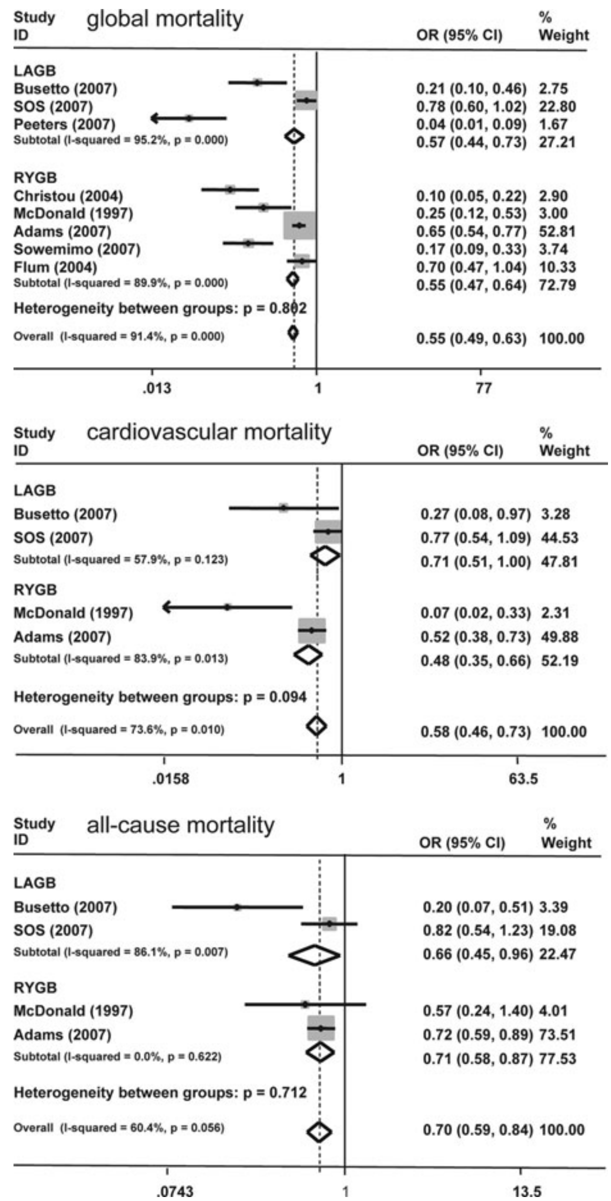

FIGURE 2. Forrest plot of meta-analysis of all studies (global mortality, cardiovascular mortality, all-cause mortality) divided according to surgical technique (LAGB and RYGB). OR indicates odds ratio (with 95% CI).

Being not-randomized trials, according to quality criteria indicated earlier,[17–23] all studies were of low methodologic quality.

DISCUSSION

A few studies were not considered in this meta-analysis; the study by Favretti[29] contains the same information of the study by Busetto;[13] there is also an old study indicating that the risk of death of obese participants undergoing surgery is significantly reduced when compared to obese participants and similar to lean participants,[8] but it does not contain crude data to be included in a meta-analysis.

The studies covered by this meta-analysis were not randomized, as it has been considered for long time unethical to use randomization in surgery studies. Therefore, all studies were of low methodologic quality.[17–23] Quite recently it has been possible to perform randomized clinical trials.[30,31]

The studies were also heterogeneous in terms of size (2 studies accounted for about 60% of all participants, and contributed for more than 75% of weight in analysis).[12,14] Also scant is the information about mortality according to sex, percentage of patients with diabetes, or with preexisting cardiovascular disease, the amount of weight lost in control groups. Interviews with authors of each article were not followed by significant improvements of data available. One should also consider loss to follow-up, to the fact that ascertainment of death was based on death certificates in many instances, and for control participants on community registries.[10,11,14–16] This might distort actual deaths reported in more than one study.

Studies were different in terms of follow-up, among, and in some cases within trials.[9,16] Studies were also different for the kind of controls; participants with obesity in a clinical program have comorbidities, and that is why they are in a clinical program. In most cases control participants were from clinics programs, and in 2 cases were from the community.[14,16] The different kind of controls did not influence ORs for global mortality.

With all these limits, the result of this meta-analysis was that bariatric surgery is associated with a lower risk of death when compared to nonsurgery, and this applies to global mortality and (when specified) all-cause mortality and CV mortality with similar ORs.

The data coming from studies covered by this meta-analysis, except for all-cause mortality, were heterogeneous. For this reason, we subdivided studies by size; in this way, larger studies were not heterogeneous, and also smaller studies were not heterogeneous. However, the preventive effect of large studies was less pronounced than the effect of small studies [global mortality: OR 0.61 (0.54–0.70) vs 0.21 (0.14–0.31)] and similar figure apply for all-cause mortality and for cardiovascular mortality. With the few data available, it seems wise to accept data coming from large studies as more indicative of the real risk reduction.

At meta-regression analysis, decrease of global mortality (Log OR) was not significantly associated with increasing BMI when all studies were considered; the association was significantly associated when one study[16] was excluded; reason for this is that one study[16] was associated with an extremely protective effect despite a low BMI. Supplementary file B shows the differences in global mortality LogOR as a function of BMI when the earlier study is considered or not considered. A relationship between BMI and reduced risk of mortality was indicated by Busetto,[13] Adams,[14] Sowemimo,[15] and Peeters.[16] In contrast, age and sex were not associated with a different OR, in agreement with the earlier studies.[13–16] No significant association was found for CV mortality and all-cause mortality; this was probably because of the fact that only 4 studies indicated CV mortality and all-cause mortality.

Only one study was in participants with type 2 diabetes;[9] in this study global mortality and all-cause mortality were not different from studies in nondiabetic participants, whereas the effect on CV mortality was extremely more pronounced. Further studies in diabetic participants are required to understand this difference.

Gastric banding and gastric by-pass differed for the amount of weight lost, as it has been reported in more than one meta-analysis.[3,4] Prevention of CV mortality, not of global and all-cause mortality, was greater for gastric by-pass, probably linked to the previously referenced trial in patients with type 2 diabetes[9]; this indication has to be considered with caution because heterogeneity was high and the number of participants undergoing the 2 kinds of surgery was greatly different.

In conclusion, this meta-analysis indicates that bariatric surgery reduces the risk of global mortality, all-cause mortality, and CV mortality, when compared to participants not undergoing surgery. Risk reduction seems to be lower in large studies than in small studies, and tends to be greater in more obese participants. Both gastric banding and gastric by-pass seem to reduce mortality risk.

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