

Effect of Weight Loss on Predicted Cardiovascular Risk: Change in Cardiac Risk After Bariatric Surgery

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Abstract

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Objective: Our goal was to assess the effect of bariatric surgery on cardiovascular risk estimations of preventable, long-term adverse outcomes.

Research Methods and Procedures: We performed a population-based, historical cohort study between 1990 and 2003 of 197 consecutive patients from Olmsted County, MN, with Class II to III obesity (defined as BMI ≥ 35 kg/m²) treated with Roux-en-Y gastric bypass and 163 non-operative patients assessed in a weight-reduction program. We used the observed change in cardiovascular risk factors and risk models derived from data from the National Health and Nutrition Examination Survey (NHANES) I and the NHANES I Epidemiological Follow-up Study (NHEFS) to calculate the predicted impact on cardiovascular events and mortality for the operative and non-operative groups.

Results: Mean follow-up was 3.3 years. Hypertension, diabetes, and dyslipidemia all improved after bariatric surgery. The estimated 10-year risk for cardiovascular events

for the operative group decreased from 37% at baseline to 18% at follow-up, while the estimated risk for the non-operative group did not change from 30% at baseline to 30% at follow-up. Risk modeling to predict 10-year outcomes estimated 4 overall deaths and 16 cardiovascular events prevented by bariatric surgery per 100 patients compared with the non-operative group.

Conclusions: Bariatric surgery induces an improvement in cardiovascular risk factors in patients with Class II to III obesity. Weight loss predicts a major, 10-year reduction in cardiovascular events and deaths. Bariatric surgery should be considered as an alternative approach to reduce cardiovascular risk in patients with Class II to III obesity.

Key words: population studies, mortality, bariatric surgery, cardiovascular risk

Introduction

An estimated 280,000 to 325,000 deaths can be linked annually to obesity in the United States (1). The Framingham Study showed that obese subjects with a BMI of >30 kg/m² at age 40, compared with those with a BMI of <25 kg/m², have a 6- to 7-year shorter life expectancy (2,3). Although obesity is thought to increase mortality, few studies have examined the effect of intentional weight loss on mortality, primarily because long-lasting substantive and intentional weight loss is rare (4).

Obesity is acknowledged as an independent cardiovascular risk factor (CVRF)¹ by the American Heart Association (5–8). Obese patients have an increased prevalence of CVRFs, such as hypertension, diabetes mellitus, hyperinsulinemia, dyslipidemia, and obstructive sleep apnea (9–17).

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¹CVRF, cardiovascular risk factor; LDL, low density lipoprotein; HDL, high density lipoprotein; NHANES, National Health and Nutrition Examination Survey; NHEFS, NHANES I Epidemiological Follow-up Study; RYGB, Roux-en-Y gastric bypass; REP, Rochester Epidemiology Project.

Weight loss promotes decreases in blood pressure, lowering the risks of microvascular and macrovascular complications, improves fasting blood glucose concentrations and the action of insulin, and induces decreases in serum triglycerides, low density lipoprotein (LDL), and total cholesterol concentrations, with concomitant increases in serum high-density lipoprotein (HDL) concentrations (18,19).

Since the NIH Consensus conference in 1991, bariatric surgery has been approved as an effective therapeutic intervention to achieve weight loss in patients who meet appropriate criteria (20). Bariatric surgery has been shown to be a relatively safe procedure, even in patients with known cardiovascular disease (21).

Several studies have tested the effect of bariatric surgery on weight loss and other CVRFs (17,22–27). With few exceptions, the majority of the studies assessing the effect of bariatric surgery on CVRFs have been completed in highly selected populations (28). To our knowledge, there are no longitudinal, community-based studies that examine the effect of the Roux-en-Y gastric bypass (RYGB) procedure on quantitative estimates of cardiovascular risk reduction after bariatric surgery. The aim of our study was to use the observed change in CVRFs and their predicted impact on cardiovascular events and mortality using risk models derived from the National Health and Nutrition Survey (NHANES) I and NHANES I Epidemiological Follow-up Study (NHEFS), in a community-based cohort of patients with Class II to III obesity (defined as BMI ≥ 35 kg/m²), who underwent gastric bypass surgery or attempted weight loss with conservative strategies.

Research Methods and Procedures

Subjects and Study Setting

We performed a population-based, longitudinal, historical study on all Olmsted County residents referred for medical consultation to the Nutrition Clinic at Mayo Clinic for possible bariatric surgery from 1990 to 2003. Using demographic information, residence was verified using United States Postal Service zip codes. All patient encounters and procedures occurred at practices in the county.

Data Resources

Data were abstracted from the Mayo Clinic medical record, the Mayo Surgical index, and the Rochester Epidemiology Project (REP). The Mayo Clinic medical record is near-complete, with fewer than 500 medical records missing since its inception. Diagnoses are abstracted regardless of the site of care or whether the episode was medical or surgical. Much is in electronic format since 1996, but all paper records are available and were abstracted for this study. The Mayo Clinic Surgical Index annotates surgeries by indication and type.

The REP is a unique and comprehensive resource of patient information on all Olmsted County residents. Pa-

tients' medical care is self-contained within this relatively isolated area and provided by Mayo Clinic or its two hospitals, St. Mary's and Rochester Methodist, or by the Olmsted Medical Center and its hospital. A central, computerized index amasses all diagnoses for the resident on a master sheet. All of the original medical records are available for review. This resource has been funded by U.S. government sources for three decades for its use in disease-related epidemiology (29). Background epidemiological studies using this population provide reasonable extrapolation to other parts of the country (29).

Surgical Cohort

The Mayo Surgical Index was abstracted to determine the procedures from 1990 to 2003 whose primary indication was weight reduction. This was cross-referenced with the REP to identify Olmsted residents. Only patients who underwent an RYGB were included. Weight-loss procedures were performed at St. Mary's Hospital, a-1157 bed tertiary care center. The majority of outpatient encounters were based at Mayo Clinic Rochester. The surgical cohort included 231 patients. Patients with a BMI < 35 ($n = 16$) or those with incomplete data ($n = 18$) were excluded, leading to 197 patients.

Non-operative Controls

All non-operative subjects were evaluated and managed at the Mayo Nutrition Clinic. These subjects declined operative treatment voluntarily, were ineligible due to denial of payment by third party payers, or lacked medical necessity or appropriate insight into their disease (obesity). A minority were excluded due to psychiatric or medical contraindications. In clinical practice, though, reasons for exclusion are often multifactorial and not due entirely to one single reason. Those patients not proceeding to operation were managed medically, with scheduled dietitian visits, promotion of physical activity with and without behavioral therapy for weight management, and, when clinically indicated, weight loss medications. Of the 252 Olmsted County residents who were referred to the Nutrition Clinic, we excluded 19 patients with a BMI < 35 , most of whom underwent revised bariatric operations, and 70 patients with only one visit and no follow-up data, limiting this group to 163 patients.

After excluding patients whose follow-up data were within 3 months of operation or initial nutrition consultation, we included 173 operative patients and 139 non-operative patients in our risk estimate analysis. We hypothesized that the true effect of bariatric surgery would not be materialized in this 3-month period.

Data Collection and Management

Each patient's medical record was abstracted. The REP was utilized to ensure adequate and proper follow-up data.

To ensure quality control of the data, ~10% of charts were abstracted in duplicate. No significant differences were found.

Definitions

Baseline time was defined as time of bariatric surgery or time of initial consultation to the nutrition clinic for the non-operative group. Censoring time included the last clinical encounter in the patient's medical record or death. Baseline values included variables present in the medical record on the baseline day or earlier. Follow-up data included the last documented record of any of these variables. We documented height, weight, blood pressure, heart rate, medication lists, and co-morbidities, including hypertension, diabetes, smoking status, dyslipidemia, and stroke. Laboratory data included fasting lipids and plasma glucose, creatinine, and glycosylated hemoglobin concentrations. We coded new diagnoses of cardiovascular conditions (International Classification of Diseases codes 390–459.9), either from the time of operative treatment or the time of initial consultation to the date of most recent follow-up. Cardiovascular death was defined as death due to any of these conditions. Mortality data were gathered using the REP and state death registries.

Hypertension was defined as a documented diagnosis or recorded blood pressure >125/85 mm Hg (30). Dyslipidemia was defined as total cholesterol of >6.2 mM (240 mg/dL) or an LDL >4.14 mM (160 mg/dL), documented diagnosis, or treatment with statins, fibrates, niacin, or bile-acid sequestrants (31).

We defined diabetes mellitus as a fasting blood glucose >7.0 mM (126 mg/dL) or treatment with insulin or oral hypoglycemic agents either at baseline or at follow-up (32). We included patients in the analysis with blood hemoglobin A_{1C} concentration of >7% due to variability in the results of the assay. Patients were classified as having resolved diabetes if they had fasting glucose <7.0 mM, had hemoglobin A_{1C} <6%, were not using insulin or oral agents, and did not have end-stage renal disease. Patients with gestational diabetes were excluded.

BMI was calculated as weight (in kilograms) divided by height (in meters) squared. All height and weight data were measured at both times by a nurse. Ideal body weight was calculated as described previously (33).

All patients signed research authorization forms permitting the use of their medical records for clinical research purposes. This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review boards.

Statistical Analysis

We performed Student's *t* tests for equal and unequal variances and Pearson χ^2 tests to compare differences in means and percentages, respectively, between groups. For intra-group comparisons, we performed matched *t* tests for

continuous and χ^2 tests for nominal data. Fisher exact tests and Wilcoxon Sign-Rank were used to provide intra-group comparisons for medication usage for categorical and non-parametric data. Inter-group comparisons were performed using Pearson χ^2 tests and Wilcoxon Rank Sums. Continuous data are presented as mean \pm standard deviation. Analyses were performed using JMP (Windows Version 5.1.2 for SAS; SAS Institute, Inc., Cary, NC).

Development of the Predictive Model

The NHANES I survey, part of the National Health Survey, was conducted from 1971 to 1975 with voluntary, non-institutionalized U.S. civilians between the ages of 25 and 74 years, selected randomly using a nationwide probability sample (34). The corresponding follow-up surveys (NHEFS) were conducted in 1982, 1986, 1987, and 1992 (35–39).

We constructed proportional hazards models for all-cause mortality, cardiovascular mortality, cardiovascular events, and combined cardiovascular events/all-cause mortality from NHANES I and NHEFS data using SAS-callable SUDAAN (Research Triangle Institute, Research Triangle Park, NC) to account for the complicated sampling in NHANES. For these models, cardiovascular mortality was defined as a cause of death with an International Classification of Disease code 390–459.9. Cardiovascular events were defined as cardiovascular mortality or hospitalizations with similar codes. Variables included age, systolic blood pressure, BMI, and total cholesterol, as well as smoking, diabetes, non-white race, and history of cardiovascular disease, each as yes or no. Separate models were developed for each sex. Beta coefficients, with their standard errors and confidence intervals, stratified by sex, and models can be seen in the appendix (available online at the Obesity web site, www.obesityresearch.org). Age (time since birth) was used as the time variable, in accordance with recommendations by Korn et al. (40). The dependence on BMI was modeled as constant for BMI 18.5 to 30.0, linear for BMI >30.0, and linear for BMI <18.5 but with an independent slope. This technique allowed for increased mortality risk at extreme BMI levels. Total cholesterol risk was modeled in a piecewise, linear fashion, with separate slopes for total serum cholesterol above or below 4.14 mM (160 mg/dL) to allow for an increase in mortality or cardiovascular risk at very low cholesterol levels. The log of the baseline hazard for each model was fit to a function of the age at time of the event including linear, quadratic, and cubic terms. Previous studies using risk models derived from NHANES have shown excellent correlation and precision with the Framingham risk estimation (41).

Risk Prediction

The resulting models were applied to both the operative and non-operative data sets to estimate for each patient (and

each risk type) the log hazard and the 10-year risk. Separate estimates were calculated using the initial risk factors and follow-up risk factors. Any patient flagged as a smoker was assumed to be an all-time smoker. The log hazard was used as a risk score for each patient, which comprised the sum of the β coefficient multiplied by the risk factor from the risk function, calculated at baseline and at follow-up. This score was tested for the effect of bariatric surgery using a general linear model with the follow-up score as the dependent variable and surgery (yes/no) as the independent variable after adjusting for all of the initial values of the risk variables used in the hazards model. Follow-up times of <3 months were excluded. This approach was tested as a covariate in the model but was not found to be significant. This finding may have been due to the presence of different follow-up times for different risk factors. The change in risk score due to bariatric surgery found in the multivariate model was used to create an adjusted estimate of the number of events prevented in the bariatric surgery cohort, which was used as a proxy for absolute risk reduction to calculate number needed to treat. Primary analyses omitted any operative mortality because it is reported to be very low (0.5%) (42). Other sensitivity analyses included a 2% operative mortality and categorized patients with type 2 diabetes as still having diabetes at follow-up even if it was resolved as per our definitions. All these analyses were carried out using SAS version 9.1 (SAS Institute Inc.).

Confidence intervals were calculated including the fluctuations due to the operative and non-operative data only; the uncertainty in the relationship of the risk scores to actual event probabilities was not included. *p* Values for differences between initial and follow-up event estimates were calculated after adjustments for fixed risk factors. *p* Values for events prevented came from the multivariate analysis. All analyses were stratified by sex to account for the use of sex-specific risk functions. *p* Values <0.05 were considered statistically significant.

Results

Baseline characteristics are shown in Table 1. Demographic and clinical features were similar between groups, except that operative patients were slightly older and had a higher BMI. The average duration of follow-up was 3.3 years for both groups.

Tables 2 and 3 depict the changes in the CVRF over time. When the Δ between both groups was compared, the bariatric surgery group had significant improvement in all parameters. The diagnosis of diabetes mellitus was 19.3% lower at follow-up in the operative group, whereas there was an 8.5% increase in patients with diabetes in the non-operative group ($p < 0.001$). There was an increase of 2.1% in the operative patients and 4.3% in the non-operative patients qualifying for a diagnosis of cardiovascular disease at follow-up. The numbers of new cardiovascular events,

primarily cardiac artery disease, atrial fibrillation, and death, were 6 and 9 at follow-up in the operative and non-operative groups, respectively (not significant; data not shown).

Our main model of risk prediction represents the estimated effect of bariatric surgery on deaths and events in 10 years when comparing the change in CVRF between the bariatric surgery and non-operative groups. There were differences in all-cause mortality, cardiovascular death, and cardiovascular events between groups ($p < 0.001$ each). Model 2 represents the proportion of deaths and events expected in the operative group had they been non-operative instead. There were minimal differences between our operative group at baseline and the predicted events at follow-up. Model 3 provides age-adjusted risk estimates for a patient 45 years of age, for both deaths and events. Although the all-cause mortality and cardiovascular mortality were slightly less at baseline, there were still changes observed at 10 years, with decreased rates compared with the control groups ($p < 0.001$). These data are depicted in Table 4. The estimated number of events prevented is shown in Table 5.

The effect of bariatric surgery appears to apply to both sexes but with different estimated risk reductions. Although the all-cause mortality, cardiovascular mortality, and cardiovascular events were significantly greater in male patients, the preventable deaths by bariatric surgery were estimated to be 11.4 and 2.4 per 100 patient-years in males and females, respectively ($p < 0.001$). All sex-specific analyses showed significant reductions in mortality and events after operative intervention (data not shown).

Sensitivity Analysis

Using diabetes mellitus as an independent variable, the all-cause mortality in the operative group remained similar to that in our main model, and there were minimal differences observed in cardiovascular deaths or events (2.9 and 15.5, respectively). In Models 2 and 3, the all-cause mortality, cardiovascular mortality, and cardiovascular events were marginally greater, at 10.5, 5.9, and 36.5 per 100 patient-years, respectively, corresponding to the higher baseline risk in the operative group.

Perioperative mortality in our operative cohort was 0.6% (1 patient). In another analysis, we assumed a 2% perioperative mortality risk to reflect a more realistic scenario in centers with low to average bariatric operative volumes. Using Model 1, the risk of death was 2.7% less at follow-up in the operative group; the number of events prevented by bariatric surgery for each 100 patients and number needed to treat were 2.2 and 45.1, respectively. In the age-adjusted model, the risk of death in the operative group decreased from 8.1% to 4.3%.

Table 1. Patient characteristics

	Operative group baseline (<i>n</i> = 197)	Non-operative group baseline (<i>n</i> = 163)	<i>p</i>
Age (yr)	44.0 ± 9.9	43.4 ± 11.2	0.01
Female sex	158 (80.2%)	119 (73.0%)	0.12
Duration of follow-up (yr)	3.3 ± 2.6	3.3 ± 2.6	0.45
History of cardiovascular disease*	31 (15.7%)	24 (14.7%)	0.75
History of:			
Systemic hypertension†	105 (53.3%)	80 (40.1%)	0.42
Type 2 diabetes mellitus‡	61 (31%)	41 (25.2%)	0.19
Dyslipidemia§	114 (57.9%)	97 (59.5%)	0.75
Obstructive sleep apnea	126 (64%)	37 (22.7%)	<0.001
Current smoker	25 (12.7%)	32 (19.6%)	0.08
BMI (kg/m ²)	49.5 ± 8.9	44.0 ± 5.7	<0.0001
Weight (kg)	139 ± 27	126 ± 21	<0.0001
Excess weight	128 ± 41	102 ± 25	<0.001
Systolic blood pressure (mm Hg)	134 ± 16	133 ± 18	0.89
Diastolic blood pressure (mm Hg)	80 ± 10	77 ± 11	0.01
Heart rate (bpm)	79 ± 11	80 ± 11	0.18
Serum cholesterol			
Total (mM)	5.14 ± 0.99	5.34 ± 1.15	0.06
High-density lipoprotein (mM)	1.17 ± 0.29	1.15 ± 0.35	0.38
Low-density lipoprotein (mM)	3.03 ± 0.83	3.13 ± 0.92	0.23
Triglycerides (mM)	2.12 ± 1.31	2.56 ± 2.43	0.04
Fasting blood glucose (mM)	6.53 ± 2.04	6.68 ± 2.82	0.57
Creatinine (μM)	88.5 ± 0.01	88.5 ± 0.01	0.44
Medications			
Beta-blocker	40 (20%)	23 (14%)	0.11
Calcium channel blocker	20 (10%)	9 (6%)	0.10
Diuretics	51 (26%)	37 (19%)	0.44
Angiotensin converting enzyme inhibitor, or angiotensin receptor blocker	44 (22%)	37 (23%)	0.98
Lipid-lowering agent	34 (17%)	23 (14%)	0.38
Insulin	32 (16%)	7 (4%)	<0.001
Oral hypoglycemic agents	28 (14%)	25 (15%)	0.80

Continuous data presented as mean ± standard deviation.

* Defined as myocardial infarction, congestive heart failure, atrial fibrillation, coronary artery bypass graft, percutaneous coronary intervention, or any clinical or a new diagnosis of coronary artery disease based on non-invasive methods, as documented in the medical chart.

† Defined as greater than 125/85 mm Hg.

‡ Defined as having a fasting blood glucose > 7 mM; taking insulin or oral hypoglycemic agents; hemoglobin A_{1c} ≥ 7%.

§ Defined as having a total serum cholesterol ≥ 6.21 mM (240 mg/dL); low-density lipoprotein ≥ 4.14 mM (160 mg/dL); taking statins, fibrates, niacin, bile-acid sequestrants; or documented with that diagnosis in the medical record.

|| Defined as ever having used any tobacco products.

Discussion

To our knowledge, this is the first population-based study examining the 10-year risk estimates of all-cause mortality,

cardiovascular mortality, and cardiovascular events in patients undergoing bariatric surgery. Our results showed that effective weight loss with bariatric surgery caused signifi-

Table 2. Change in cardiovascular risk factors over time

	Operative group			Non-operative group			Difference between operative and non-operative group change		
	Baseline (n = 197)	Follow-up (n = 197)	Change	p	Baseline (n = 163)	Follow-up (n = 163)	Change	p	
Weight (kg)	139 ± 27	96 ± 25	-44	<0.001	126 ± 9	126 ± 26	0.4	0.71	<0.001
% excess weight	128 ± 41	57 ± 40	-71	<0.001	102 ± 13	103 ± 36	0.2	0.85	<0.001
BMI (kg/m ²)	49.5 ± 8.9	34.1 ± 8.2	-15	<0.001	44.0 ± 5.7	43.8 ± 7.8	0.02	0.93	<0.001
Blood pressure									
Systolic (mm Hg)	134 ± 16	121 ± 16	-12	<0.001	133 ± 18	128 ± 16	-5	<0.001	<0.001
Diastolic (mm Hg)	80 ± 10	72 ± 11	-8	<0.001	77 ± 11	76 ± 10	-1	0.26	<0.001
Heart rate (bpm)	79 ± 11	72 ± 11	-6	<0.001	80 ± 11	78 ± 13	-2	0.15	0.006
Laboratory data									
Serum cholesterol									
Total (mM)	5.14 ± 0.99	3.97 ± 0.84	-1.17	<0.001	5.34 ± 1.15	5.00 ± 1.08	-0.34	<0.001	<0.001
High-density lipoprotein (mM)	1.17 ± 0.29	1.42 ± 0.39	0.24	<0.001	1.15 ± 0.35	1.26 ± 0.32	0.11	<0.001	<0.001
Low-density lipoprotein (mM)	3.03 ± 0.83	1.99 ± 0.63	-1.04	<0.001	3.13 ± 0.92	2.82 ± 0.85	-0.32	<0.001	<0.001
Triglycerides (mM)	2.12 ± 1.31	1.25 ± 0.66	-0.87	<0.001	2.56 ± 2.43	1.99 ± 1.09	-0.57	<0.001	<0.001
Fasting blood glucose (mM)	6.53 ± 2.04	5.27 ± 1.19	-1.25	<0.001	6.68 ± 2.82	6.50 ± 2.46	-0.17	0.32	<0.001
Creatinine (μ M)	88.5 ± 0.01	81.3 ± 13.3	-4.42	<0.001	88.5 ± 0.01	88.4 ± 16.8	0	0.78	-4.42 NS

NS, not significant.

* p values are for the differences between means of groups.

Table 3. Medication use among operative and non-operative patients at baseline and at latest follow-up

	Operative group (n = 197)		Non-operative group (n = 163)		Change (%)	P
	Baseline [n (%)]	Follow-up [n (%)]	Baseline [n (%)]	Follow-up [n (%)]		
Use of anti-hypertensive medications	90 (45)	66 (33)	62 (38)	88 (54)	-21	<0.001
Median number of anti-hypertensive medications	2 (1-4)	1 (1-4)	1 (1-5)	2 (1-4)	-1	<0.001
Use of lipid-lowering medications	33 (16)	13 (6)	23 (14)	58 (35)	-29	<0.001
Use of statin medications	29 (14)	12 (6)	20 (12)	51 (31)	-25	<0.001
Use of insulin or oral hypoglycemic agents	45 (22)	15 (7)	29 (17)	50 (30)	-23	<0.001

Blood pressure medications included: angiotensin converting enzymes, angiotensin receptor blockers, beta-blockers, calcium channel blockers, and diuretics (loop/thiazide). Lipid-lowering medications = Questran, fibrates, niacin, and statins.

cant, long-lasting improvements in CVRF. Using risk functions derived from the NHANES data in our cohort, all-cause mortality and cardiovascular death were reduced significantly, preventing 16.2 cardiovascular events, 4.1 overall deaths, and 3.0 cardiac-related deaths per 100 patient years.

The use of medications to treat diabetes mellitus, hypertension, and dyslipidemia was significantly less at follow-up in the operative group, suggesting that the differences seen were due to weight loss and not to medications. The all-cause and cardiovascular mortality risks in both groups were similar at baseline but decreased in the bariatric surgery group by 44.2% and 55.2%, respectively. Age-adjusted risk estimates validated these results.

Previous studies assessing the effect of bariatric surgery, including RYGB, on CVRF have shown significant improvements in diabetes, hypertension, and dyslipidemia (22-27). Such studies validate our own, although ours is the only community-based study with a non-operative group and a long-term follow-up, including only RYGB bariatric intervention. The largest prospective study testing the effect of bariatric surgery on CVRF, the Swedish Obesity Study, determined that bariatric surgery can improve weight and lead to recovery from diabetes, hypertriglyceridemia, and hypertension, but not hypercholesterolemia, after 10 years (28). Unfortunately, they did not report changes in medication usage that would explain the lack of differences in serum LDL and HDL concentrations at follow-up (28,43). Their results likely have underestimated the effects of RYGB, because most patients underwent the less effective vertical-banded gastroplasty, with only 34 patients in the RYGB group (28,44). RYGB is the most common weight-reduction procedure in the United States, and the one with the lowest percentage of weight regain (28,45-47).

Limited studies have analyzed the possible effect of weight loss on cardiovascular events or mortality (48-52). Weight and fat losses are associated with reduced all-cause mortality (52-57). Prospective studies have shown that, in patients with obesity-related co-morbidities, intentional weight loss is associated with reduced overall and cardiovascular mortality, with no differences seen in those without obesity-related complications (4,58-60). In a recent meta-analysis, weight loss in the obese patient with co-morbidities was associated with improved outcomes and a survival benefit (52). Furthermore, weight loss reduces the prevalence of diabetes mellitus, which had an additional beneficial effect on mortality (59). Methodologic problems limit the interpretation of studies that associate weight loss in overweight patients with increased mortality, as they are unable to distinguish between intentional and unintentional weight loss and do not account for weight cycling and smoking (61-64).

Few studies have examined the effect of bariatric surgery on cardiovascular events or mortality (48,49). Gastric by-

Table 4. Risk models examining all-cause mortality, cardiovascular mortality, and cardiovascular events

	Operative group			Non-operative group			
	Baseline (%) (n = 173)	Follow-up (n = 173)	% change 95% CI	Baseline (%) (n = 139)	Follow-up (n = 139)	% change 95% CI	Intergroup <i>p</i>
Model 1: main model							
All-cause mortality	10.4 (n = 18)	5.8 (n = 10.1)	-4.6 3.62 to 5.51*	9.4 (n = 13.1)	9.2 (n = 12.8)	-0.2 -0.6 to 1.02†	<0.001*
CV death	5.8 (n = 10.1)	2.6 (n = 4.5)	-3.3 2.3 to 4.2*	5.3 (n = 7.4)	4.9 (n = 6.8)	-0.4 -0.37 to 1.24†	<0.001*
CV event	37.0 (n = 64)	18.2 (n = 31.5)	-18.8 16.8 to 20.7*	30.0 (n = 41.8)	29.9 (n = 41.5)	-0.2 -1.77 to 2.08†	<0.001*
Model 2: proportion of deaths expected in the operative group if they had been in the non-operative group instead							
All-cause mortality	10.4 (n = 18)	9.9 (n = 17.2)	-0.5				
CV death	5.8 (n = 10.1)	5.6 (n = 9.6)	-0.3				
CV events	37.0 (n = 64)	34.3 (n = 59.3)	-2.7				
Model 3: 10-year estimates if all patients were 45 years old							
All-cause mortality	8.1 (n = 14)	4.3 (n = 7.4)	-3.8 3.12 to 4.42*	6.7 (n = 9.3)	7.0 (n = 9.7)	0.3 -0.95 to 0.32†	<0.001*
CV death	4.4 (n = 7.6)	1.8 (n = 3.1)	-2.6 1.98 to 3.2*	3.6 (n = 5.0)	3.6 (n = 5.1)	0.1 -0.61 to 0.49†	<0.001*
CV events	38.1 (n = 65.9)	17.7 (n = 30.6)	-20.4 18.4 to 22.4*	30.8 (n = 42.8)	31.2 (n = 43.5)	0.5 -2.62 to 1.67†	<0.001*

CI, confidence interval; CV, cardiovascular; NHANES, National Health and Nutrition Examination Study. Data show the changes in the 10-year risk estimates for operative and non-operative patients based on NHANES I risk functions. The number represents risk estimates per 100 patient years. In parentheses, the estimated total number of patients are given based on each sample size. Percentages were rounded to the nearest tenth, and changes were rounded to the nearest thousandth. 95% CIs represent the mean number of events estimated.

* *p* < 0.001.

† *p* > 0.05, not statistically significant.

Table 5. Predicted deaths and events prevented by bariatric surgery in 10 years for each 100 patients

	Prevented	95% CI	No. needed to treat
All-cause mortality	4.1 deaths	3.04–5.16	24.4
CV death	3.0 deaths	1.93–3.99	33.7
CV events	16.1 CV events	13.6–18.5	6.2
CV events or death	15.6 events	13.3–17.9	6.4

CI, confidence interval; CV, cardiovascular.

pass reduces the progression of and risk of mortality from non-insulin-dependent diabetes mellitus (65). Christou et al. examined mortality in bariatric surgery patients vs. non-operative patients and showed a reduction of 89% in the relative risk of death in the surgical group (48,49). Unfortunately, this study did not account for changes in CVRF at follow-up and had no information about weight loss in the non-operative group. Flum and Dellinger examined both the short- and long-term impact of bariatric surgery, showing a significant reduction in death at 15-year follow-up from 16.3% to 11.8% (49). The authors used, as controls, patients who were discharged from the hospital who did not undergo bariatric surgery, potentially overestimating the mortality in the control group and magnifying any potential survival benefit with bariatric surgery. Another study, which was limited to patients with type 2 diabetes who underwent an RYGB, found a lower mortality in the operative group due to reduced cardiovascular deaths (65). To our knowledge, no study has estimated the effect of bariatric surgery on cardiovascular events and deaths using risk-prediction models.

Our results have substantial and potentially far-reaching implications. The obesity epidemic continues to grow, with prevalence of obesity nearly doubling in the last 30 years alone (66–68). Cardiovascular disease is the most common cause of death in obese patients, and overweight and obesity are the most prevalent CVRFs in patients with cardiovascular disease, present in 72% of all indexed cases in a community-based study examining 2277 post-myocardial infarct patients (69). Despite obesity being regarded as an independent CVRF, it is often overlooked by physicians managing patients with cardiovascular disease because of largely ineffective treatment options and, possibly, a lack of awareness of the value of bariatric surgery (70).

Risk factor modification is essential in reducing long-term mortality and events. Understandably, weight reduction is an important, albeit difficult, task, and few patients with obesity achieve long-term weight loss with conservative measures, as exemplified in our non-operative group. The benefits of major weight loss may extend beyond CVRF reduction because weight loss decreases body fat,

blood leptin, insulin levels, fatty acid turnover, and systemic inflammation, while improving endothelial function (71,72).

Our estimates were extremely sensitive to operative mortality. A recent study has suggested that there is a considerably higher mortality risk with bariatric surgery in centers or by surgeons with low surgical volume or experience (49,73). Our results suggest that the estimated risk reduction can be applied to patient populations or centers with a low perioperative mortality rate. Bariatric surgery should not be considered as first-line treatment in obesity, but rather as an effective alternative, particularly for patients who fail conservative methods and for those with multiple CVRFs.

Strengths

To our knowledge, this is the first community-based study examining risk estimates of the effect of bariatric surgery on cardiovascular outcomes and all-cause mortality. We examined a geographically circumscribed area encompassing the entire population of patients undergoing bariatric surgery who met inclusion criteria, and we minimized selection and referral bias. To our knowledge, our study is the first consisting of patients who underwent solely RYGB. We included patients who were attempting to lose weight but who did not undergo bariatric surgery, allowing us to determine their long-term change in CVRFs. Very few of these patients achieved more than the average amount of weight loss observed in the operative group, suggesting that the elimination of specific groups, such as the under-insured, would not have a significant effect on our results. Our mean follow-up was 3.3 years. Long follow-up provides a more realistic view of weight change and justifies the use of CVRF data in risk estimates with a 10-year horizon. Most studies on improvement of CVRF with bariatric surgery have follow-up data of 1 year or less.

Limitations

Our study has the limitations of an historical cohort study. The decision to undergo bariatric surgery instead of a non-operative approach was not determined randomly. However, the logistics of a randomized design would be difficult

because bariatric surgery is now used widely. We had no control over the ordering of laboratory data or the clinical follow-up. Therefore, factors that account for those decisions may also account for some of the differences between groups at follow-up. Patients may differ in other cultural, sociodemographic, and clinical factors that were not taken into account. Although there were differences in BMI and insulin use among the operatively-treated patients at baseline, adjustments were made in the analysis to account for this. Furthermore, requiring insulin treatment and having a higher BMI may be more likely to confound toward the null hypothesis; therefore, our findings may have underestimated a larger difference in cardiovascular disease risk change. We recognize that a weakness in our study was that the non-operative group was not matched; however, this was not feasible due to the limited number of patients in the control group.

Various assumptions were made in our data analysis. Uniform definitions were applied across both study groups for the diagnosis of diabetes, dyslipidemia, and hypertension. Our risk estimates assume that BMI and mortality are associated in a “U”-shaped fashion, with underweight patients and overweight patients having higher risks (74). We might have penalized patients who achieved maximum weight loss. We assumed that the risk of cardiovascular disease due to total cholesterol is associated in a “J”-shaped fashion, thereby penalizing patients who achieved a cholesterol reduction below 4.14 mM (160 mg/dL) (75,76).

Most risk-estimate studies use the Framingham model to assess 10-year cardiac risk. Although the utility of the Framingham criteria has been validated extensively, it does not include BMI or obesity as part of its equation (77,78). We opted to use risk functions derived from NHANES I data for our analysis because this approach incorporates body weight, a critical outcome after bariatric surgery. These risk functions allowed us to use a defined combination of risk factors and to observe their interactions in comparing the operative and non-operative groups. It allowed us to translate risk profiles into estimated events for a representative U.S. population consisting of a similar ethnicity. It was inherent that our obese patient cohort group consisted of extreme risk profiles, thereby involving some extrapolation, as few members of the NHANES population would be as obese as our patients. Additionally, to increase the reliability of our risk functions, we used well-established risk factors. Outcomes of a given predictive risk factor, such as cardiovascular disease, have been calculated regardless of whether treatment was initiated or maintained; this approach has been well described and validated in NHANES. Hence, the relative impact on the 10-year risk by changes in dynamic risk factors is accounted for. The risk estimates are based on the longitudinal behavior of a population representative of the United States at that time period. Patients' risk factors also evolved, and, hence, we assumed that our

own population followed a similar evolution of risk factors over a 10-year period. Although treatments and social and environmental influences change, today's population will likely be somewhat different from that of NHANES I, possibly affecting the accuracy of our estimates. In addition, to the best of our knowledge, there are no data regarding the percentage of NHANES patients who were treated for obesity with operative intervention.

Evaluating cardiovascular events, cardiovascular mortality, and all-cause mortality was not part of our specific study aims, and we recognize that our study was under-powered to make any significant conclusions with respect to these outcomes.

In summary, bariatric surgery induces a considerable and long-lasting improvement in CVRFs in patients with Class II to III obesity that predicts a significant 10-year reduction in cardiovascular events and cardiovascular deaths. Bariatric surgery should be considered as an alternative approach to reduce cardiovascular risk in patients with Class II to III obesity.

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