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Effects of Bariatric Surgery on Mortality in Swedish Obese Subjects

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ABSTRACT

BACKGROUND

Obesity is associated with increased mortality. Weight loss improves cardiovascular risk factors, but no prospective interventional studies have reported whether weight loss decreases overall mortality. In fact, many observational studies suggest that weight reduction is associated with increased mortality.

METHODS

The prospective, controlled Swedish Obese Subjects study involved 4047 obese subjects. Of these subjects, 2010 underwent bariatric surgery (surgery group) and 2037 received conventional treatment (matched control group). We report on overall mortality during an average of 10.9 years of follow-up. At the time of the analysis (November 1, 2005), vital status was known for all but three subjects (follow-up rate, 99.9%).

RESULTS

The average weight change in control subjects was less than ±2% during the period of up to 15 years during which weights were recorded. Maximum weight losses in the surgical subgroups were observed after 1 to 2 years: gastric bypass, 32%; vertical-banded gastroplasty, 25%; and banding, 20%. After 10 years, the weight losses from baseline were stabilized at 25%, 16%, and 14%, respectively. There were 129 deaths in the control group and 101 deaths in the surgery group. The unadjusted overall hazard ratio was 0.76 in the surgery group ($P=0.04$), as compared with the control group, and the hazard ratio adjusted for sex, age, and risk factors was 0.71 ($P=0.01$). The most common causes of death were myocardial infarction (control group, 25 subjects; surgery group, 13 subjects) and cancer (control group, 47; surgery group, 29).

CONCLUSIONS

Bariatric surgery for severe obesity is associated with long-term weight loss and decreased overall mortality.

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In the United States from 1980 through 2004, the prevalence of obesity — defined as a body-mass index (BMI) (the weight in kilograms divided by the square of the height in meters) of 30 or more — doubled, rising to include more than 30% of the population.[1,2] The majority of large and long-term epidemiologic studies have indicated that obesity is associated with increased mortality.[3-9] The life expectancy of severely obese persons is reduced by an estimated 5 to 20 years.[10]

Weight loss is known to be associated with improvement of intermediate risk factors for disease,[11] suggesting that weight loss would also reduce mortality. However, controlled, interventional studies showing that weight loss actually reduces the risk of death have been lacking. To date, most observational epidemiologic studies have indicated that the rate of death from cardiovascular and all other causes is increased after weight loss,[12] even in subjects who were obese at baseline.[13-15] This discrepancy concerning the effects of weight loss on risk factors, as compared with mortality, has been related to certain limitations inherent in observational studies, particularly the inability of such studies to distinguish intentional from unintentional weight loss. Thus, the observed weight loss might be the consequence of conditions that lead to death rather than the cause of increased mortality.

However, three observational epidemiologic reports,[16-18] all based on data from the American Cancer Society, suggested that intentional weight loss is, in fact, associated with decreased mortality, though the information on intentionality was based on retrospective, self-reported baseline data. Whether these weight losses at baseline were maintained is unknown, since changes in weight during the studies were not reported. Two retrospective cohort studies involving obese subjects[19,20] and one involving obese subjects with diabetes[21] suggested that bariatric surgery may also result in a marked reduction in mortality. Elsewhere in this issue of the *Journal*, Adams et al.[22] provide further support for this opinion on the basis of a new, very large retrospective cohort study on gastric bypass.

The use of bariatric surgery has increased dramatically during the past decade; more than 100,000 procedures were performed in the United States in 2003.[23] However, whether the long-term weight loss induced by bariatric surgery has favorable effects on life span remains unclear.

To ascertain conclusively the effects of intentional weight loss on mortality, controlled, prospective interventional trials are needed. In the Swedish Obese Subjects (SOS) study, we used bariatric surgery to achieve weight loss, since such surgery was and still is the only available technique with established long-term effects on weight loss. Our study examines whether bariatric surgery is associated with lower mortality, as compared with conventional treatment, during a mean follow-up period of 10.9 years.

Methods

Study Design

Our prospective, matched, surgical interventional trial[11,24] enrolled 4047 obese subjects at 25 surgical departments and 480 primary health care centers. Seven regional ethics review boards approved the study protocol. Written or oral informed consent was obtained from all subjects, who agreed to participate in the study for 10 years. Of those subjects, 1471 who underwent bariatric surgery and 1444 who received conventional treatment also consented to participate in follow-up examinations at 15 and 20 years. Subjects were recruited over a 13.4-year period, from September 1, 1987, to January 31, 2001; the cutoff date for our current analysis was November 1, 2005. The follow-up period thus ranged from 4 years 9 months to 18 years 2 months, with a mean (±SD) of 10.9±3.5 years.

As a result of recruitment campaigns, 11,453 subjects sent standardized application forms to the SOS secretariat, and 6905 completed a matching examination. Among those who underwent matching examination, 2010 eligible subjects desiring surgery constituted the surgery group; on the basis of data from the matching examination, a contemporaneously matched control group of 2037 subjects was created using 18 matching variables.[24]

Baseline examinations of subjects in both groups took place 4 weeks before surgery. The intervention began on the day of surgery for subjects in the surgery group and for their matched controls. Individual dates of all subsequent examinations and questionnaires (at 0.5, 1, 2, 3, 4, 6, 8, 10, and 15 years) in both study groups were calculated on the basis of the date of surgery. Subjects in both study groups had to be between the ages of 37 and 60 years and have a BMI of

34 or more for men and 38 or more for women. The BMI cutoffs corresponded to an approximate doubling in the rate of death in each sex.[25] Exclusion criteria, described elsewhere,[24] were minimal and were aimed at obtaining an operable surgery group. The two study groups had identical inclusion and exclusion criteria. Subjects with hypertension, diabetes, or lipid disturbances were allowed to participate, as were subjects who had had a myocardial infarction or a stroke more than 6 months before inclusion.

CLINICAL AND BIOCHEMICAL ASSESSMENTS

At each visit, measurements of weight, height, waist circumference, other anthropometric measures, and blood pressure were obtained (Table 1).[24] The sagittal diameter of the trunk was measured, with subjects in the supine position, as the vertical distance between a firm examination table and a carpenter's level kept horizontally across the abdomen at the height of the iliac crest. The sagittal diameter is closely related to the volume of visceral fat, as measured with a multiscan computed tomographic technique.[26] Biochemical variables were measured at the matching examination, at the baseline examination, and at years 2, 10, and 15. Blood samples were obtained in the morning after a fast of 10 to 12 hours and analyzed at the Central Laboratory of Sahlgrenska University Hospital (accredited according to European Norm 45001).

The baseline questionnaire included self-reported information on previous myocardial infarction, stroke, and cancer and questions designed to assess the likelihood of the presence of sleep apnea.[27] Psychosocial variables were also evaluated, including monotony avoidance, a personality trait characterized by abnormal attempts to avoid routine and to seek change and action (i.e., thrill- or sensation-seeking behavior), and psychasthenia, which is characterized by tiredness, concentration and memory difficulties, and various sensations including palpitations.[28]

TREATMENT

Of the 2010 subjects in the surgery group, 376 underwent nonadjustable or adjustable banding, 1369 underwent vertical banded gastroplasty, and 265 underwent gastric bypass.[29] For adjustable banding, the Swedish Adjustable Gastric Band (Obtech Medical), similar to the American lap band, was used. Subjects in the control group received the customary nonsurgical treatment for obesity at their given center of registration. No attempt was made to standardize the conventional treatment, which ranged from sophisticated lifestyle intervention and behavior modification to no treatment whatsoever.

RATE OF DEATH

All social security numbers from the SOS database were cross-checked against the Swedish Population and Address Register (SPAR) every year on November 1. SPAR provides information on all deceased nonemigrants. For the purpose of this study, we cross-checked our data against those in SPAR in June 2006 to add any additional subject registrations. Social security numbers for all deceased subjects as of November 1, 2005, were cross-checked against the Swedish Cause of Death Register to obtain the official cause of death. For recent deaths that had not been registered in the central registry, actual death certificates were examined. In addition, all relevant case sheets and autopsy reports were adjudicated independently by two of the authors, who were unaware of study-group assignments. Causes of death were established according to a previously described classification scheme (Table 2).[30] If the two examiners differed on a cause of death, a third coauthor (who also was unaware of study-group assignments) reviewed the case so that a final decision could be made. If the study-determined cause of death did not agree with the official cause, the study-determined cause of death was used.

SPAR also provides dates for emigration but cannot track new addresses or death notices. We therefore contacted relatives and Swedish embassies worldwide, successfully tracing the 24 emigrants who had previously participated in the SOS study.

STATISTICAL ANALYSIS

The study had a power of 80% ($P=0.05$) to detect a 23% reduction in total mortality in 2000 subjects in the surgery group, as compared with 2000 in the control group, at 10 years of follow-up.[24] Mean values and standard deviations or 95% confidence intervals were used to describe the baseline characteristics and changes over time in the two study groups. Time to death was compared between study groups with the use of a Wald test for the estimated hazard ratio from a Cox proportional-hazards model[31] with a single

Table 1. Characteristics of the Subjects at Matching and Baseline Examinations.*

Variable	Matching Examination					Baseline Examination				
	Surgery Group (N=2010)	No. with Missing Data	Control Group (N=2037)	No. with Missing Data	P Value	Surgery Group (N=2010)	No. with Missing Data	Control Group (N=2037)	No. with Missing Data	P Value
Sex (no.)										
Male	590	0	590	0		590	0	590	0	
Female	1420	0	1447	0	0.79	1420	0	1447	0	0.79
Women who were postmenopausal (% of women)†	31.8	0	35.5	0	0.04	37.2	0	41.3	0	0.02
Age at examination (yr)	46.1±5.8	0	47.4±6.1	0	<0.001	47.2±5.9	0	48.7±6.3	0	<0.001
Daily smoking (%)	27.9	0	20.2	0	<0.001	25.8	2	20.8	10	<0.001
Coexisting conditions										
Diabetes (%)	7.4	0	6.1	0	0.12	10.7	5	11.4	12	0.52
Sleep apnea (%)†	23.8	8	22.4	31	0.30	25.1	46	22.2	48	0.03
Lipid-lowering therapy (%)	1.8	0	1.6	0	0.67	1.8	0	1.6	0	0.67
Previous myocardial infarction (no.)	29	0	22	0	0.30	31	0	29	0	0.76
Previous stroke (no.)	15	0	19	0	0.52	15	0	23	0	0.21
Previous stroke or myocardial infarction (no.)†	44	0	39	0	0.54	46	0	49	0	0.81
Previous cancer (no.)	23	0	20	0	0.62	24	0	21	0	0.62
Weight (kg)	119.2±16.1	0	116.9±15.4	0	<0.001	121.0±16.6	0	114.7±16.5	0	<0.001
Height (m)	1.69±0.09	0	1.69±0.09	0	0.64	1.69±0.09	0	1.69±0.09	0	0.68
Body-mass index†	41.8±4.4	0	40.9±4.3	0	<0.001	42.4±4.5	0	40.1±4.7	0	<0.001
Waist-to-hip ratio†	0.99±0.07	0	0.98±0.07	1	0.17	0.99±0.08	7	0.98±0.07	0	<0.001
Measurement of size (cm)										
Waist circumference	124.1±10.7	1	122.2±10.2	0	<0.001	125.8±11.0	6	120.2±11.3	0	<0.001
Hip circumference	125.9±9.7	1	124.4±9.3	1	<0.001	127.1±10.0	7	123.2±10.0	0	<0.001
Sagittal diameter	28.4±3.6	2	27.9±3.4	1	<0.001	28.9±3.7	8	27.4±3.7	0	<0.001
Neck circumference	43.4±4.2	5	43.4±4.2	1	0.97	43.7±4.3	10	42.9±4.29	0	<0.001
Upper-arm circumference	39.6±3.8	2	39.3±3.6	0	0.01	39.8±3.8	6	38.7±3.8	0	<0.001
Thigh circumference	74.9±7.0	1	74.1±7.0	2	<0.001	75.5±7.5	7	73.4±7.5	0	<0.001
Blood pressure (mm Hg)										
Systolic	140.6±18.7	2	140.0±18.0	0	0.25	145.0±18.8	6	137.9±18.0	4	<0.001
Diastolic	87.5±11.2	3	87.1±10.7	3	0.30	89.9±11.1	7	85.2±10.7	7	<0.001
Pulse pressure†	53.1±13.4	3	52.9±13.1	3	0.53	55.2±14.5	8	52.8±13.0	7	<0.001

covariate for the study group. The Wald test was chosen to provide consistency between reported P values and 95% confidence intervals. Rates of death were analyzed by the Kaplan–Meier method.

Multivariate Cox proportional-hazards models on the basis of matching data or baseline data were also used to evaluate time to death while adjusting for potentially significant risk factors. The following variables listed in Table 1 were not used, owing to concern regarding collinearity: menopausal status, presence or absence of previous myocardial infarction or stroke, the BMI, the waist-to-hip ratio, and pulse pressure. Levels of high-density lipoprotein cholesterol and the presence or absence of sleep apnea were omitted from the multivariate analysis because of a rela-

Table 1. (Continued.)

Variable	Matching Examination					Baseline Examination				
	Surgery Group (N=2010)	No. with Missing Data	Control Group (N=2037)	No. with Missing Data	P Value	Surgery Group (N=2010)	No. with Missing Data	Control Group (N=2037)	No. with Missing Data	P Value
Laboratory values										
Glucose (mmol/liter)	5.32±1.98	0	5.32±2.00	3	0.99	5.45±2.11	8	5.20±1.92	5	<0.001
Insulin (mU/liter)	21.4±14.4	6	20.0±12.7	3	0.002	21.5±13.7	9	18.0±11.4	3	<0.001
Triglycerides (mmol/liter)	2.23±1.44	2	2.15±1.50	0	0.09	2.25±1.54	4	2.02±1.41	2	<0.001
Cholesterol (mmol/liter)										
Total	5.84±1.12	2	5.75±1.08	0	0.004	5.86±1.12	4	5.61±1.06	2	<0.001
High-density lipoprotein†	1.20±0.29	69	1.20±0.31	39	0.88	1.20±0.28	87	1.19±0.29	60	0.84
Uric acid (μmol/liter)	352.5±80.6	2	350.4±81.0	2	0.42	359.2±79.8	5	352.3±79.9	3	0.006
Aspartate aminotransferase (μkat/liter)	0.42±0.25	0	0.41±0.24	2	0.94	0.43±0.23	3	0.39±0.21	2	<0.001
Alanine aminotransferase (μkat/liter)	0.60±036	0	0.60±0.40	2	0.85	0.63±0.39	4	0.56±0.42	2	<0.001
Alkaline phosphatase (μkat/liter)	3.06±0.86	0	3.03±0.86	2	0.31	3.12±0.84	3	3.01±0.87	2	<0.001
Bilirubin (μmol/liter)	9.24±4.08	0	9.53±3.96	2	0.02	9.51±4.28	4	9.93±5.27	2	0.005
Psychosocial measurement‡										
Current health score	21.4±6.10	0	22.7±6.2	0	<0.001					
Monotony avoidance score	22.5±5.1	0	22.6±5.0	0	0.525					
Psychasthenia score	23.9±5.2	0	23.2±5.3	0	<0.001					
Social support										
Quantity	6.02±2.4	0	6.08±2.45	1	0.48					
Quality	4.25±1.32	0	4.28±1.31	0	0.55					
Stressful life events	2.49±1.30	0	2.43±1.28	0	0.09					

* Plus–minus values are means ±SD. Body-mass index is the weight in kilograms divided by the square of the height in meters. To convert the values for glucose to milligrams per deciliter, divide by 0.05551. To convert the values for insulin to picomoles per liter, multiply by 6. To convert the values for triglycerides to milligrams per deciliter, divide by 0.01129. To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for uric acid to milligrams per deciliter, divide by 59.48. To convert the values for aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase to units per liter, divide by 0.01667. To convert the values for bilirubin to milligrams per deciliter, divide by 17.1.

† This variable was not used in the multivariable stepwise-regression analysis either because it was derived from other variables or because a large number of data were missing.

‡ For psychosocial measurements, higher scores represent better current health (range, 9 to 36), more of the personality trait on monotony avoidance (range, 10 to 40) and psychasthenia (range, 10 to 40), a higher quantity of social support (range, 0 to 12), a better quality of social support (range, 0 to 5), and a greater number of stressful life events (range, 0 to 8).

tively large number of missing data. For all other variables in Table 1, missing values were replaced by medians specific for a combination of time (matching and baseline data) and study group. For yes-or-no variables, the median corresponds to simple majority. In this way, data from all the subjects could be used for multivariate adjustments.

Since it was not obvious whether matching or baseline data should be used for the multivariate adjustments in this nonrandomized study, we used both data sets to determine whether the resulting models provided similar hazard ratios for mortality with respect to the surgery group, as compared with the control group. The models were built using a forward stepwise procedure, with additional checks to determine whether single-term substitutions could improve a model

Table 2. Cause of Death.*

Variable	Surgery Group (N=2010)	Control Group (N=2037)
	no. of subjects	
Cardiovascular condition		
Any event	43	53
Cardiac	35	44
Myocardial infarction	13	25
Heart failure	2	5
Sudden death	20	14
Stroke	6	6
Intracerebral hemorrhage	2	4
Infarction	1	2
Subarachnoid bleeding	3	0
Other	2	3
Aortic aneurysm	1	2
Aortic thrombosis	0	1
Diabetic gangrene	1	0
Noncardiovascular condition		
Any event	58	76
Tumor	29	48
Cancer	29	47
Meningioma	0	1
Infection	12	3
Thromboembolic disease	5	7
Pulmonary embolism	4	7
Vena caval thrombosis	1	0
Other	12	18
Total no. of deaths	101	129

* During the first 90 days after study initiation, there were five deaths in the surgery group (four from peritonitis with organ failure and one sudden death) and two deaths in the control group (one from cancer of the pancreas and one from alcohol-related causes).

with a given number of predictors. At each step, all terms were required to be marginally significant, at the 0.05 level. For two models of the same size, in which all predictors in both models were significant, the model preferred was that with the better overall model fit by the chi-square test. Schoenfeld residuals from the models were examined to assess possible departures from model assumptions.[32] All reported P values are two-sided. Statistical analyses were carried out with the use of R statistical software, version 2.3.1.[33]

RESULTS

BASELINE CHARACTERISTICS

In this study, 2010 obese subjects who were treated surgically were contemporaneously matched with 2037 conventionally treated obese controls. Table 1 details matching and baseline information. The matching procedure created two groups that were very similar, although subjects in the surgery group were on average 2.3 kg (5.07 lb) heavier (P<0.001), were 1.3 years younger (P<0.001), and more frequently were smokers (P<0.001) than subjects in the control group. The higher body weight in the surgery group was associated with higher values in several anthropometric measurements and in some biochemical variables.

Between the matching and baseline examinations, there was an increase in mean weight in the surgery group (1.7 kg [3.75 lb], P<0.001) and a decrease in the mean weight in the control group (2.2 kg [4.85 lb], P<0.001) (Table 1). These diverging weight changes caused most variables to become significantly different between the study groups at baseline. However, age, thigh circumference, and bilirubin levels were the only variables that were significantly different between groups, were associated with a significant univariate difference in survival, and would benefit survival in the surgery group. Thus, most differences between the study groups that were observed at matching and at baseline constitute survival disadvantages for the surgery group in a univariate analysis.

PARTICIPATION RATES AND FOLLOW-UP

On November 1, 2005, the vital status was known for all but three of the initial study subjects, two who requested to be deleted from the SOS database and one who left the study and later obtained an unlisted social security number. Thus, the follow-up rate with respect to vital status on the date of analysis was 99.9%.

In the surgery group, participation rates of subjects at follow-up examination at 2, 10, and 15 years were 94%, 84%, and 66%, respectively. Corresponding examination rates among subjects in the control group were 83%, 75%, and 87%.

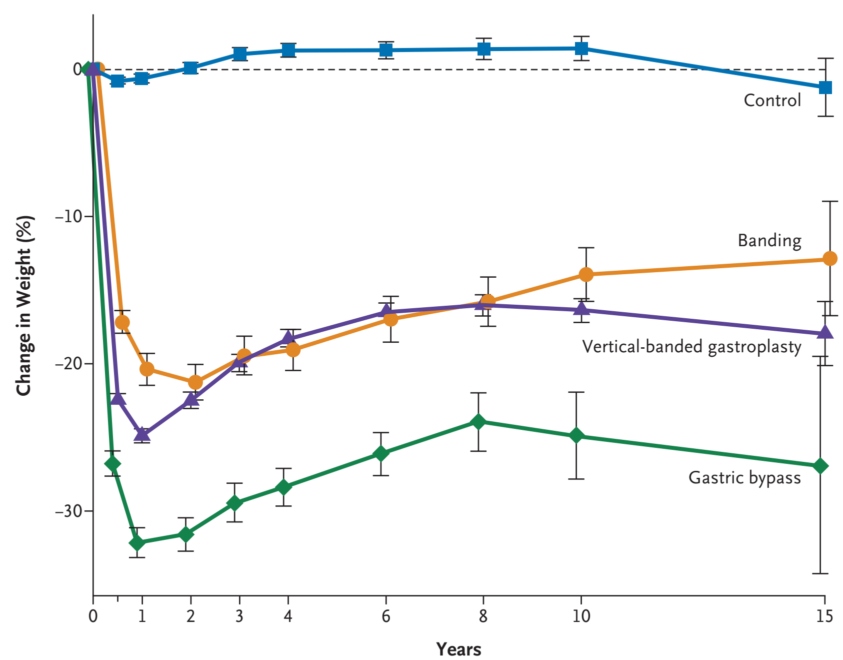
WEIGHT CHANGE

Figure 1 shows the weight changes for up to 15 years after baseline for the two study groups. The number of observations decreased over time, mainly owing to the 13-year-long recruitment period but also to dropout from examinations. In the control group, the average change in weight remained within ±2% during the observation period. In the three surgical subgroups, the mean (±SD) weight loss was maximal after 1 to 2 years (gastric bypass, 32±8%; vertical-banded gastroplasty, 25±9%; and banding, 20±10%). An increase in weight was observed in all surgical subgroups in the following years, but the weight gain ("relapse curves") leveled off after 8 to 10 years (Fig. 1). After 10 years, the weight losses were 25±11% for gastric bypass, 16±11% for vertical-banded gastroplasty, and 14±14% for banding, as compared with the baseline weight. After 15 years, the corresponding weight losses were 27±12%, 18±11%, and 13±14%, respectively.

OVERALL MORTALITY

Figure 2 depicts the cumulative overall mortality during a period of up to 16 years. Subjects in the surgery group had a hazard ratio of 0.76, as compared with the control group (95% confidence interval, 0.59 to 0.99; P=0.04). During the follow-up period, 129 subjects (6.3%) in the control group died, as compared with 101 (5.0%) in the surgery group.

There were no significant interactions between study group and the covariables of sex, presence or absence of diabetes, BMI, age, and previous cardiovascular events (Fig. 1 of the Supplementary Appendix, which is available with the full text of this article at www.nejm.org). Although certain subgroups may derive an additional benefit from surgery, the low cumulative mortality in our study hindered the detection of modest differences. For example, we did not find significant differences in mortality (starting at year 2) according to the degree of weight loss during the first year within either of the study groups. Undergoing any bariatric surgery appeared more relevant than either the degree of subsequent weight loss or the type

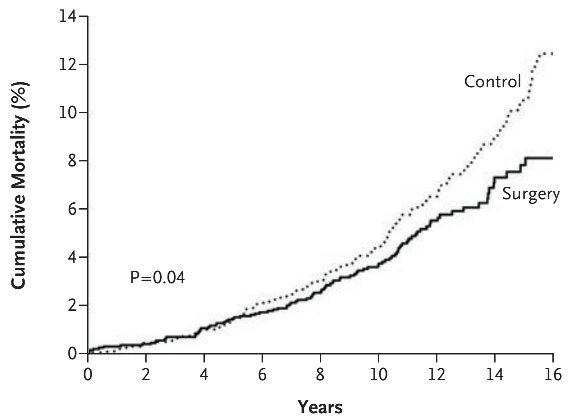


No. Examined

Control	2037	1768	1660	1553	1490	1281	982	886	190
Banding	376	363	357	328	333	298	267	237	52
Vertical-banded gastroplasty	1369	1298	1244	1121	1086	1004	899	746	108
Gastric bypass	265	245	245	211	209	166	92	58	10

Figure 1. Mean Percent Weight Change during a 15-Year Period in the Control Group and the Surgery Group, According to the Method of Bariatric Surgery.

I bars denote 95% confidence intervals.



No. at Risk

Surgery	2010	2001	1987	1821	1590	1260	760	422	169
Control	2037	2027	2016	1842	1455	1174	749	422	156

Figure 2. Unadjusted Cumulative Mortality.

The hazard ratio for subjects who underwent bariatric surgery, as compared with control subjects, was 0.76 (95% confidence interval, 0.59 to 0.99; P=0.04), with 129 deaths in the control group and 101 in the surgery group.

of surgery, though the study was not powered to compare types of intervention or different degrees of weight loss within the surgery group.

The causes of death are summarized in Table 2. There were 53 deaths from cardiovascular causes in the control group and 43 in the surgery group. The most common cardiovascular causes of death were myocardial infarction, sudden death, and cerebrovascular damage. Cancer was the most common cause of death from noncardiovascular causes.

In Table 3, hazard ratios for overall mortality are shown from stepwise multivariate analyses on the basis of matching and baseline data. Univariate hazard ratios for all measured risk factors are shown in Table 4. The adjusted hazard ratio for surgery is similar on the basis of matching data (0.73, P=0.02) and of baseline data (0.71, P=0.01), although the two models did not use exactly the same variables. In both models, the strongest predictors were age and smoking (Table 3), and the strongest univariate predictors were levels of plasma triglycerides and blood glucose (Table 4).

Overall mortality was higher in subjects who had had cardiovascular events (myocardial infarction or stroke) before baseline (24.5% in the control group and 19.6% in the surgery group) than in subjects without such events (5.9% and 4.7%, respectively). However, there was no interaction between study group and previous cardiovascular events (Fig. 1 of the Supplementary Appendix), and the unadjusted hazard ratio for subjects without previous cardiovascular events at baseline was 0.77 (P=0.06), which differs only marginally from the hazard ratio of 0.76 for all subjects. Hence, the inclusion of patients with previous cardiovascular events did not seem to drive our findings.

ADVERSE EVENTS

Within 90 days after surgery, five subjects in the surgery group (0.25%) and two subjects in the control group (0.10%) died. No postoperative deaths occurred among subjects who had previously had cardiovascular events. Postoperative complications have been reported previously.[11] Among 1338 subjects who were followed for at least 10 years, the frequencies of reoperations or conversion surgeries (excluding operations caused by postoperative complications) were as follows: banding, 31%; vertical-banded gastroplasty, 21%; and gastric bypass, 17%.

DISCUSSION

In this prospective, controlled study, we showed that bariatric surgery in obese subjects was associated with a reduction in overall mortality, as compared with conventional treatment in contemporaneously matched, obese controls. The observed reduction in the rate of death was further improved after adjustment for major confounders. Our findings are in agreement with surgical, retrospective cohort studies[19-22] and with observational prospective studies that attempted to separate intentional from unintentional weight loss occurring before the baseline examination.[16-18] However, our observations are at variance with most other observational studies regarding weight loss.[12-15,34] We cannot evaluate the effects of weight loss on death rate separately within the two study groups, given the limits of our study's statistical power. Therefore, we cannot determine whether the favorable survival effect of bariatric surgery is explained by weight loss or by other beneficial effects of the surgical procedures.

Our study began 4 years before the consensus conference on bariatric surgery was convened by the National Institutes of Health in 1991.[35] Thus, we had to define BMI cutoffs for the study. On the basis of the largest epidemiologic study avail-

Table 3. Stepwise Multivariate Analyses of Overall Mortality Performed Separately on Data from Matching and Baseline Examinations.*

Variable	Matching Examination			Baseline Examination		
	Hazard Ratio (95% CI)	Chi-Square	P Value	Hazard Ratio (95% CI)	Chi-Square	P Value
Bariatric surgery	0.73 (0.56–0.95)	5.45	0.02	0.71 (0.54–0.92)	6.45	0.01
Male sex	NA	NA	NA	1.61 (1.21–2.16)	10.47	0.001
Age at examination (per yr)	1.07 (1.04–1.09)	27.98	<0.001	1.07 (1.04–1.09)	32.60	<0.001
Daily smoking	2.41 (1.83–3.18)	38.62	<0.001	2.31 (1.75–3.05)	34.51	<0.001
Coexisting condition						
Diabetes	2.08 (1.43–3.03)	14.53	<0.001	1.61 (1.07–2.42)	5.15	0.023
Previous myocardial infarction	2.39 (1.37–4.17)	9.40	0.002	2.17 (1.27–3.69)	8.04	0.005
Previous stroke	3.01 (1.13–7.99)	4.88	0.03	3.19 (1.37–7.42)	7.22	0.007
Previous cancer	NA	NA	NA	2.28 (1.02–5.10)	4.00	0.05
Measurement of size (per 10 cm)						
Hip circumference	1.23 (1.07–1.41)	8.35	0.004	NA	NA	NA
Sagittal diameter	NA	NA	NA	1.87 (1.34–2.61)	13.40	<0.001
Neck circumference	2.14 (1.56–2.92)	22.81	<0.001	NA	NA	NA
Thigh circumference	0.70 (0.55–0.89)	8.60	0.003	NA	NA	NA
Laboratory values						
Glucose (per 1 mmol/liter)	NA	NA	NA	1.08 (1.01–1.14)	5.79	0.02
Total cholesterol (per 1 mmol/liter)	1.21 (1.08–1.35)	10.36	0.001	1.17 (1.04–1.33)	6.28	0.01
Psychosocial measurement						
Psychasthenia (per 5 score units)	1.16 (1.01–1.32)	4.54	0.03	1.16 (1.02–1.32)	4.95	0.03

* Variables used in these analyses were included in the univariate analyses in Table 4. Missing values were replaced by medians specific for the combination of time (matching and baseline data) and study group. For yes-or-no variables, the median corresponds to simple majority. In this way, data from all 4047 subjects were used in the multivariate analyses. Psychosocial information was available only at the matching examination but was used also in the multivariate analysis on the basis of baseline data to optimize the comparison between the two data sets. NA denotes not applicable.

able in the Nordic countries,[25] we selected cutoffs at which the mortality approximately doubled, as compared with BMI in the range of 20 to 25. This resulted in a BMI of 34 or more for men and of 38 or more for women. Although our study was not powered to look at BMI subgroups, it appears that the reduction in the risk of death in the surgery group was about 30% in subjects above the median BMI (40.8) and about 20% in subjects below the median BMI. Subjects under the age of 37 years were excluded to ensure high overall mortality and thus limit the size of the study. Although our study was also not powered to look at age subgroups, the risk reduction achieved by surgery appears much larger in older subjects (25%) than in younger subjects (6%).

In studies of midsize populations, long follow-up periods have been necessary for the negative effect of obesity on mortality to be evident.[9] In the Framingham[36] and Manitoba[37] studies, obesity became a significant predictor of mortality only after 26 years. Thus, it is not surprising that it took many years until a favorable treatment effect on mortality could be shown in our study.

The main limitation of our study was the absence of randomization. When the study was approved as a matched, prospective intervention study in 1987, six of the seven ethics review boards in Sweden considered the high death rate after bariatric surgery (1 to 5% in the 1970s and 1980s[38]) unacceptable for randomization. Such high postoperative rates of death are still reported today for some surgeons.[20,39] One unanswered question is whether randomization will ever be possible in bariatric surgery trials designed to study mortality. The few patients who would be prepared to accept random allocation between surgical and conventional treatments in long-term trials probably would not be representative of obese subjects in general.

Table 4. Univariate Analyses of Overall Mortality.*

Variable	Matching Examination			Baseline Examination		
	Hazard Ratio	Chi-Square	P Value	Hazard Ratio	Chi-Square	P Value
Bariatric surgery	0.76 (0.59–0.99)	4.14	0.04	0.76 (0.59–0.99)	4.14	0.04
Male sex	2.09 (1.61–2.70)	30.94	<0.001	2.09 (1.61–2.70)	30.94	<0.001
Age at examination (per yr)	1.08 (1.06–1.10)	45.12	<0.001	1.08 (1.05–1.10)	44.29	<0.001
Daily smoking	2.28 (1.75–2.96)	38.01	<0.001	2.19 (1.68–2.85)	34.03	<0.001
Coexisting conditions						
Diabetes	2.98 (2.11–4.21)	38.35	<0.001	2.85 (2.11–3.86)	46.46	<0.001
Lipid-lowering therapy	2.66 (1.25–5.69)	6.40	0.01	2.66 (1.25–5.69)	6.40	0.01
Previous myocardial infarction	5.71 (3.50–9.34)	48.32	<0.001	5.56 (3.45–8.96)	49.55	<0.001
Previous stroke	3.94 (1.68–9.21)	9.99	0.002	3.69 (1.59–8.59)	9.20	0.002
Previous cancer	2.16 (0.87–5.36)	2.77	0.10	2.48 (1.09–5.65)	4.68	0.03
Weight (per 10 kg)	1.13 (1.05–1.22)	11.05	0.001	1.12 (1.04–1.20)	9.42	0.002
Height (per 10 cm)	1.22 (1.07–1.40)	8.62	0.003	1.22 (1.06–1.39)	7.99	0.005
Measurement of size (per 10 cm)						
Waist circumference	1.25 (1.12–1.39)	15.88	<0.001	1.29 (1.16–1.43)	23.55	<0.001
Hip circumference	1.05 (0.92–1.20)	0.54	0.46	0.99 (0.87–1.13)	0.03	0.8
Sagittal diameter	2.56 (1.86–3.54)	32.83	<0.001	2.36 (1.74–3.19)	30.97	<0.001
Neck circumference	2.74 (2.06–3.65)	47.78	<0.001	2.61 (1.97–3.46)	44.91	<0.001
Upper-arm circumference	1.19 (0.84–1.69)	0.92	0.336	1.25 (0.87–1.81)	1.43	0.232
Thigh circumference	0.61 (0.50–0.74)	23.42	<0.001	0.71 (0.59–0.85)	13.24	<0.001
Blood pressure (per 100 mm Hg)						
Systolic	1.99 (0.98–4.04)	3.59	0.06	1.65 (0.81–3.36)	1.87	0.17
Diastolic	3.16 (0.86–11.54)	3.03	0.082	2.97 (0.95–9.26)	3.53	0.06
Laboratory values						
Glucose (per 1 mmol/liter)	1.17 (1.12–1.21)	57.97	<0.001	1.17 (1.12–1.21)	58.60	<0.001
Insulin (per 10 mU/liter)	1.12 (1.08–1.17)	31.51	<0.001	1.14 (1.07–1.20)	18.84	<0.001
Triglycerides (per 1 mmol/liter)	1.14 (1.11–1.18)	63.68	<0.001	1.16 (1.12–1.20)	65.09	<0.001
Total cholesterol (per 1 mmol/liter)	1.31 (1.18–1.46)	24.94	<0.001	1.30 (1.15–1.45)	19.53	<0.001
Uric acid (per 100 μmol/liter)	1.45 (1.24–1.69)	21.53	<0.001	1.28 (1.09–1.50)	9.40	0.002
Aspartate aminotransferase (per 1 μkat/liter)	1.39 (1.03–1.88)	4.63	0.03	1.71 (0.99–2.98)	3.64	0.06
Alanine aminotransferase (per 1 μkat/liter)	1.15 (0.88–1.50)	1.00	0.32	1.28 (0.86–1.91)	1.47	0.23
Alkaline phosphatase (per 1 μkat/liter)	1.10 (0.95–1.26)	1.61	0.20	1.16 (0.99–1.37)	3.17	0.08
Bilirubin (per 10 μmol/liter)	0.65 (0.45–0.93)	5.66	0.02	1.01 (0.52–1.96)	0.00	0.97
Psychosocial measurement (per 5 score units)						
Current health	0.84 (0.76–0.94)	9.98	0.002			
Monotony avoidance	0.98 (0.86–1.11)	0.09	0.77			
Psychasthenia	1.24 (1.09–1.41)	10.61	0.001			
Social support						
Quantity	0.66 (0.49–0.88)	7.70	0.006			
Quality	0.63 (0.40–0.99)	4.05	0.04			
Stressful life events	1.08 (0.67–1.74)	0.10	0.75			

* All variables were included in the stepwise multivariate analyses in Table 3.

In earlier reports from our ongoing study, bariatric surgery was associated with beneficial effects on diabetes, other cardiovascular risk factors, cardiovascular symptoms, progression of intima–media thickness, sleep apnea, joint pain, and health-related quality of life.[29,40,41] Our current report indicates that bariatric surgery was also associated with a marked reduction in overall mortality, suggesting that it may be a favorable option for treating severe obesity. Further studies are needed to elucidate the mechanisms through which bariatric surgery leads to decreased mortality.

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