Bariatric Surgery and Long-term Cardiovascular Events

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Context Obesity is a risk factor for cardiovascular events. Weight loss might protect against cardiovascular events, but solid evidence is lacking.

Objective To study the association between bariatric surgery, weight loss, and cardiovascular events.

Design, Setting, and Participants The Swedish Obese Subjects (SOS) study is an ongoing, nonrandomized, prospective, controlled study conducted at 25 public surgical departments and 480 primary health care centers in Sweden of 2010 obese participants who underwent bariatric surgery and 2037 contemporaneously matched obese controls who received usual care. Patients were recruited between September 1, 1987, and January 31, 2001. Date of analysis was December 31, 2009, with median follow-up of 14.7 years (range, 0-20 years). Inclusion criteria were age 37 to 60 years and a body mass index of at least 34 in men and at least 38 in women. Exclusion criteria were identical in surgery and control patients. Surgery patients underwent gastric bypass (13.2%), banding (18.7%), or vertical banded gastroplasty (68.1%), and controls received usual care in the Swedish primary health care system. Physical and biochemical examinations and database cross-checks were undertaken at preplanned intervals.

Main Outcome Measures The primary end point of the SOS study (total mortality) was published in 2007. Myocardial infarction and stroke were predefined secondary end points, considered separately and combined.

Results Bariatric surgery was associated with a reduced number of cardiovascular deaths (28 events among 2010 patients in the surgery group vs 49 events among 2037 patients in the control group; adjusted hazard ratio [HR], 0.47; 95% CI, 0.29-0.76; $P=.002$). The number of total first time (fatal or nonfatal) cardiovascular events (myocardial infarction or stroke, whichever came first) was lower in the surgery group (199 events among 2010 patients) than in the control group (234 events among 2037 patients; adjusted HR, 0.67; 95% CI, 0.54-0.83; $P<.001$).

Conclusion Compared with usual care, bariatric surgery was associated with reduced number of cardiovascular deaths and lower incidence of cardiovascular events in obese adults.

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Most epidemiological studies have shown that obesity is associated with increased cardiovascular morbidity and mortality.[1,2] Weight loss improves diabetes and other intermediate risk factors for cardiovascular disease,[3-6] suggesting that weight loss could also reduce the incidence of cardiovascular events. However, weight loss has been paradoxically associated

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with an increased incidence of cardiovascular events in most epidemiological studies,[7-9] even in participants who were overweight or obese at baseline.[10] Some observational studies suggest that self-reported intentional weight loss is associated with a decreased incidence of cardiovascular events.[11] Other studies suggest the opposite.[12,13] Results of these studies might be confounded by inclusion of participants with unintentional weight loss.[11-13]

Lifestyle interventions to prohibit diabetes[14] have not prevented cardiovascular events, not even after 10 to 20 years of follow-up.[15,16] Similarly lifestyle interventions combined with antiobesity medications have either shown no effect on primary cardiovascular end points[17] or an increased incidence of cardiovascular events in the drug treatment group.[18] Taken together, nonsurgical weight loss trials in obese participants have failed to yield a benefit in terms of cardiovascular event rates.[15-18]

Retrospective cohort studies of bariatric surgery demonstrated an association between bariatric surgery with a reduced incidence of cardiovascular events.[19,20] However, these studies were limited because of incomplete information about the participants causing uncontrolled, confounding conditions that might have influenced the results of these studies. To date, carefully controlled, prospective analyses on cardiovascular events in patients who have had bariatric surgery and matched obese participants have not been reported.

Two prospective, controlled, long-term studies examining the relationship between weight loss and cardiovascular outcomes are ongoing (Look AHEAD [Actions for HEAlth in Diabetes][21] and SOS [Swedish Obese Subjects]).[5,22-24] Look AHEAD's 4-year results on weight loss and risk factors were recently published,[21] but the 12-year results of lifestyle intervention on cardiovascular events are not yet available in the 5145 participants.

The rationale for the nonrandomized, prospective, controlled SOS study was to fill the knowledge gap regarding the association between type of treatment (bariatric surgery vs usual care) and hard end points (primarily mortality). For ethical reasons related to the high postoperative mortality in the 1980s, a randomized design was not approved and a matched study was therefore undertaken.[5,22-24] We have previously reported that bariatric surgery is associated with reduced incidence of diabetes (median follow-up time, 2 years)[5] and cancer (10.9 years)[24] and with reduced overall mortality (10.9 years),[23] the primary end point of the SOS study.

In this article, we test the hypothesis that bariatric surgery is associated with a reduced incidence of cardiovascular events. These were defined as a combination variable of fatal and nonfatal acute myocardial infarction (MI) and stroke, whichever came first. Myocardial infarction and stroke were also examined as separate end points. These secondary end points were predefined in 1987 in the original study protocol. Because current guidelines and position statements for selection of patients undergoing bariatric surgery[25-28] are based on expert opinions and not on treatment effects in prospective, controlled interventions, we have undertaken post hoc analyses to explore if baseline characteristics in the SOS study predict the surgical treatment benefit with respect to cardiovascular events. In addition, we have examined the relationship between weight change and the incidence of cardiovascular events.

METHODS

Study Design and Participants

The ongoing, nonrandomized, matched, prospective, controlled Swedish Obese Subjects (SOS) intervention study has previously been described in detail.[5,22-24] The SOS study is an academically initiated and implemented study run by the SOS secretariat at the Institute of Medicine, University of Gothenburg, Gothenburg, Sweden. The 4047 obese participants were enrolled between September 1, 1987, and January 31, 2001. Myocardial infarction and stroke were predefined secondary end points but the cutoff date for the analysis (December 31, 2009) was not prespecified in the original protocol.

Recruitment campaigns were undertaken in mass media and at 25 public surgical departments and 480 primary health care centers. The same sites have been responsible for data collection during follow-up. A matching examination (eTable 1, available at http://www.jama.com) was completed by 6905 individuals, 5335 of which were eligible (eFigure 1). Among the eligible patients, 2010 individuals electing surgery constituted the surgery group and a contemporaneously matched control group of 2037 participants was created by an automatic matching program using 18 matching variables (eTable 1).

Baseline examinations took place approximately 4 weeks before the start of the intervention (eTable 1). The inclusion criteria, which were identical in both study groups,[22,24] were aged 37 to 60 years and having a body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) of at least 34 for men and at least 38 for women. The exclusion criteria of both groups were earlier surgical operation for gastric or duodenal ulcer, earlier bariatric surgery, gastric ulcer during the past 6 months, ongoing malignancy, active malignancy during the past 5 years, MI during the past 6 months, bulimic eating pattern, drug or alcohol (>0.75 L 40% liquor per week or corresponding amount of ethanol) abuse, psychiatric or cooperative problems contraindicating bariatric surgery, and other contraindicating conditions, such as continuous glucocorticoid or anti-inflammatory treatment. Laboratory examinations were undertaken at the Central Laboratory, Sahlgrenska University Hospital, Gothenburg, Sweden (accredited according to

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European Norm 45001).[5,22-24] Psychosocial variables were evaluated with methods described previously (eTable 1).[29]

All regional ethical review boards in Sweden approved the study protocol, and all patients gave informed consent to participate.

Interventions

In the surgery group, 376 individuals (18.7%) underwent nonadjustable or adjustable banding, 1369 (68.1%) underwent vertical banded gastroplasty, and 265 (13.2%) underwent gastric bypass.[30] Control participants were given the customary treatment for obesity at their centers of registration (ie, essentially the standard obesity care in Sweden, ranging from advanced lifestyle advice at many sites to no treatment in other sites). During the 13 years of recruitment, the dominant technology changed from open to laparoscopic surgery. With this exception, the methods were not changed since study start.

Data Collection Intervals

Physical examinations and questionnaires were completed at matching and baseline and after 0.5, 1, 2, 3, 4, 6, 8, 10, 15, and 20 years. Centralized laboratory examinations were performed at the matching and baseline examinations and after 2, 10, 15, and 20 years. The SOS study database was cross-checked annually against public databases.

Outcome Measures

The primary end point (overall mortality) of the entire SOS project was published in 2007.[23] The study had 80% power (at $\alpha = .05$) to detect a 23% difference in mortality between 2000 surgically treated patients and 2000 controls followed up for 10 years.[23] We have also published results on some secondary end points (diabetes[5] and gall bladder disease[31]). This article reports on the predefined secondary end points, MI and stroke, considered separately and combined. Fatal and total incidence rates are given. These end points have not been changed during the course of the study. The following *International Classification of Diseases, Ninth Revision/International Statistical Classification of Diseases, Tenth Revision* codes were used (for MI: codes 410/I21, I22; for intracerebral bleeding: codes 431/I61; for cerebral artery occlusion: codes 433, 434/I63, I65, I66; and for acute but nondefined stroke in terms of bleeding or occlusion: codes 436/I64).

Angina pectoris, claudication, transitory ischemic attacks, and subarachnoidal bleeding were not included in the analyses. The incidence of MI and stroke was obtained by cross-checking the SOS database with the Swedish National Patient Register, the Cause of Death Registry, and the Registry of the Total Population. Currently (as of October 26, 2011), the Swedish National Patient Register, which limits this follow-up, is complete until December 31, 2009.

Statistics

The statistical procedures in the SOS study have previously been described in detail.[23,24] In brief, the methods included *t* test, Fisher exact test, Kaplan-Meier method estimates of cumulative incidence, log-rank test, and univariable and multivariable Cox proportional hazard regression models. In multivariable Cox proportional hazard regression models, missing baseline values on covariates were replaced by sex and treatment group specific medians. For all end points (cardiovascular events, MI, and stroke) in this study, the time × treatment interaction was nonsignificant, indicating that the proportional hazard assumption was not violated.

In subgroup × treatment interaction calculations, dichotomous variables could have 1 of 2 values (eg, men vs women; diabetes, yes vs no). For other variables, the interaction tests were conducted using the original continuous variables. The risk factor × treatment interactions included participants with or without the metabolic syndrome at baseline,[32] and individuals with different values on the European SCORE for risk of cardiovascular events.[33] In total, we performed 20 post hoc subgroup × treatment analyses in men and women combined. No adjustment for multiple testing was performed. With 20 performed tests, one statistically significant interaction test ($P < .05$) would be expected due to chance alone. The expected number of surgeries needed to prevent 1 cardiovascular event over 15 years (numbers needed to treat [NNT]) was calculated as the reciprocal of the absolute risk difference (obtained from Kaplan-Meier cardiovascular risk estimates over 15 years) between individuals in the surgery and control groups.

All *P* values are 2-sided and $P < .05$ was considered statistically significant. In all calculations, the intention-to-treat principle was applied. Statistical analyses were performed using the Stata statistical package version 10.1 (StataCorp LP).

RESULTS

Characteristics at Study Baseline

Descriptions of patients at the matching and the baseline examinations are given in eTable 1. Between the 2 examinations, body weight increased in the surgery group but decreased in the control group. At baseline, mean BMI was 40.1 in the control group and 42.4 in the surgery group, and most risk factors were less favorable in the surgery group.

Follow-up Rate and Changes in Body Weight

On the date of analysis (December 31, 2009), the median follow-up was 14.7 years (range, 0-20 years). On this date, we had information on the time until the first MI or first stroke (fatal or nonfatal) after study baseline in 2022 of 2037 controls (99% follow-up) and in 1993 of 2010 patients receiving surgery (99% follow-up) (eFigure 1). The mean changes in body weight after 2, 10, 15, and 20 years were –23%, –17%, –16%, and –18% in the surgery group and 0%, 1%, –1%, and –1% in the control group (FIGURE 1).

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Baseline Risk Factors and Cardiovascular Events During Follow-up

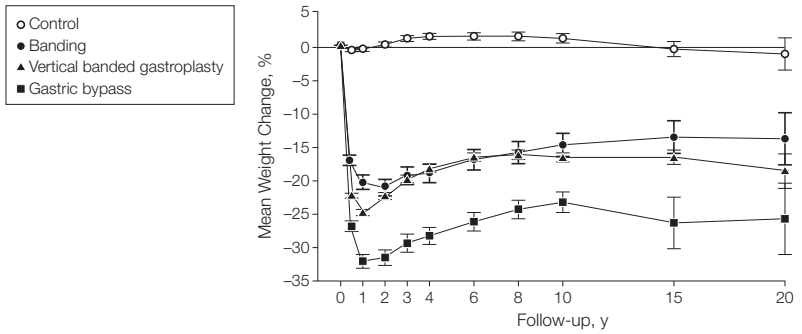
In univariable Cox proportional hazard regression analyses, the majority of classic baseline risk factors were associated with the incidence of cardiovascular events (eTable 2). However, in this obese population, baseline BMI was not related to cardiovascular events during follow-up.

Incidence of Fatal and Nonfatal Cardiovascular Events

There were 49 cardiovascular deaths among the 2037 patients in the control group and 28 cardiovascular deaths among the 2010 patients in the surgery group (unadjusted hazard ratio [HR], 0.56; 95% CI, 0.35-0.88; log-rank $P=.01$) (FIGURE 2). In total (fatal and nonfatal), there were 234 cardiovascular events among 2037 patients in the control group and 199 cardiovascular events among 2010 patients in the surgery group (unadjusted HR, 0.83; 95% CI, 0.69-1.00; log-rank $P=.05$) (Figure 2). After multivariable adjustments for baseline conditions, bariatric surgery was associated with reduced number of fatal cardiovascular deaths (adjusted HR, 0.47; 95% CI, 0.29-0.76; $P=.002$) and lower incidence of total cardiovascular events (adjusted HR, 0.67; 95% CI, 0.54-0.83; $P<.001$) (TABLE 1).

Surgery was associated with reduced number of fatal MI (22 deaths in the surgery group vs 37 deaths in the control group; HR, 0.58; 95% CI, 0.34-0.98; log-rank $P=.04$) (eFigure 2). In unadjusted analyses, surgery was not associated with the incidence of total MI cases (122 in the surgery group vs 136 in the control group; HR, 0.88; 95% CI, 0.69-

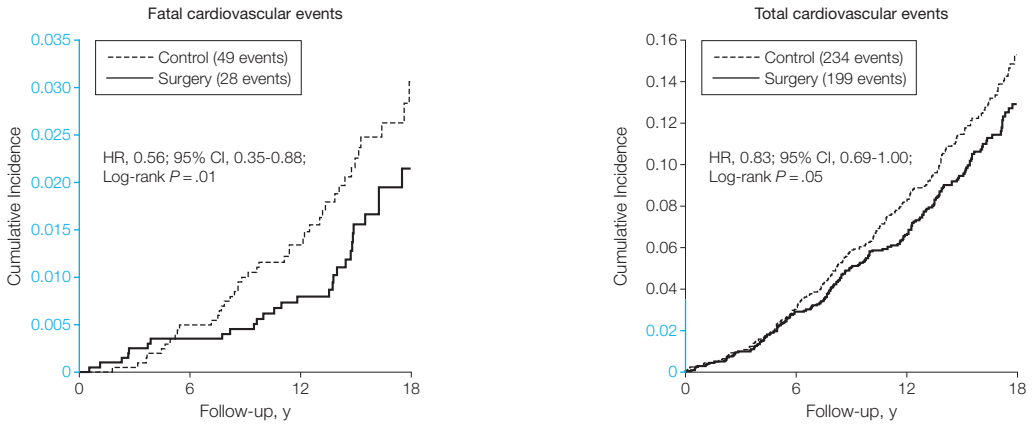
Figure 1. Mean Weight Change Percentages From Baseline for Controls and the 3 Surgery Groups Over 20 Years in the Swedish Obese Subjects Study



No. of patients						
Control	2037	1490	1242	1267	556	176
Banding	376	333	284	284	150	50
Vertical banded gastroplasty	1369	1086	987	1007	489	82
Gastric bypass	265	209	184	180	37	13

Data shown for controls obtaining usual care and for surgery patients obtaining banding, vertical banded gastroplasty, or gastric bypass at baseline. Percentage weight changes from the baseline examination and onward are based on data available on July 1, 2011. Error bars represent 95% CIs.

Figure 2. Kaplan-Meier Unadjusted Cumulative Incidence of Fatal and Total Cardiovascular Events in the Control and Surgery Groups of the Swedish Obese Subjects Study



No. at risk				
Control	2037	1993	1423	405
Surgery	2010	1970	1557	412

No. at risk				
Control	2037	1945	1326	361
Surgery	2010	1921	1468	375

The combined end point of myocardial infarction and stroke, whichever came first, with fatal cardiovascular events and total (fatal and nonfatal) cardiovascular events are shown. The incidence data are based on observations until December 31, 2009. Follow-up time is truncated at 18 years, because number of persons at risk beyond this point was low. All persons are included in the calculation of hazard ratios (HRs). The incidence rates per 1000 person-years for fatal cardiovascular events were 0.9 (95% CI, 0.6-1.3) in the surgery group and 1.7 (95% CI, 1.3-2.2) in the control group; and for total cardiovascular events, 6.9 (95% CI, 6.0-8.0) and 8.3 (95% CI, 7.3-9.4), respectively. Y-axis regions shown in blue indicate range from 0 to 0.035.

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1.12; log-rank $P=.30$) (eFigure 2). However, after multivariable adjustments for baseline conditions, bariatric surgery was related both to reduced fatal MI incidence (HR, 0.52; 95% CI, 0.31-0.89; $P=.02$) and total MI incidence (HR, 0.71; 95% CI, 0.54-0.94; $P=.02$) (Table 1).

In unadjusted analyses, bariatric surgery was not related to fatal stroke incidence (6 events in the surgery group vs 12 events in the control group; HR, 0.49; 95% CI, 0.18-1.30; log-rank $P=.14$) or to total number of stroke events (93 events in the surgery group vs 111 events in the control group; HR, 0.82; 95% CI, 0.62-1.08; log-rank $P=.15$) (eFigure 3). However, after adjustments for baseline conditions, bariatric surgery was associated both with reduced number of fatal stroke events (HR, 0.34; 95% CI, 0.12-1.00; $P=.05$) and total stroke events (HR, 0.66; 95% CI, 0.49-0.90; $P=.008$) (Table 1).

Secondary Subgroup Analyses

In the control group, most classic high-risk subgroups at baseline (eg, men vs women, high vs low triglycerides) had higher incidence of total cardiovascular events compared with the corresponding low-risk subgroups (TABLE 2 and TABLE 3). The only exceptions were high vs low BMI ($P=.49$) and low vs high hip circumference ($P=.24$), in which no differences could be demonstrated (Table 2). The surgical treatment benefit with respect to cardiovascular events was significantly associated with baseline plasma insulin (P for interaction $<.001$), with greater relative treatment benefit in participants with higher insulin (Table 3). The NNT was 21 (95% CI, 12-66) in participants with baseline plasma insulin concentrations above the median (>17.0 mU/L) and 173 (95% CI, 32-∞) in individuals below or at the median (≤17.0 mU/L) insulin concentration (Table 3).

Table 1. Multivariable Cox Proportional Hazards Regression Models for Fatal and Total Cardiovascular End Points in the Swedish Obese Subjects Study[a]

	Cardiovascular Events[b]		MI		Stroke	
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Fatal Cardiovascular End Points						
Surgery, yes vs no	0.47 (0.29-0.76)	.002	0.52 (0.31-0.89)	.02	0.34 (0.12-1.00)	.05
Male sex, yes vs no	3.23 (1.93-5.41)	<.001	3.28 (1.80-5.98)	<.001	3.12 (1.10-8.81)	.03
Age, per 6.1 y	1.48 (1.14-1.91)	.003	1.56 (1.18-2.08)	.002	1.24 (0.68-2.26)	.49
MI or stroke before baseline, yes vs no	3.11 (1.52-6.35)	.002	3.24 (1.47-7.13)	.003	2.09 (0.32-13.8)	.44
Diabetes at baseline, yes vs no[c]	1.44 (1.21-1.73)	<.001	1.38 (1.13-1.68)	.002	1.68 (1.16-2.42)	.006
Smoking at baseline, yes vs no	1.47 (1.19-1.81)	<.001	1.40 (1.11-1.78)	.005	1.76 (1.17-2.65)	.007
Systolic BP, per 18.7 mm Hg	1.18 (0.92-1.51)	.19	1.11 (0.84-1.47)	.47	1.44 (0.88-2.36)	.14
Total cholesterol, per 42.4 mg/dL	1.32 (1.05-1.66)	.02	1.47 (1.15-1.88)	.002	0.90 (0.56-1.45)	.66
HDL cholesterol, per 12.3 mg/dL	1.07 (0.83-1.38)	.60	0.88 (0.64-1.20)	.41	1.81 (1.20-2.72)	.005
Total Cardiovascular End Points						
Surgery, yes vs no	0.67 (0.54-0.83)	<.001	0.71 (0.54-0.94)	.02	0.66 (0.49-0.90)	.008
Male sex, yes vs no	1.78 (1.38-2.29)	<.001	1.91 (1.36-2.67)	<.001	1.49 (1.05-2.12)	.03
Age, per 6.1 y	1.45 (1.30-1.61)	<.001	1.46 (1.27-1.68)	<.001	1.43 (1.21-1.68)	<.001
MI or stroke before baseline, yes vs no	2.83 (1.93-4.16)	<.001	3.64 (2.35-5.63)	<.001	1.51 (0.76-3.03)	.24
Diabetes at baseline, yes vs no[b]	1.71 (1.35-2.18)	<.001	1.73 (1.27-2.36)	.001	1.68 (1.20-2.37)	.003
Insulin, per 12.7 mU/L	1.12 (1.05-1.20)	.001	1.12 (1.04-1.21)	.005	1.04 (0.93-1.17)	.48
Smoking at baseline, yes vs no	1.92 (1.55-2.38)	<.001	2.05 (1.57-2.69)	<.001	1.81 (1.31-2.50)	<.001
BMI, per 4.7 units	1.06 (0.87-1.28)	.57	1.05 (0.81-1.36)	.71	1.02 (0.78-1.33)	.90
Waist circumference, per 11.5 cm	1.11 (0.92-1.35)	.28	1.12 (0.87-1.43)	.39	1.25 (0.95-1.66)	.11
Hip circumference, per 10.2 cm	0.82 (0.69-0.98)	.03	0.84 (0.67-1.04)	.11	0.81 (0.63-1.03)	.09
Systolic BP, per 18.7 mm Hg	1.36 (1.23-1.50)	<.001	1.31 (1.15-1.50)	<.001	1.46 (1.27-1.68)	<.001
Total cholesterol, per 42.4 mg/dL	1.30 (1.17-1.43)	<.001	1.49 (1.32-1.69)	<.001	1.03 (0.89-1.18)	.69
HDL cholesterol, per 12.3 mg/dL	0.94 (0.84-1.06)	.31	0.85 (0.73-0.98)	.03	1.03 (0.87-1.21)	.76
Triglycerides, per 131.2 mg/dL	0.97 (0.88-1.06)	.47	0.95 (0.84-1.06)	.34	0.96 (0.84-1.11)	.60
Lipid-lowering medication, yes vs no	1.52 (0.92-2.53)	.10	2.11 (1.22-3.64)	.008	0.68 (0.22-2.04)	.49
Antihypertensive medication, yes vs no	1.18 (0.95-1.46)	.13	1.03 (0.77-1.36)	.86	1.41 (1.05-1.89)	.02

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; HDL, high-density lipoprotein; MI, myocardial infarction.
SI conversions: To convert total and HDL cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; and insulin to pmol/L, multiply by 6.945.

[a] Hazard ratios for continuous variables are expressed per 1-SD difference at baseline in the study population with men and women combined. For fatal cardiovascular end points, the number of events for surgery and control groups were 28 and 49, respectively, for cardiovascular events; 22 and 37, respectively, for MI; and 6 and 12, respectively, for stroke. For total cardiovascular end points, the number of events for surgery and control groups were 199 and 234, respectively, for cardiovascular events; 122 and 136, respectively, for MI; and 93 and 111, respectively, for stroke.

[b] Cardiovascular events included MI and stroke combined, whichever came first.

[c] Self-reported diabetes medication and/or fasting blood glucose of at least 109.9 mg/dL (corresponding to fasting plasma glucose of ≥126.1 mg/dL).

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In contrast, the surgical treatment benefit with respect to cardiovascular events was not related to baseline BMI (*P* for interaction=.58) (Table 2). The NNT was 52 (95% CI, 20-∞) in participants below or at median BMI (≤40.8) and 81 (95% CI, 24-∞) in individuals above median BMI (>40.8) (Table 2). Similarly no significant risk factor × treatment interactions were observed with respect to waist-hip ratio, waist circumference, hip circumference, or metabolic variables other than insulin (Table 2 and Table 3). The insulin × treatment and BMI × treatment interactions are shown in FIGURE 3.

The association between weight change and the incidence of cardiovascular events was examined separately in the surgery and control

Table 2. Demographic and Anthropometric Risk Factor Treatment Interaction Analyses in the Swedish Obese Subjects Study

	Incidence of Cardiovascular Events, IR per 1000 Person-Years[a]							Relative Treatment Effects			
	Surgery			Control							
Risk Factors, Subgrouping at Baseline	No.	Person-Years	IR (95% CI)	No.	Person-Years	IR (95% CI)	Log-rank *P* Value[b]	HR (95% CI)[c]	*P* Value[c]	*P* for Interaction[d]	Number Needed to Treat (95% CI)[e]
Total	2010	28 695	6.9 (6.0-8.0)	2037	28 350	8.3 (7.3-9.4)		0.83 (0.69-1.00)	.05		50 (24-∞)
Sex											
Men	590	8052	12.2 (10.0-14.8)	590	7980	14.4 (12.0-17.3)	<.001	0.85 (0.65-1.11)	.22	.92	28 (12-∞)
Women	1420	20 643	4.9 (4.0-5.9)	1447	20 370	5.8 (4.9-7.0)		0.82 (0.63-1.07)	.15		83 (30-∞)
Age, y											
≤47.8	1106	16 123	4.8 (3.8-6.0)	919	13 417	5.1 (4.1-6.5)	<.001	0.92 (0.67-1.28)	.63	.76	161 (32-∞)
>47.8	904	12 573	9.7 (8.1-11.6)	1118	14 933	11.0 (9.5-12.9)		0.86 (0.68-1.09)	.22		46 (18-∞)
Systolic BP, mm Hg											
≤140	1014	14 467	3.9 (3.0-5.1)	1308	18 337	6.3 (5.2-7.5)	<.001	0.63 (0.46-0.86)	.004	.31	25 (16-61)
>140	991	14 159	10.0 (8.4-11.7)	725	9943	12.0 (10.0-14.3)		0.82 (0.64-1.04)	.10		46 (17-∞)
Diastolic BP, mm Hg											
≤88	830	11 735	4.0 (3.0-5.3)	1225	16 886	6.3 (5.2-7.6)	<.001	0.63 (0.45-0.89)	.008	.71	24 (15-55)
>88	1174	16 895	8.9 (7.6-10.4)	805	11 352	11.3 (9.5-13.4)		0.78 (0.62-0.99)	.04		39 (17-∞)
Smoking											
No	1490	21 498	6.2 (5.3-7.4)	1605	22 538	6.8 (5.8-8.0)	<.001	0.9 (0.72-1.14)	.39	.10	127 (33-∞)
Yes	518	7172	9.1 (7.1-11.6)	422	5691	13.9 (11.1-17.3)		0.65 (0.47-0.90)	.009		14 (8-53)
Diabetes[f]											
No	1658	23 902	5.7 (4.8-6.7)	1771	25 035	6.7 (5.8-7.8)	<.001	0.84 (0.67-1.06)	.14	.20	64 (28-∞)
Yes	345	4715	13.4 (10.4-17.1)	262	3266	19.9 (15.6-25.4)		0.63 (0.45-0.90)	.01		12 (6-127)
Previous MI or stroke											
No	1964	28 189	6.6 (5.7-7.6)	1988	27 832	7.7 (6.8-8.8)	<.001	0.84 (0.69-1.02)	.08	.71	55 (26-∞)
Yes	46	506	27.7 (16.4-46.7)	49	519	36.6 (23.4-57.4)		0.79 (0.40-1.56)	.49		13 (3-∞)
BMI											
≤40.8	795	11 318	7.9 (6.4-9.7)	1229	17 205	8.6 (7.3-10.1)	.49	0.91 (0.70-1.18)	.48	.58	52 (20-∞)
>40.8	1215	17 377	6.3 (5.3-7.6)	808	11 145	7.7 (6.2-9.5)		0.8 (0.60-1.06)	.12		81 (24-∞)
Body weight, kg											
≤116	885	12 726	6.3 (5.0-7.8)	1165	16 446	7.4 (6.2-8.8)	.04	0.85 (0.64-1.13)	.26	.96	64 (23-∞)
>116	1125	15 969	7.5 (6.2-8.9)	872	11 904	9.5 (7.9-11.4)		0.77 (0.59-0.99)	.04		33 (16-∞)
Waist-hip ratio											
≤0.985	939	13 767	4.0 (3.1-5.2)	1083	15 486	5.2 (4.2-6.5)	<.001	0.75 (0.53-1.06)	.10	.73	61 (25-∞)
>0.985	1065	14 840	9.6 (8.2-11.4)	954	12 864	11.9 (10.2-13.9)		0.8 (0.64-1.00)	.06		28 (14-1272)
Waist circumference, cm											
≤122	812	11 829	5.6 (4.4-7.1)	1213	17 135	6.8 (5.7-8.2)	.001	0.81 (0.60-1.09)	.17	.86	45 (20-∞)
>122	1193	16 798	7.9 (6.6-9.3)	824	11 215	10.4 (8.7-12.5)		0.74 (0.57-0.94)	.02		29 (15-1276)
Hip circumference, cm											
≤124	853	12 182	8.0 (6.6-9.8)	1198	16 701	8.8 (7.5-10.3)	.24	0.9 (0.70-1.17)	.44	.38	50 (20-∞)
>124	1151	16 424	6.1 (5.0-7.4)	839	11 649	7.5 (6.1-9.2)		0.8 (0.60-1.07)	.13		86 (25-∞)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; HR, hazard ratio; IR, incidence rate; MI, myocardial infarction.

[a] Acute MI and stroke combined in high-risk and low-risk subgroups. For continuous variables, subgrouping is based on median baseline values.

[b] Difference in IR between high-risk and low-risk subgroups among the control group only.

[c] HR and *P* value for treatment effect in surgery vs control subjects of indicated subgroup.

[d] For each continuous variable, the test of interaction was calculated using the original continuous variable. Dichotomous variables could have 1 of 2 values (eg, men vs women; diabetes, yes vs no). The interaction *P* value reflects difference in relative treatment effect between indicated high-risk and low-risk subgroups.

[e] Number of patients who needed to be operated on to prevent 1 cardiovascular event over 15 years. No significant difference in any of the subgroups with respect to number of individuals needed to operate on to prevent 1 cardiovascular event.

[f] Self-reported diabetes medication and/or fasting blood glucose of at least 109.9 mg/dL (corresponding to fasting plasma glucose of ≥126.1 mg/dL).

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groups. In the control group, unadjusted calculations suggested that weight loss during the first 2 years was related to increased cardiovascular events from year 4 and onward ($P=.046$), but after adjustments for baseline conditions, no significant relationships remained ($P=.79$) (eTable 3). In the surgery group, no significant unadjusted ($P=.09$) or adjusted ($P=.28$) relationships between weight change and cardiovascular events could be demonstrated (eTable 3).

Adverse Events

Within 90 days from the start of the study, 5 of 2010 patients (0.2%) in the surgery group and 2 of 2037 patients (0.1%) in the control group had died. As reported elsewhere for 1164 patients having surgery,[24] 151 (13%) had 193 postoperative complications.

COMMENT

In this nonrandomized, controlled, prospective, matched intervention study, bariatric surgery was associated with reduced incidence of fatal and total cardiovascular events, MI, and stroke after adjustment for baseline conditions. In post hoc analyses, a higher baseline insulin concentration was associated with a more favorable outcome of bariatric surgery on cardiovascular events, while no significant interactions could be demonstrated for BMI or other metabolic and anthropometric variables.

The increased incidence of cardiovascular events after nonsurgically induced weight loss in observational studies[7-10,12,13] has often been explained by unintentional weight loss, the presence of illness associated with weight loss, or both. However, the few controlled, prospective lifestyle interventions that have been performed in obese individuals have all failed to show favorable effects on primary cardiovascular outcomes.[15-18] Negative results of nonsurgically

Table 3. Metabolic Risk Factor Treatment Interaction Analyses in the Swedish Obese Subjects Study

	Incidence of Cardiovascular Events, IR per 1000 Person-Years[a]							Relative Treatment Effects			
	Surgery			Control							
Risk Factors, Subgrouping at Baseline	No.	Person-Years	IR (95% CI)	No.	Person-Years	IR (95% CI)	Log-rank *P* Value[b]	HR (95% CI)[c]	*P* Value[c]	*P* for Interaction[d]	Number Needed to Treat (95% CI)[e]
Triglycerides, mg/dL											
≤160	904	13 028	5.1 (4.0-6.4)	1119	15 722	5.6 (4.5-6.9)	<.001	0.89 (0.64-1.22)	.46	.93	95 (28-∞)
>160	1102	15 609	8.5 (7.1-10.0)	916	12 606	11.6 (9.8-13.6)		0.73 (0.57-0.92)	.007		23 (13-107)
HDL cholesterol, mg/dL											
≤51	1003	14 376	7.4 (6.1-8.9)	1005	14 006	9.7 (8.2-11.5)	.002	0.75 (0.58-0.97)	.03	.26	32 (16-4631)
>51	920	13 035	5.9 (4.7-7.4)	972	13 536	6.3 (5.1-7.8)		0.93 (0.68-1.26)	.62		142 (29-∞)
Total cholesterol, mg/dL											
≤219	910	12 793	5.0 (3.9-6.4)	1121	15 452	5.5 (4.4-6.8)	<.001	0.9 (0.65-1.24)	.52	.28	210 (33-∞)
>219	1096	15 843	8.5 (7.1-10.0)	914	12 877	11.6 (9.9-13.6)		0.73 (0.57-0.92)	.007		22 (13-75)
Apo B/Apo A-I ratio											
≤0.901	940	13 803	5.0 (3.9-6.3)	1066	15 264	5.8 (4.7-7.1)	<.001	0.85 (0.62-1.16)	.31	.23	74 (26-∞)
>0.901	1051	14 616	8.8 (7.4-10.5)	954	12 867	11.2 (9.5-13.2)		0.78 (0.62-0.99)	.04		30 (15-4095)
Blood glucose, mg/dL											
≤81	931	13 389	5.6 (4.5-7.0)	1091	15 469	5.7 (4.6-7.0)	<.001	0.98 (0.72-1.33)	.89	.13	150 (31-∞)
>81	1071	15 218	8.1 (6.8-9.7)	942	12 832	11.3 (9.6-13.3)		0.71 (0.56-0.90)	.005		25 (13-139)
Plasma insulin, mU/L											
≤17.0	867	12 445	5.2 (4.1-6.7)	1154	16 158	5.6 (4.5-6.8)	<.001	0.93 (0.67-1.28)	.64	<.001	173 (32-∞)
>17.0	1134	16 136	8.2 (6.9-9.7)	880	12 161	11.7 (9.9-13.8)		0.69 (0.54-0.87)	.002		21 (12-66)
Metabolic syndrome[f]											
No	591	8477	4.0 (2.9-5.6)	850	11 944	4.9 (3.8-6.3)	<.001	0.81 (0.53-1.24)	.33	.73	103 (27-∞)
Yes	1397	19 900	8.2 (7.0-9.6)	1170	16 159	10.8 (9.3-12.6)		0.75 (0.60-0.93)	.008		25 (14-94)
SCORE[g]											
≤0.85	1011	14 855	2.9 (2.1-3.9)	999	14 421	3.3 (2.5-4.4)	<.001	0.85 (0.56-1.28)	.44	.86	125 (36-∞)
>0.85	987	13 678	11.3 (9.6-13.2)	1022	13 716	13.4 (11.6-15.5)		0.83 (0.67-1.03)	.09		33 (15-∞)

Abbreviations: Apo, apolipoprotein; HDL, high-density lipoprotein; HR, hazard ratio; IR, incidence rate.

SI conversions: To convert triglycerides to mmol/L, multiply by 0.0113; total and HDL cholesterol to mmol/L, multiply by 0.0259; blood glucose to mmol/L, multiply by 0.0555; and plasma insulin to pmol/L, multiply by 6.945.

[a] Acute myocardial infarction and stroke combined in high-risk and low-risk subgroups. For continuous variables, subgrouping is based on median baseline values.

[b] Difference in IR between high-risk and low-risk subgroups among the control group only.

[c] HR and *P* value for treatment effect in surgery vs control subjects of indicated subgroup.

[d] For each continuous variable, the test of interaction was calculated using the original continuous variable. Dichotomous variables could have 1 of 2 values (eg, men vs women; diabetes, yes vs no). The interaction *P* value reflects difference in relative treatment effect between indicated high-risk and low-risk subgroups.

[e] Number of patients who needed to be operated on to prevent 1 cardiovascular event over 15 years. No significant difference in any of the subgroups with respect to number of individuals needed to operate on to prevent 1 cardiovascular event.

[f] Components of IDF 2009 criteria (≥3 of the following cutoffs: waist circumference, glucose, triglycerides, HDL cholesterol, blood pressure).[34]

[g] Estimated 10-year risk of fatal cardiovascular disease according to the European SCORE project.[35]

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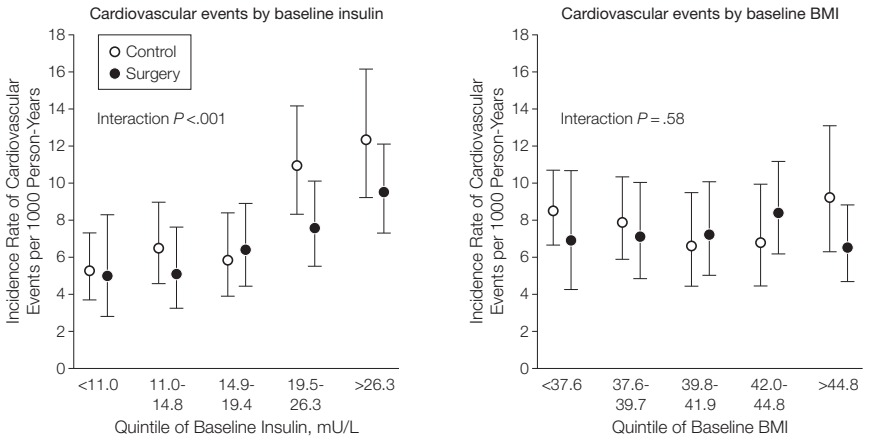
induced weight loss were unanticipated because modest weight loss (5-10 kg) typically improves cardiovascular risk factors over 1 to 4 years.[3,4,6,34,35] However, cardiovascular events are the consequence of progressive vascular disease that develops over time. The SOS study has shown that risk factor improvement over 10 years requires sustained and very large (10-40 kg) weight loss[36] that typically cannot be achieved with lifestyle intervention.

Bariatric surgery prevents cardiovascular events, as demonstrated by our prospective, controlled outcomes. Our results confirm in a prospectively studied group of patients that were matched on 18 variables what was suggested in prior retrospective bariatric surgery studies. The cardiovascular morbidity and mortality study by Christou et al[19] compared 1305 patients with bariatric surgery with 5746 matched controls over up to 5 years. The HR was 0.18 (95% CI, 0.12-0.22) in favor of surgery. Similarly, in a cardiovascular mortality analysis by Adams et al,[20] which compared 7925 patients with bariatric surgery with the same number of matched controls, the HR calculated over 7 years was 0.51 (95% CI, 0.36-0.73). Our observed HR of the cardiovascular benefit from bariatric surgery of 0.67 (95% CI, 0.54-0.83) probably reflects better matching between surgery and control groups than what was possible in these prior studies. To our knowledge, no other controlled prospective bariatric surgery interventions are available for comparison.

Given the known association between obesity and cardiovascular disease, intuition would have predicted that the reduced incidence of cardiovascular events would be related to weight loss. However, in the surgery group of the SOS study, we were unable to detect a significant association between weight loss and cardiovascular events. The lack of association between weight loss and reduction of cardiovascular events in our study could be related to inadequate statistical power to detect this relationship. Alternatively, following relatively modest weight loss induced by bariatric surgery, there is no further risk reduction attributable to greater, subsequent weight loss. Our negative findings also emphasize the need to explore weight loss independent effects of bariatric surgery.[37]

Figure 3. Age and Sex Standardized Incidence Rates of Cardiovascular Events per 1000 Person-Years by Treatment Group and by Quintiles of Baseline Insulin Concentrations and Baseline BMI in the Swedish Obese Subjects Study



Cardiovascular events include fatal and nonfatal myocardial infarction and stroke events combined. Error bars represent 95% CIs. BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared). For the 5 quintiles (<11.0, 11.0-14.8, 14.9-19.4, 19.5-26.3, and >26.3 mU/L) of interaction between control and surgery groups for baseline insulin, the mean values were 8.3, 12.9, 17.0, 22.6, and 38.0 mU/L, respectively. To convert insulin to pmol/L, multiply by 6.945. For the 5 quintiles (<37.6, 37.6-39.7, 39.8-41.9, 42.0-44.8, and >44.8) of interaction between control and surgery groups for baseline BMI, the mean values were 35.3, 38.7, 40.8, 43.1, and 48.3, respectively.

When the relationship between baseline characteristics and the surgical treatment benefit were examined, there was no BMI × treatment interaction with respect to cardiovascular events (*P* for interaction = .58). We have shown the lack of a BMI × surgical treatment interaction also for overall mortality (*P* for interaction = .60)[23] and cancer (*P* = .90).[24] Taken together these post hoc findings may demonstrate that among the obese a higher baseline BMI is not associated with a greater health benefit of bariatric surgery. The benefit of bariatric surgery in obese individuals with higher and lower BMIs has not previously been examined in studies other than the SOS study, in spite of the widespread use of BMI as the main criterion for eligibility for bariatric surgery in guidelines and position statements.[25-28]

Our current post hoc results may also suggest that high insulin may be a better selection criterion for bariatric surgery than high BMI, as far as cardiovascular events are concerned. However, before insulin can be generally recommended as a predictor of treatment success, the relationships between baseline insulin and other end points, including overall mortality, diabetes, and cancer, need to be documented.

In the SOS study, obese men and women of white race with or without diabetes, previous MI, stroke, and cancer were recruited from all over Sweden, making it likely that our results are generalizable for middle-aged obese individuals in most western countries. Ideally, our post hoc findings on relative and absolute treatment benefits should be confirmed by prospective controlled trials specifically designed to study treatment effects on predefined end points, such as well-documented cardiovascular events or death in high-risk subgroups specified at baseline. It may well take at least 10 years to obtain such results, and meanwhile, clinical decisions must be based on best evidence available.

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The main limitation of the SOS study is that the intervention was not randomized, and this was due to the high postoperative mortality in the 1980s.[38] At baseline, the prevalence of previous cardiovascular events was not significantly different in the surgery and control groups but several risk factors were less favorable in the surgery group. Nevertheless, the subsequent adjusted cardiovascular event incidence was lowest in the surgery group.

In conclusion, this is the first prospective, controlled intervention to our knowledge reporting that bariatric surgery is associated with reduced incidence of cardiovascular deaths and cardiovascular events. These results—together with our previously reported associations between bariatric surgery and favorable outcomes regarding long-term changes of body weight,[5] cardiovascular risk factors,[5] quality of life,[39] diabetes,[5] cancer,[24] and mortality[23]—demonstrate that there are many benefits to bariatric surgery and that some of these benefits are independent of the degree of the surgically induced weight loss.

Author Contributions: Dr Peltonen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Study supervision: L. Sjöström, Karason, Dahlgren, L. Carlsson.
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The test of real and vigorous thinking, the thinking which ascertains truths instead of dreaming dreams, is successful application to practice.

—John Stuart Mill (1806-1873)

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