Review

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Review of the key results from the Swedish Obese Subjects (SOS) trial – a prospective controlled intervention study of bariatric surgery

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Abstract. L. Sjöström (The Sahlgrenska Academy, The University of Gothenburg, Gothenburg, Sweden). Review of the key results from the Swedish Obese Subjects (SOS) trial – a prospective controlled intervention study of bariatric surgery (Review). *J Intern Med* 2013; **273**: 219–234.

Obesity is a risk factor for diabetes, cardiovascular disease events, cancer and overall mortality. Weight loss may protect against these conditions, but robust evidence for this has been lacking. The Swedish Obese Subjects (SOS) study is the first long-term, prospective, controlled trial to provide information on the effects of bariatric surgery on the incidence of these objective endpoints. The SOS study involved 2010 obese subjects who underwent bariatric surgery [gastric bypass (13%), banding (19%) and vertical banded gastroplasty (68%)] and 2037 contemporaneously matched obese control subjects receiving usual care. The age of participants was 37–60 years and body mass index (BMI) was ≥ 34 kg m^{-2} in men and ≥ 38 kg m^{-2} in women. Here, we review the key SOS study results published between 2004 and 2012. Follow-up periods varied from 10 to 20 years in different reports. 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 respectively. Compared with usual care, bariatric surgery was associated with a long-term reduction in overall mortality (primary endpoint) [adjusted hazard ratio (HR) = 0.71, 95% confidence interval (CI) 0.54–0.92; $P = 0.01$] and decreased incidences of diabetes (adjusted HR=0.17; $P < 0.001$), myocardial infarction (adjusted HR = 0.71; $P = 0.02$), stroke (adjusted HR=0.66; $P = 0.008$) and cancer (women: adjusted HR = 0.58; $P = 0.0008$; men: n.s.]. The diabetes remission rate was increased severalfold at 2 years [adjusted odds ratio (OR) = 8.42; $P < 0.001$] and 10 years (adjusted OR = 3.45; $P < 0.001$). Whereas high insulin and/or high glucose at baseline predicted favourable treatment effects, high baseline BMI did not, indicating that current selection criteria for bariatric surgery need to be revised.

Keywords: bariatric surgery, incidence of diabetes, mortality, myocardial infarction, obesity, stroke and cancer.

Introduction

The prevalence of obesity (body mass index (BMI) $\geq$ 30 kg m^{-2}) in the USA increased markedly between 1980 and 2004 [1], and in 2009–2010 the age-adjusted prevalence of obesity was 35.5% in adult men and 35.8% in adult women [2]. Forecasts for the prevalence of adult obesity in 2030 have varied between 42% [3] and 51% [4] depending on the model used. In fact, the prevalence of obesity has increased in most parts of the world over the last 20–30 years [5]. The findings from the majority of large and long-term epidemiological studies indicate that being overweight or obese is associated with increased mortality [6–8]; the lifespan of severely obese individuals is decreased by an estimated 5 to 20 years depending on gender, age and race [8, 9].

Weight loss is known to be associated with improvement of intermediate risk factors for disease [10–13], suggesting that weight loss would also reduce mortality. However, with the exception of the Swedish Obese Subjects (SOS) trial, controlled intervention studies demonstrating that weight loss in fact reduces mortality have been lacking. To date, most observational epidemiological studies have indicated that overall and cardiovascular disease mortality are increased after weight loss [14–19], even in subjects who were

overweight or obese at baseline [17, 20]. This discrepancy concerning the effects of weight loss on risk factors as compared with mortality has been related to certain limitations inherent to 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. Three observational epidemiological studies [21–23], all based on data from the American Cancer Society, have suggested that self-reported intentional weight loss is indeed associated with decreased mortality. However, the results of two other studies of intentional weight loss have suggested the opposite [24, 25]. It should be noted that intentionality in the American Cancer Society studies was based on retrospective, self-reported data collected at baseline. The results of all five studies [21–25] might be confounded by inclusion of participants with unintentional weight loss.

Lifestyle interventions to prevent diabetes have not prevented cardiovascular disease events after 10–20 years of follow-up [26, 27]. Similarly, lifestyle interventions combined with antiobesity medications have either shown no effect on primary cardiovascular disease endpoints [28] or an increased incidence in the drug-treated group [29]. Taken together, trials of nonsurgical weight loss in obese participants have failed to demonstrate a benefit in terms of reduced mortality or decreased cardiovascular disease event rates [26–29].

The results of retrospective cohort studies in obese subjects without [30–32] and with diabetes [33] have suggested that bariatric surgery may result in a marked reduction in mortality. As discussed below, these retrospective results are in agreement with the prospective results from the SOS study.

SOS is an ongoing intervention study designed to offer controlled prospective long-term conditions [34] to investigate the effects of bariatric surgery and weight loss on mortality [35] and other objective endpoints [12, 36–38]. This review is focusing on key results. A more detailed review will appear separately [39].

The SOS study

Study aims

The primary aim of the SOS study was to examine whether (i) bariatric surgery and (ii) weight loss induced by bariatric surgery are associated with lower mortality compared with the death rates during conventional treatment in contemporaneously matched, obese control subjects. Predefined secondary aims included the effects of bariatric surgery and weight loss on cardiovascular disease (myocardial infarction, stroke, claudication, angina pectoris and hypertension), diabetes, biliary disease, health-related quality of life and cost efficiency.

Substudies

To date (as of Oct. 2012), 92 peer-reviewed reports from the ongoing SOS study have been published. The overall study consists of four substudies:

- The SOS matching study (n = 6905) was an one-off examination from which patients were recruited into the intervention study.
- The SOS intervention study includes a surgery group (n = 2010) and a control group of nonsurgically treated obese subjects (n = 2037).
- The SOS reference study (n = 1135) was a small substudy of randomly selected subjects from the general population examined at the same time and in the same way as subjects in the matching and intervention studies.
- The SOS sib-pair study (n = 768) investigated weight-discordant siblings and their biological parents.

Design of the SOS matching and intervention studies

The SOS matching study

After recruitment campaigns in the media and at 480 primary health care centres, an one-off matching examination was performed in 6905 patients, 5335 of whom were found to be eligible for study participation [34, 37]. Of these, 2010 individuals electing surgery constituted the surgery group, and a control group (n = 2037) was created using 18 matching variables: gender, age, weight, height, waist and hip circumferences, systolic blood pressure, serum cholesterol and triglyceride levels, smoking status, diabetes, menopausal status, four psychosocial variables with documented associations with the risk of death and two personality traits related to treatment preferences. Although individual patients in the surgery group and their conventionally treated controls always started the study on the

day of first bariatric surgery, matching was not performed at an individual level. Instead the matching algorithm selected controls so that the mean values of the matching variables in the control group were kept as similar as possible to the mean values in the surgery group according to the method of sequential treatment assignment [40].

The SOS intervention study

The SOS intervention trial [12, 34–38] is a prospective, matched, surgical intervention study involving 4047 obese subjects. Patients were recruited through the matching examination between 1 September 1987 and 31 January 2001 (13.4 years recruitment period). To date (Oct. 2012), the follow-up duration is 12–25 years.

A baseline examination of the surgical subjects and their matched controls was undertaken 4 weeks before surgery. The intervention began on the day of surgery (index date) for surgically treated subjects and their matched controls. Dates of all subsequent examinations and questionnaires (at 0.5, 1, 2, 3, 4, 6, 8, 10, 15 and 20 years) for surgically treated and control subjects were calculated based on the index date. Inclusion criteria for the intervention study were age 37–60 years and BMI ≥ 34 kg m^{-2} for men and ≥ 38 kg m^{-2} for women. These lower BMI cut-off values corresponded to an approximate doubling in mortality rate for each gender compared with mortality in the BMI range 20–25 kg m^{-2} [41]. The exclusion criteria, which were identical for both study arms, were previous surgery for gastric or duodenal ulcer, previous bariatric surgery, gastric ulcer during the past 6 months, ongoing malignancy, active malignancy during the past 5 years, myocardial infarction during the past 6 months, bulimic eating pattern, drug or alcohol (>33.9 g alcohol per day) abuse, psychiatric or cooperation problems contraindicating bariatric surgery and other contraindicating conditions such as continuous glucocorticoid or anti-inflammatory treatment.

The matching and baseline examinations as well as all later follow-up examinations were performed at 480 primary health care centres and 25 surgical departments in Sweden. At each examination, measurements of weight, height, waist circumference, other anthropometric measures (see Table 1) and blood pressure were obtained [37]. Biochemical variables (see Table 1) were measured at the matching examination, at the baseline examination (year 0 of the intervention study) and at 2, 10, 15 and 20 years. Blood samples were obtained in the morning after a 10- to 12-h fast and analysed at the Central Laboratory of Sahlgrenska University Hospital (accredited according to European Norm 45001). The baseline questionnaire included questions to provide self-reported information on previous myocardial infarction, stroke and cancer, as well as questions designed to assess the likelihood of sleep apnoea [42]. Psychosocial variables were also evaluated [43].

Treatments. The surgically treated subjects underwent nonadjustable or adjustable banding ($n = 376$), vertical banded gastroplasty (VBG; $n = 1369$) or gastric bypass (GBP; $n = 265$) operations [44]. The matched controls received the standard nonsurgical obesity treatment for their primary health care centres. No attempt was made to standardize the conventional treatment, which ranged from sophisticated lifestyle intervention and behaviour modification to, in many practices, no treatment at all.

Cross-checking. All social security numbers from the SOS database were cross-checked against the Swedish Person and Address Register (SPAR) every year on 1 November. On several occasions, the SOS database has also been cross-checked against the Swedish Social Insurance System, Statistics Sweden and the Swedish Hospital Discharge Register to obtain objective data on sick leave, disability pension, hospital care and annual income.

SPAR provides current addresses of living participants and information on all deceased persons. Social security numbers of all deceased subjects were cross-checked against the Swedish Cause of Death Register to obtain the official cause of death.

The statistical procedures in the SOS study have previously been described in detail [12, 35–38]. In brief, the methods used for statistical analyses included t test, Fisher's exact test, Kaplan–Meier estimates of cumulative incidence, log-rank test and univariable and multivariable Cox proportional hazards regression models. Subgroup–treatment interactions were calculated for original continuous variables and for dichotomous variables. The expected number of surgeries needed to prevent one event over 10 or 15 years (numbers needed to treat) was calculated as the reciprocal of the absolute risk difference (obtained from Kaplan–Meier estimates over 10 or 15 years) between

Table 1 *Selected characteristics of the surgically treated and control patients at the matching and baseline examinations of the Swedish Obese Subjects (SOS) study*

	Matching examination					Baseline examination				
	Surgery		Control			Surgery		Control		
Variable	Mean (SD) or % (*n*)	Missing *n*	Mean (SD) or % (*n*)	Missing *n*	*P*-value	Mean (SD) or % (*n*)	Missing *n*	Mean (SD) or % (*n*)	Missing *n*	*P*-value
Total, *n*	2010	0	2037			2010		2037		
Males*,% (*n*)	29.4 (590)	0	29.0 (590)	0	0.81	29.4 (590)	0	29.0 (590)	0	0.81
Females*,% (*n*)	70.6 (1420)	0	71.0 (1447)	0		70.6 (1420)	0	71.0 (1447)	0	
Postmenopausal women*,% (*n*)	31.8 (452)	0	35.5 (513)	0	0.04	37.2 (525)	7	41.3 (594)	8	0.03
Age at examination*, years	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*,% (*n*)	27.9 (560)	0	20.2 (412)	0	<0.001	25.8 (518)	2	20.8 (422)	10	<0.001
Diabetes*,% (n)	7.4 (148)	0	6.1 (125)	0	0.13	10.7 (215)	5	11.4 (230)	12	0.55
Previous MI,% (*n*)	1.4 (29)	0	1.1 (22)	0	0.33	1.5 (31)	0	1.4 (29)	0	0.80
Previous stroke,% (*n*)	0.7 (15)	0	0.9 (19)	0	0.61	0.7 (15)	0	1.1 (23)	0	0.25
Previous cancer,% (*n*)	1.1 (23)	0	1.0 (20)	0	0.65	1.2 (25)	0	1.1 (22)	0	0.66
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	168.9 (9.1)	0	169.0 (9.2)	0	0.68	168.9 (9.1)	0	169.0 (9.2)	0	0.64
BMI, kg/m^2	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 circumference*, cm	124.1 (10.7)	1	122.2 (10.1)	0	<0.001	125.8 (11.0)	5	120.2 (11.3)	0	<0.001
Hip circumference*, cm	125.9 (9.7)	1	124.4 (9.3)	1	<0.001	127.1 (10.0)	6	123.2 (9.9)	0	<0.001
Waist/hip ratio	1.0 (0.1)	1	1.0 (0.1)	1	0.17	1.0 (0.1)	6	1.0 (0.1)	0	<0.001
Systolic blood pressure*, mmHg	140.6 (18.7)	2	140.0 (18.0)	0	0.24	145.0 (18.8)	5	137.9 (18.0)	4	<0.001
Diastolic blood pressure, mmHg	87.5 (11.2)	3	87.1 (10.7)	3	0.31	89.9 (11.1)	6	85.1 (10.7)	7	<0.001
Glucose, mg/dL	91.1 (33.9)	0	91.1 (34.3)	1	0.99	93.3 (36.2)	8	89.0 (32.8)	4	<0.001

Table 1 (*Continued*)

Variable	Matching examination				Baseline examination			
	Surgery		Control		Surgery		Control	
	Mean (SD) or % (*n*)	Missing *n*	Mean (SD) or % (*n*)	Missing *n*	*P*-value	Mean (SD) or % (*n*)	Missing *n*	Mean (SD) or % (*n*)	Missing *n*	*P*-value
Insulin, mU/L	21.4 (14.4)	6	20.0 (12.6)	1	0.002	21.5 (13.7)	9	18.0 (11.4)	3	<0.001
Triglycerides*, mg/dL	196.9 (127.4)	2	189.9 (132.8)	0	0.09	199.3 (136.6)	4	178.6 (125.0)	2	<0.001
Total cholesterol*, mg/dL	225.7 (43.3)	2	221.8 (41.6)	0	0.004	226.2 (43.4)	4	216.7 (40.8)	2	<0.001
HDL cholesterol, mg dL^{-1}	52.4 (12.5)	69	52.4 (13.4)	37	0.87	52.2 (12.3)	87	52.1 (12.7)	60	0.84

*Indicates matching variable. To convert conventional units to SI units, multiply the conventional units in the table by 0.0259 for total and HDL cholesterol to convert to mmol L^{-1}; by 0.0113 for triglycerides to convert to mmol L^{-1}; by 0.0555 for glucose to convert to mmol L^{-1} and by 6.945 for insulin to convert to pmol L^{-1}.
From Sjöström L *et al.* JAMA 2012 [37].

individuals in the surgery and control groups. All *P*-values are two-sided and $P < 0.05$ was considered statistically significant. If not stated otherwise, the intention-to-treat principle was applied.

Design of the SOS reference study

The SOS reference study is a cross-sectional study of randomly selected individuals. The main purpose was to create a reference sample for the obese SOS subjects for genetic association studies and comparative analyses of clinical conditions.

Between August 1994 and December 1999, i.e. during the period when the majority of patients were included in the SOS intervention study, 524 men and 611 women were included in the SOS reference study. Body composition and biochemical characteristics of the SOS reference study participants have been reported previously [45–48]. Results from the SOS reference study will not be further discussed in this review.

Design of the SOS sib-pair study

The SOS sib-pair study consists of nuclear families established via a pair of adult BMI-discordant siblings. Discordance was defined as a BMI difference of at least 10 kg m^{-2}. Minimum BMI in the obese sibling was 32 kg m^{-2}. The primary aim of the sib-pair study was to conduct positional cloning.

A total of 159 nuclear families with between four and 10 members were recruited, resulting in a study population of 768 subjects, including 231 obesity-discordant sib-pairs. The SOS reference and sib-pair studies (in combination with Very Low Calorie Diet studies) have resulted in the publication of 22 genetic reports to date (Oct. 2012), which will not be further discussed in this review.

Baseline characteristics of participants in the SOS intervention study

The matching procedure created a control group that was on average 2.3 kg lighter ($P < 0.001$) and 1.3 years older ($P < 0.001$) than the surgery group (Table 1) [37]. The higher body weight of patients in the surgery group was associated with significantly higher values of several anthropometric measurements and some biochemical variables [37]. In addition, smoking was more common in the surgery group ($P < 0.001$). The matching procedure was mathematically optimized using the method of

sequential treatment assignment [40]; however, through real-life experience of the matching procedure we found that the heaviest patients tended to chose surgery, thus leaving a lighter group of subjects (potential controls; $n = 3325$) from which to select the control group ($n = 2037$). A better match would have required a severalfold larger group of potential controls, but this was not possible with the available resources in our academically driven study. A randomized design was not approved for ethical reasons because of a high postoperative mortality rate in the 1980s [49]. In a randomized study, the surgery and control groups would probably have been more similar but the dropout rate from physical examinations might have been even larger than in the current SOS study (see below) due to a large number of unsatisfied control subjects requesting surgery.

Between the matching and baseline examinations, there was an increase in body weight in the surgically treated patients (1.73 kg; $P < 0.001$) and a decrease in weight in the control group (2.23 kg; $P < 0.001$). These diverging weight changes caused a weight difference of 6.3 kg between the surgery and control groups at baseline, and most baseline risk factors were significantly increased in the surgery group (Table 1) [37]. However, it should be noted that with approximately 2000 subjects per group small differences become statistically significant and from a clinical point of view the differences were modest. Furthermore, most observed baseline differences were related to the higher body weight in the surgery group and increased risk factors constituted disadvantages for the surgery group in univariate analyses of mortality [35] and cardiovascular disease events [37]. Thus, the favourable outcomes of surgery described below were seen in spite of, not due to, the more unfavourable risk factor pattern in the surgery group at baseline.

Follow-up rates

In study analyses based on cross-checking of the SOS database with the Swedish Mortality Register and the Swedish Hospital Discharge Register, follow-up rates of more than 99% have been reported [35–37]. By contrast, the follow-up rates for physical and laboratory examinations are much lower. Levels of diabetes prevention [12, 38] and remission [12] are influenced by these lower follow-up rates. For instance, in a recent investigation of diabetes prevention in 1658 surgical patients and 1771 obese controls without diabetes at baseline, the overall participation rates at 2 and 10 years were 87.1% and 68.8% respectively [38]. Based on data from 1 January 2012, the participation rate at 15 years was only 32.0%. However, this low figure was partly explained by the fact that 30.9% of the original participants were not eligible because they had not yet reached the time for their 15-year examination. Various sensitivity and imputation analyses have indicated that the 10- and 15-year SOS data on diabetes prevention are valid in spite of the limited participation rate [38].

Weight changes

Figure 1 shows the weight changes over 20 years for the control and surgery subgroups of the SOS intervention study [37]. In the control group, the average weight change remained within ±3% over the entire observation period. In the three surgery subgroups, mean (±SD) weight loss was maximal after 1–2 years (GBP 32 ± 8%, VBG 25 ± 9% and banding 20 ± 10%). Weight increases were seen in all surgery subgroups in subsequent years, although the weight increase curves levelled off after 8–10 years (Figure 1). After 10 years, weight losses were 25 ± 11% (GBP), 16 ± 11% (VBG) and 14 ± 14% (banding) below the baseline weight. After 15 years, the corresponding weight losses were 27 ± 12%, 18 ± 11% and 13 ± 14% respectively. The 20-year weight changes should be interpreted with caution due to the low number of participants so far examined at this time-point.

Surgical complications and postoperative mortality

In total, 89% of all operations in the SOS study were undertaken as open surgery. Over the first 90 days after inclusion in the intervention study, five deaths (0.25%) were observed in the surgery group and two (0.1%) in the control group [37]. Amongst the 2010 patients in the surgery group, four died during the primary hospital stay (three due to anastomotic leaks with general organ failure and one due to myocardial infarction). The fifth surgical patient died 60 days postsurgery from an acute myocardial infarction.

Amongst the patients in the surgery group, 292 (14.5%) had at least one nonfatal complication over the first 90 days. Pulmonary complications were most common (total 5.2%, including thromboembolism in 0.8%) followed by vomiting (3.0%), wound infection (2.1%), haemorrhage (1.3%) and anasto-

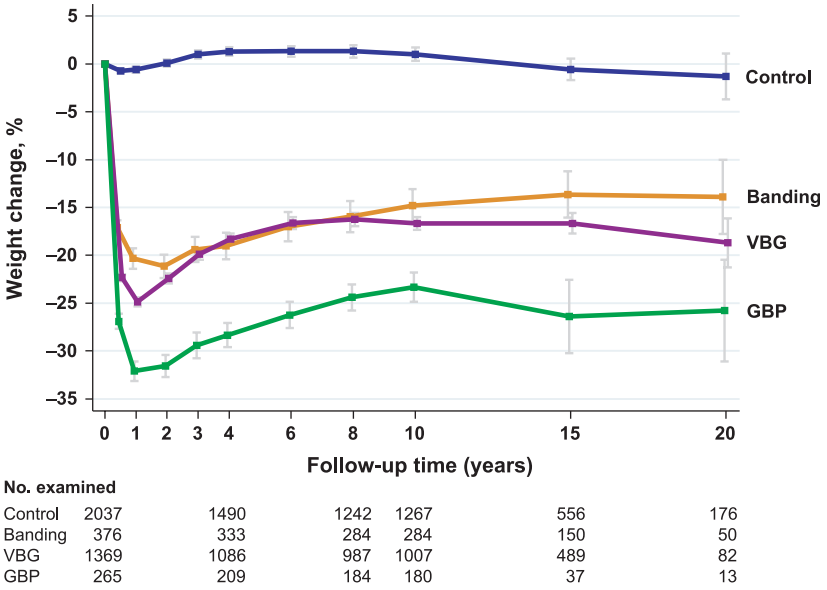

Fig. 1 *Mean percentage weight change from baseline amongst patients in the control and the three surgery groups during 20 years of follow-up in the Swedish Obese Subjects study. Data shown for controls receiving usual care and for surgery patients undergoing banding, vertical banded gastroplasty (VBG) or gastric bypass (GBP) at baseline. Percentage weight changes from the baseline examination are based on data available on 1 July 2011. Error bars represent 95% confidence intervals. From Sjöström L et al., JAMA 2012 with permission [37].*

motic leak (1.2%). In 2.9% of the patients, these complications were serious enough to require a second operation during the first 90 days [37].

Limitations of SOS

The main limitation of the SOS study is that it is a matched rather than a randomized trial. When the study was approved in 1987, six of the seven ethics review boards in Sweden considered that randomized investigations were unacceptable because of the high postoperative death rate after bariatric surgery (1%–5% during the 1970s and 1980s [49]).

Study outcomes

Effects of bariatric surgery on overall mortality

Mortality was the primary endpoint of the entire SOS project. The effect of bariatric surgery on overall mortality was reported in 2007 [35]. Figure 2 shows the cumulative overall mortality during follow-up to 16 years. Surgery was associated with an unadjusted hazard ratio (HR) of 0.76 relative to usual care for the control subjects [95% confidence interval (CI) 0.59–0.99; $P = 0.04$]. After multivariable adjustments for baseline conditions, the risk reduction was almost 30% (HR = 0.71, 95% CI 0.54–0.92). During the follow-up period, 129 subjects died in the control group and 101 in the surgery group. Mortality in the surgery group includes

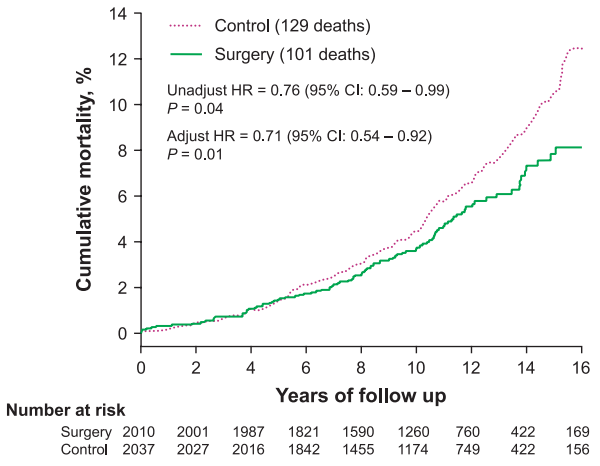

Fig. 2 *Unadjusted cumulative mortality amongst patients in the control and the surgery groups during 16 years of follow-up in the Swedish Obese Subjects study. Unadjusted and adjusted hazard ratios (HRs) are shown. Calculations based on data available on 1 November 2005. From Sjöström L et al., New Engl J Med 2007 with permission [35].*

postoperative deaths occurring within the first 90 days after surgery (see above).

Using multivariate models in an iterative way, it was possible to show that the favourable effects of surgery only became statistically significant after

approximately 13 study years [35]. Given that it took 26 years until obesity became a significant independent predictor of cardiovascular disease in the Framingham Study [50] and in the Manitoba Study [51], it may not be surprising that long follow-up periods are required to demonstrate favourable effects of obesity treatment.

Cancer was the single most common cause of death; 47 cancer deaths occurred in the control group, and 29 amongst those in the surgery group. Fatal myocardial infarction, which was the second most common cause of death, occurred in 25 control subjects and 13 patients undergoing surgery [35]. Because of a lack of power, it was not possible to estimate the risk reduction for specific causes of death in 2007 [35].

Four retrospective cohort studies have demonstrated reduced mortality after bariatric surgery [30–33]. The results of the prospective SOS study support the retrospective findings on mortality [35], and taken together these five studies provide evidence that bariatric surgery indeed reduces overall mortality.

Effects of bariatric surgery on remission of diabetes

Diabetes prevention and remission were secondary endpoints of the SOS project. Preliminary observations with regard to type 2 diabetes (T2D) were published in 2004. After 2 years of follow-up, 72% of SOS patients with T2D at baseline were in remission in the surgery group (Fig 3, upper panel) [12]. This is in good agreement with a meta-analysis by Buchwald and colleagues in 2009 showing 57% remission of diabetes after banding and 80% remission after GBP [52]. Similar diabetes remission rates after bariatric surgery have been confirmed in randomized 1- to 2-year studies [53–56]. The 1- to 2-year remission rates after bariatric surgery are extremely high compared with those seen after usual care in the SOS control group (Fig 3, upper panel) and after lifestyle interventions [57], exercise alone [58], weight loss medication [59] or antidiabetic drug treatment [60, 61].

It is noteworthy, however, that in 2004 we also reported that amongst patients who underwent surgery with remission of diabetes at 2 years, 50% had relapsed after 10 years (Fig 3, upper panel) [12]. There are no other 10-year diabetes relapse-rate data available for comparison in patients operated with VBG, banding or GBP. However,

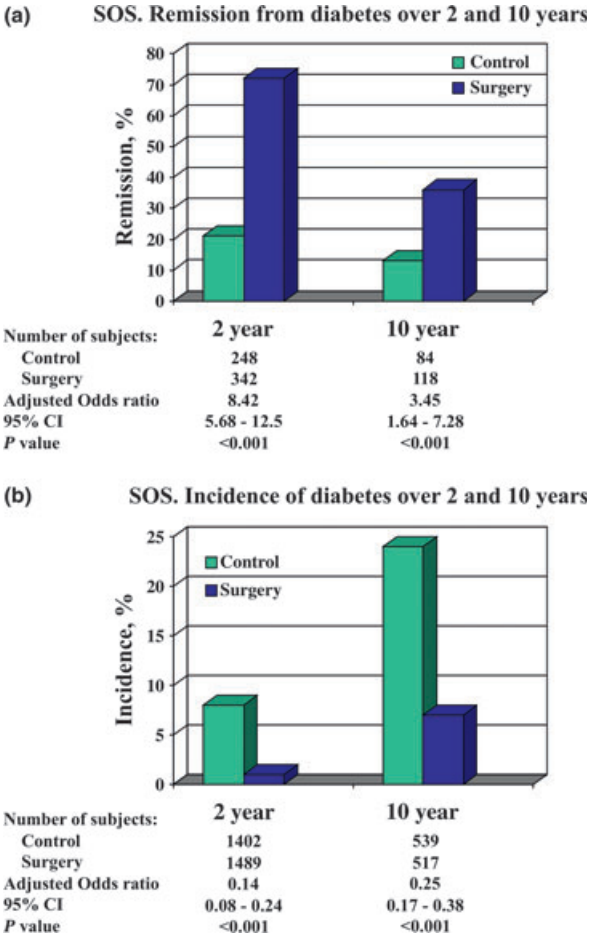

Fig. 3 *Diabetes remission and prevention during follow-up for 2 and 10 years in the control and surgery groups of the Swedish Obese Subjects study. Upper panel: Diabetes remission in 248 controls and 342 surgery patients with type 2 diabetes at baseline. Lower panel: Diabetes incidence in 1402 controls and 1489 surgery patients without diabetes at baseline. Calculations based on data available on 1 Jan 2004. Adapted from Sjöström L et al., New Engl J Med 2004 with permission [12].*

there was no 10-year diabetes relapse in 22 patients who underwent bilio-pancreatic diversion. [62].

Recently, we obtained evidence for a long-term reduction in macrovascular disease after bariatric surgery. In SOS participants with T2D at baseline, the incidence of myocardial infarction was reduced in surgery as compared with control patients (HR = 0.56, 95% CI: 0.34–0.93, $P = 0.025$)[63]. Thus there seems to be a long-term macrovascular benefit of bariatric surgery in patients with T2D in

spite of a considerable 'biochemical' relapse rate after the initial 2-year remission.

Effects of bariatric surgery on diabetes prevention

In 2004, we also reported that bariatric surgery reduced the incidence of new cases of T2D in nondiabetic subjects by at least 75% both at 2 and 10 years (Fig 3, lower panel) [12]. In a recent update including data from all SOS subjects without diabetes at baseline (1771 controls and 1658 in the surgery group), bariatric surgery (as compared with usual care) reduced the risk of developing T2D by 96%, 84% and 78% after 2, 10 and 15 years respectively [38]. Thus, in contrast to the declining remission effect with time, the strong prevention effect was only moderately reduced over 10 and 15 years.

The cumulative incidence rates of T2D are shown separately for different subgroups in Fig. 4 [38]. In the control group, there was no difference in the

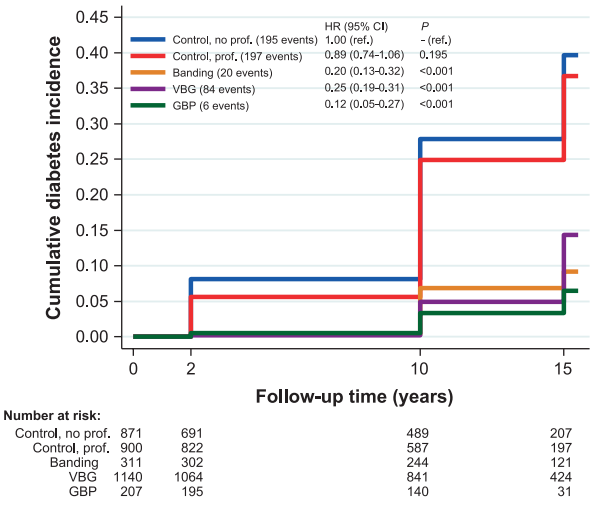

Fig. 4 *Cumulative incidence of diabetes during 15 years of follow-up in subgroups of the Swedish Obese Subjects study. Diabetes incidence rates and hazard ratios (HRs) are given for controls receiving professional help with lifestyle changes (prof.) and for controls not receiving such help (no prof.). Incidence rates and HRs are also given for patients undergoing banding, vertical banded gastroplasty (VBG) and gastric bypass (GBP) at baseline. Compared with the incidence of diabetes in the control group, the incidences were significantly lower in all three surgery subgroups. The HRs were not significantly different amongst the surgery subgroups. Calculations were based on data available on 1 January 2012. From Carlsson LMS et al., New Engl J Med 2012 with permission [38].*

incidence of T2D between those who had tried to lose weight under professional guidance and those who received no such help (HR = 0.89; $P = 0.195$). All types of surgery were associated with a reduced incidence of T2D. The HR for GBP was 0.12 (95% CI 0.05–0.27; $P < 0.001$), but based on only six diabetes cases amongst the 207 subjects. The HR values for banding (0.20, 95% CI 0.13–0.32; $P < 0.001$) and VBG (0.25, 95% CI 0.19–0.31; $P < 0.001$) were not significantly different from the value for GBP.

As compared with normal fasting glucose (NFG), impaired fasting glucose at baseline was associated with a more pronounced diabetes preventive effect of bariatric surgery (interaction *P*-value 0.002) [38]. NNT (Number Needed to Treat) to prevent one diabetes case over 10 years was only 1.3 in patients with IFG as compared to 7.0 in patients with NFG ($P < 0.05$). In other words, for 13 IFG patients operated with bariatric surgery, T2D seems to be prevented in 10 individuals over at least 10 years.

By contrast, baseline BMI did not predict the diabetes preventive effect of bariatric surgery (interaction *P*-value 0.545) [38].

The risk reduction observed in several diabetes prevention studies using lifestyle changes and/or medication has been in the order of 40%–50% over the first 2–6 years [64–66] (for meta-analysis, see [67, 68]) and the preventive effect has persisted, at least in part, over 10–20 years [26, 27, 69, 70]. These risk reductions are also impressive, but they have been observed in sophisticated scientific trial settings and they represent only about half of the preventive effect of bariatric surgery. It has been questioned whether risk reductions in the order of 40%–50% can be achieved with usual care in an ordinary primary health care system [71].

Guidelines from the International Diabetes Federation [72], the ADA [73] and others [74, 75] recognize bariatric surgery as an option for established diabetes in the obese; however, bariatric surgery has not been recommended for prevention of diabetes. Our results clearly indicate that this could be considered as an option.

Effects of bariatric surgery on cardiovascular disease events

Myocardial infarction and stroke, either separately or in combination, were predefined secondary endpoints in the SOS trial [34]. As discussed

above, no association between weight loss and reduced incidence of cardiovascular disease events has been demonstrated in epidemiological studies or in nonsurgical interventions. The results of three retrospective cohort studies have suggested that bariatric surgery is associated with reduced incidence of cardiovascular disease events [30, 31, 33], but there is a lack of data from prospective studies.

In January 2012 [37], we reported that bariatric surgery is associated with a reduced number of cardiovascular deaths and with a lower number of total first-time (fatal or nonfatal) cardiovascular events (myocardial infarction or stroke, whichever came first) (Fig. 5). A larger treatment effect was observed in subjects with high fasting serum insulin levels at baseline (*P*-value for interaction < 0.001), whereas no other subgroup–treatment interactions were found.

As discussed above we have also demonstrated that bariatric surgery significantly reduces the incidence of myocardial infarction in SOS patients with diabetes at baseline [63].

Effects of bariatric surgery on incidence of cancer

Cancer was not a predefined secondary endpoint in the SOS study because information available at the start of the trial in 1987 indicated that 2000 subjects in each arm would not be enough to see a treatment effect on the incidence of cancer. Unexpectedly, cancer was the most common cause of death, as reported in 2007 (overall 76 cancer deaths compared to 38 deaths due to myocardial infarction), but the study was not sufficiently powered to assess mortality due to specific causes [35]. Therefore, an analysis was performed to investigate whether bariatric surgery is associated with reduced overall incidence of fatal plus nonfatal cancer [36]. Given the strong effect of cancer on mortality in the SOS study, we consider this exploratory examination to be of considerable importance [36] despite the fact that cancer incidence was not a predefined endpoint.

Obesity is a risk factor for cancer. Intentional weight loss in the obese might protect against malignancy, but evidence for this is limited. To our knowledge, the SOS study is the first intervention trial in the obese population to provide prospective, controlled data regarding cancer incidence.

The number of first-time cancers after inclusion was lower in the surgery group (n = 117) than in the control group (n = 169; HR=0.67, 95% CI 0.53–0.85; P = 0.0009) [36]. There were no covariate–treatment interactions with respect to menopausal status, diabetes, BMI, age or smoking status. The *P*-value for the gender–treatment interaction was 0.054. In women, the number of first-time cancers after inclusion was lower in the surgery group (n = 79) than in the control group (n = 130; unadjusted HR=0.58, 95% CI 0.44–0.77; P = 0.0001), whereas there was no effect of surgery in men

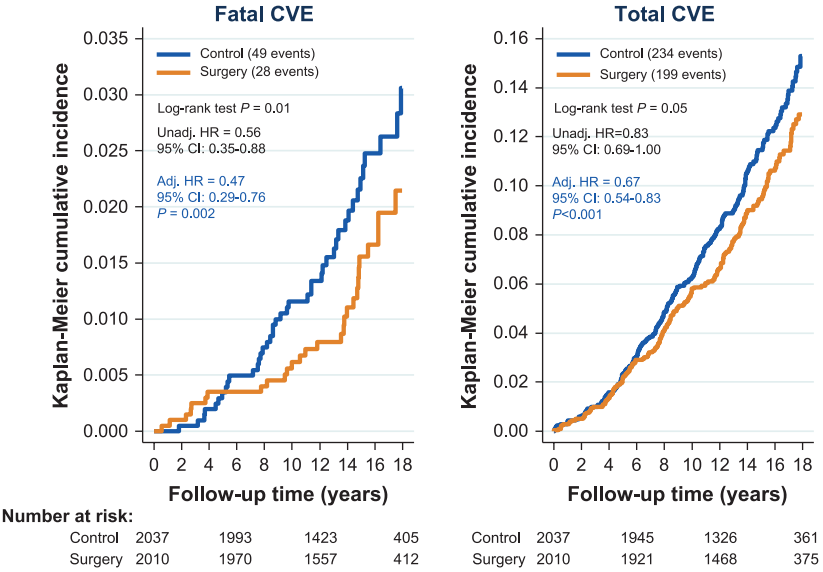

Fig. 5 *Cumulative incidence of fatal and total cardiovascular events (myocardial infarction + stroke) in the control and surgery groups of the Swedish Obese Subjects study. Left panel: Fatal cardiovascular events (myocardial infarction + stroke) in control subjects and patients undergoing surgery during follow-up for up to 18 years. Right panel: Total cardiovascular events, i.e. fatal or nonfatal events, in control and surgery patients for up to 18 years. Calculations are based on data available on 1 July 2011. From Sjöström L et al., JAMA 2012 with permission [37].*

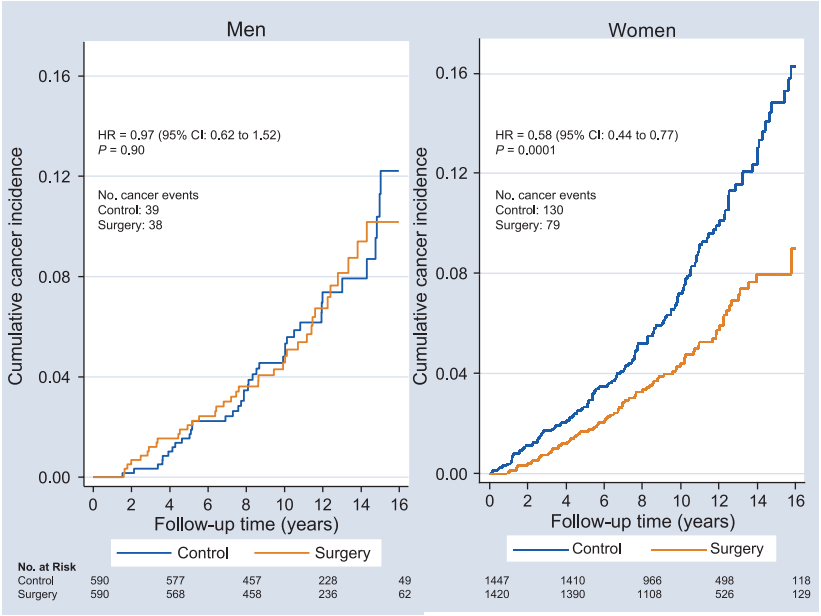

Fig. 6 *Unadjusted cumulative fatal plus nonfatal cancer incidence by gender during 16 years of follow-up in surgically treated obese individuals and in obese control individuals in the Swedish Obese Subjects study. Calculations are based on data available on 31 December 2005. From Sjöström L et al., Lancet Oncol 2009 with permission [36].*

($n = 38$ in the surgery group vs. $n = 39$ in the control group; unadjusted HR=0.97, 95% CI 0.62–1.52; $P = 0.90$) (Figure 6). Similar results were obtained after exclusion of all cancer cases during the first 3 years of the intervention. The treatment effect in women (adjusted HR=0.58, 95% CI 0.44–0.77; $P = 0.0002$) remained highly significant also after taking into account significant baseline confounders [36].

The results of epidemiological studies suggest that the beneficial effect of weight loss on cancer is greater in women than in men [21, 22]. In agreement with the SOS findings [36], results of retrospective studies have also suggested that bariatric surgery is associated with decreased cancer incidence in women [76, 77] but not in men [76]. These findings have been discussed recently by Renehan [78].

Are the favourable effects of bariatric surgery mediated by weight loss?

Diabetes and most other cardiovascular disease risk factors are favourably influenced by nonsurgically [10, 64–66, 79–82] and surgically [11–13, 83] induced weight loss. Weight loss induced by bariatric surgery has positive effects on risk factors when analysed both over 2 [11, 12, 83] and 10 [12, 13] years.

By contrast, we have not been able to demonstrate that the favourable effects of bariatric surgery on cardiovascular disease events, cancer incidence and overall mortality are mediated by weight loss. Thus we have found no association between weight change over the first 2 years and subsequent morbidity or mortality, amongst patients within either the control or the surgery group [35–37]. The lack of associations could possibly be due to a more important influence of recent weight changes or to inadequate statistical power to detect weight change–incidence relationships. Alternatively, following a relatively modest weight loss induced by bariatric surgery, there may be no further risk reduction attributable to greater, subsequent weight loss. Our negative results emphasize the need to further explore weight loss-independent effects of bariatric surgery.

BMI does not predict the effects of surgical treatment on outcomes

All current guidelines for bariatric surgery in obese individuals without [84–86] and with diabetes [72–75] are based on BMI alone or in combination with other criteria. Over time, the lower BMI cut-off in these guidelines has typically been reduced, and controlled studies of GBP in nonobese diabetic subjects are currently ongoing [87]. However, the value of BMI as a predictor of treatment effect does not seem to have been evaluated except in the SOS study.

Figure 7 summarizes the BMI–treatment (surgery vs. control) interactions found in the SOS study

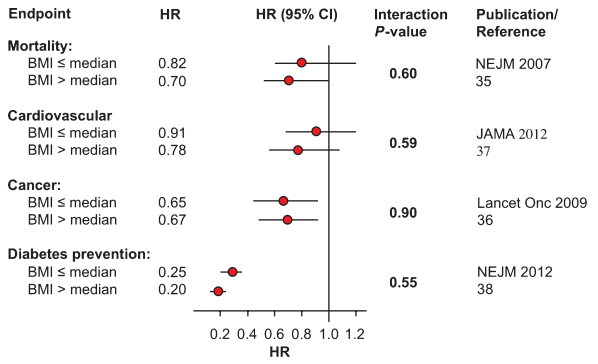

Fig. 7 *Surgical treatment effects (HR) on indicated endpoints in subgroups below and above the median BMI at baseline as well as BMI–treatment (surgery vs. control) interactions (interaction P-*value) for each endpoint. The treatment effect was not significantly related to BMI (interaction *P*-value nonsignificant) for any of the analysed endpoints. Results shown are from references [35–38].

with respect to mortality (*P* for interaction = 0.60), and the incidence rates of cardiovascular disease events (*P* = 0.59), cancer (*P* = 0.90) and diabetes (*P* = 0.55). BMI thus did not predict the effect of surgery on any of these endpoints. By contrast, insulin predicted the treatment effect with respect to mortality (*P* for interaction = 0.013) [35], cardiovascular events (*P* < 0.001) [37] and incidence of diabetes (*P* = 0.007) [38] (data not shown). There was also a strong impaired fasting glucose–treatment interaction with respect to diabetes incidence (*P* = 0.002)[38].

These findings suggest that guidelines for bariatric surgery need to be modified. To select those patients who are most likely to benefit from surgery, more importance should be given to metabolic variables and less to BMI.

Additional effects of bariatric surgery

In smaller subsamples we found that bariatric surgery as compared with usual care decreased left ventricular mass and improved the systolic as well as the diastolic function of the left ventricle [88–91]. Similarly, bariatric surgery improved effort-related dyspnoea, chest discomfort [92] and calf pain [93].

At baseline, sleep apnoea was associated with World Health Organization grade 4 daytime dyspnoea, elevations of baseline blood pressure and levels of insulin and triglycerides and also with previous admission to hospital with chest pain or myocardial infarction[42, 94]. According to our sleep apnoea questionnaire, a high likelihood of sleep apnoea was observed in 23% of 1210 surgically treated patients at baseline, but in only 8% at 2 years after surgery. In the obese control group (n = 1099), the corresponding values were 22% and 20% ($P < 0.001$ for the difference in change between groups) [92].

Obese women treated with bariatric surgery had a lower 2- and 6-year incidence of work-restricting pain in the knee and ankle joints than conventionally treated obese women [odds ratio (OR) 0.51–0.71)[95]. Recovery rates from baseline symptoms were higher after bariatric surgery than after conventional treatment (OR 1.4–4.8) in knee and ankle joints amongst men, and in neck and back or hip, knee and ankle joints amongst women [95].

Bariatric surgery was associated with increased physical activity over 2 [12, 92] and 10 [12] years of follow-up. Thus, physical inactivity not only contributes to the development of obesity [96], but obesity may favour physical inactivity. This vicious cycle seems to be broken by surgical treatment.

Over 10 years, health-related quality of life was significantly more improved in the surgery group, compared with the conventionally treated obese control group, in the domains of current health perception, social interaction, psychosocial functioning and depression, whereas no significant differences between groups were found for overall mood and anxiety [97].

A number of analyses of the SOS data have indicated that the direct and indirect costs of obesity are similar after surgical and nonsurgical treatment [98–101]. Taking into account the reduced morbidity and the improved quality of life, the surgical approach seems justified. Formal cost-effectiveness analyses based on 10- to 20-year SOS data are ongoing.

Conclusions

The prevalence of obesity is high and is increasing; this is important because obesity is associated with dramatically increased morbidity and mortality. As illustrated by the conventionally treated obese control group of the SOS study, nonpharmacological obesity treatment at primary health care cen-

tres is not, in general, associated with any weight loss in the short or long term. Unfortunately, most obese patients worldwide do not have access to specialized obesity treatment.

Treatment with currently available antiobesity drugs typically results in 7%–10% weight reduction over 2 to 4 years as compared to 4%–6% in placebo groups or those treated with lifestyle modification. This is encouraging, but more efficient drugs are clearly needed. Results from the SOS study have demonstrated that maintained effects on risk factors over 10 years require 10%–30% maintained weight loss.

Obese patients with prediabetes and type 2 diabetes require extra care. It is more difficult to achieve conventional or pharmacologically induced weight loss in diabetic obese patients. Even when weight loss is achieved, almost all patients relapse within a few years. Moreover, treatment with sulphonylureas or insulin causes weight gain. Thus, obesity not only causes diabetes but obesity is also a complication of diabetes treatment with some medications; this circle must be broken.

Surgery is the only treatment for obesity resulting in an average of more than 15% documented weight loss over 10 years. This treatment has dramatic positive effects on most but not on all cardiovascular disease risk factors over a 10-year period. It has favourable effects on established diabetes and prevents the development of new cases of diabetes. The diabetes preventive effect of bariatric surgery is particularly strong amongst patients with impaired fasting glucose at baseline. The incidence rates of cardiovascular disease events and cancer as well as overall mortality are reduced by bariatric surgery. No other obesity treatments have such documented effects. Quality of life is also markedly improved. In spite of these favourable effects, the measured total medical costs of obesity were similar after surgical and nonsurgical treatment.

Until more efficient antiobesity drugs are available, surgical treatment of obesity must be more universally accessible. Most countries do not have bariatric surgery capacity enough and with limited resources it has become very important to select those individuals who would benefit most from bariatric surgery. The findings of the SOS study have clearly demonstrated that, in contrast to baseline glucose and insulin, baseline BMI does not predict the surgical treatment effect on outcomes. Thus, current guidelines for bariatric surgery need to be updated.

Conflict of interest statement

No conflict of interest was declared.

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References

1 Flegal KM. Epidemiologic aspects of overweight and obesity in the United States. *Physiol Behav* 2005; **86:** 599–602.
2 Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. *JAMA* 2012; **307:** 491–7.
3 Finkelstein EA, Khavjou OA, Thompson H *et al.* Obesity and severe obesity forecasts through 2030. *Am J Prev Med* 2012; **42:** 563–70.
4 Wang Y, Beydoun MA, Liang L, Caballero B, Kumanyika SK. Will all Americans become overweight or obese? estimating the progression and cost of the US obesity epidemic. *Obesity* 2008; **16:** 2323–30.
5 Finucane MM, Stevens GA, Cowan MJ *et al.* National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet* 2011; **377:** 557–67.
6 Sjöström L. Mortality of severly obese subjects. *Am J Clin Nutr* 1992; **55(Suppl):** 516S–23S.
7 Adams KF, Schatzkin A, Harris TB *et al.* Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *N Engl J Med* 2006; **355:** 763–78.
8 Whitlock G, Lewington S, Sherliker P *et al.* Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009; **373:** 1083–96.
9 Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB. Years of life lost due to obesity. *JAMA* 2003; **289:** 187–93.
10 Wood PD, Stefanick ML, Dreon DM *et al.* Changes in plasma lipinds and lipoproteins in overweight men during weight loss through dieting as compared with exercise. *N Engl J Med* 1988; **319:** 1173–9.

11 Sjöström CD, Lissner L, Sjöström L. Relationships between changes in body composition and changes in cardiovascular risk factors: the SOS Intervention Study. *Swedish Obese Subjects. Obes Res* 1997; **5:** 519–30.
12 Sjöström L, Lindroos AK, Peltonen M *et al.* Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 2004; **351:** 2683–93.
13 Sjöström CD, Lystig T, Lindroos AK. Impact of weight change, secular trends and ageing on cardiovascular risk factors: 10-year experiences from the SOS study. *Int J Obes* 2011; **35:** 1413–20.
14 Lee IM PRJ. Change in body weight and longevity. *JAMA* 1992; **268:** 2045–9.
15 Walker M, Whincup PH, Shaper AG. Weight change and risk of heart attack in middle-aged British men. *Int J Epidemiol* 1995; **24:** 694–703.
16 Nilsson PM, Nilsson JA, Hedblad B, Berglund G, Lindgarde F. The enigma of increased non-cancer mortality after weight loss in healthy men who are overweight or obese. *J Intern Med* 2002; **252:** 70–8.
17 Strandberg TE, Strandberg AY, Salomaa VV *et al.* Explaining the obesity paradox: cardiovascular risk, weight change, and mortality during long-term follow-up in men. *Eur Heart J* 2009; **30:** 1720–7.
18 Myers J, Lata K, Chowdhury S, McAuley P, Jain N, Froelicher V. The obesity paradox and weight loss. *Am J Med* 2011; **124:** 924–30.
19 Doehner W, Erdmann E, Cairns R *et al.* Inverse relation of body weight and weight change with mortality and morbidity in patients with type 2 diabetes and cardiovascular comorbidity: an analysis of the Proactive study population. *Int J Cardiol* 2011; **162:** 20–26.
20 Pamuk ER, Williamson DF, Serdula MK, Madans J, Byers TE. Weight loss and subsequent death in a cohort of U.S. adults. *Ann Intern Med* 1993; **119:** 744–8.
21 Williamson DF, Pamuk E, Thun M, Flanders D, Byers T, Heath C. Prospective study of intentional weight loss and mortality in never- smoking overweight US white women aged 40–64 years [published erratum appears in Am J Epidemiol 1995;142:369]. *Am J Epidemiol* 1995; **141:** 1128–41.
22 Williamson DF, Pamuk E, Thun M, Flanders D, Byers T, Heath C. Prospective study of intentional weight loss and mortality in overweight white men aged 40–64 years. *Am J Epidemiol* 1999; **149:** 491–503.
23 Williamson D, Thompson T, Thun M, Flanders D, Pamuk E, Byers T. Intentional weight loss and mortality among overweight individuals with diabetes. *Diabetes Care* 2000; **23:** 1499–504.
24 Yaari S, Gouldbourt U. Voluntary and involuntary weight loss: associations with long-term mortality in 9228 middle-aged and elderly men. *Am J Epidemiol* 1998; **148:** 546–55.
25 Wannamethee SG, Sharper AG, Whincup PH, Walker M. Characteristics of older men who lose weight intentionally or unintentionally. *Am J Epidemiol* 2000; **151:** 667–75.
26 Li G, Zhang P, Wang J *et al.* The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet* 2008; **371:** 1783–9.
27 Uusitupa M, Peltonen M, Lindstrom J *et al.* Ten-year mortality and cardiovascular morbidity in the Finnish Diabetes Prevention Study–secondary analysis of the randomized trial. *PLoS ONE* 2009; **4:** e5656.
28 Nissen SE, Nicholls SJ, Wolski K *et al.* Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease: the STRADIVARIUS randomized controlled trial. *JAMA* 2008; **299:** 1547–60.
29 James WP, Caterson ID, Coutinho W *et al.* Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med* 2010; **363:** 905–17.
30 Adams TD, Gress RE, Smith SC *et al.* Long-term mortality following gastric bypass surgery. *New Engl J Med* 2007; **356:** 753–61.
31 Christou NV, Sampalis JS, Liberman M *et al.* Surgery decreases long-term mortality, morbidity, and health care use in morbidly obese patients. *Ann Surg* 2004; **240:** 416–23; discussion 23-4.
32 Flum DR, Dellinger EP. Impact of gastric bypass operation on survival: a population-based analysis. *J Am Coll Surg* 2004; **199:** 543–51.
33 MacDonald KG Jr, Long SD, Swanson MS *et al.* The gastric bypass operation reduces the progression and mortality of non-insulin-dependent diabetes mellitus. *J Gastrointest Surg* 1997; **1:** 213–20.
34 Sjöström L, Larsson B, Backman L *et al.* Swedish obese subjects (SOS). Recruitment for an intervention study and a selected description of the obese state. *Int J Obes Relat Metab Disord* 1992; **16:** 465–79.
35 Sjöström L, Narbro K, Sjöström CD *et al.* Effects of bariatric surgery on mortality in Swedish Obese Subjects. *New Engl J Med* 2007; **357:** 741–52.
36 Sjöström L, Gummesson A, Sjöström CD *et al.* Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. *Lancet Oncol* 2009; **10:** 653–62.
37 Sjöström L, Peltonen M, Jacobson P *et al.* Bariatric surgery and long-term cardiovascular events. *JAMA* 2012; **307:** 56–65.
38 Carlsson LM, Peltonen M, Ahlin S *et al.* Bariatric surgery and prevention of type 2 diabetes in Swedish Obese Subjects. *The New England J Med* 2012; **367:** 695–704.
39 Sjöström L. Swedish Obese Subjects, SOS: A review of results from a prospective controlled intervention trial. In: Bray GA, Bochard C, eds. *Handbook of Obesity, Volume 2: Clinical Applications*. New York: Informa; 2013 (in press).
40 Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975; **31:** 103–15.
41 Waaler H. Height, weight and mortality. The Norwegian experience. *Acta Med Scand Suppl* 1984; **679:** 1–56.
42 Grunstein RR, Stenlöf K, Hedner JA, Sjöström L. Impact of self-reported sleep-breathing disturbances on psychosocial performance in the Swedish Obese Subjects (SOS) study. *Sleep* 1995; **18:** 635–43.
43 Karlsson J, Sjöström L, Sullivan M. Swedish Obese Subjects (SOS)–an intervention study of obesity. measuring psychosocial factors and health by means of short-form questionnaires. results from a method study. *J Clin Epidemiol* 1995; **48:** 817–23.
44 Sjöström L. Surgical intervention as a strategy for treatment of obesity. *Endocrine* 2000; **13:** 213–30.
45 Larsson I, Lindroos AK, Peltonen M, Sjöström L. Potassium per kilogram fat-free mass and total body potassium:

predictions from sex, age, and anthropometry. *Am J Physiol Endocrinol Metab* 2003; **284:** E416–23.
46 Larsson I, Berteus Forslund H, Lindroos AK *et al.* Body composition in the SOS (Swedish Obese Subjects) reference study. *Int J Obes Relat Metab Disord* 2004; **28:** 1317–24.
47 Larsson I, Lindroos AK, Lustig TC, Näslund I, Sjöström L. Three definitions of the metabolic syndrome: relations to mortality and atherosclerosis. *Metabolic Syndrome and Related Disorders* 2005; **3:** 102–12.
48 Larsson I, Henning B, Lindroos AK, Näslund I, Sjöström CD, Sjöström L. Optimized predictions of absolute and relative amounts of body fat from weight, height, other anthropometric predictors, and age 1. *Am J Clin Nutr* 2006; **83:** 252–9.
49 Brolin RE. Results of obesity surgery. *Gastroenterol Clin North Am* 1987; **16:** 317–38.
50 Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation* 1983; **67:** 968–77.
51 Rabkin SW, Mathewson FA, Hsu PH. Relation of body weight to development of ischemic heart disease in a cohort of young North American men after a 26 year observation period: the manitoba study. *Am J Cardiol* 1977; **39:** 452–8.
52 Buchwald H, Fahrbach K, Banel D *et al.* Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med* 2009; **122:** 248–56.
53 Dixon J, O'Brien P, Playfair J *et al.* Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. *JAMA* 2008; **299:** 316–23.
54 Schauer PR, Kashyap SR, Wolski K *et al.* Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *The New England J Med* 2012; **366:** 1567–76.
55 Mingrone G, Panunzi S, De Gaetano A *et al.* Bariatric surgery versus conventional medical therapy for type 2 diabetes. *The New England J Med* 2012; **366:** 1577–85.
56 Zimmet P, Alberti KG. Surgery or medical therapy for obese patients with type 2 diabetes? *The New England J Med* 2012; **366:** 1635–6.
57 Norris SL, Zhang X, Avenell A *et al.* Long-term non-pharmacologic weight loss interventions for adults with type 2 diabetes. *Cochrane Database Syst Rev* 2005:CD004095.
58 Thomas DE, Elliott EJ, Naughton GA. Exercise for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2006; **3:** CD002968.
59 Norris SL, Zhang X, Avenell A, Gregg E, Schmid CH, Lau J. Pharmacotherapy for weight loss in adults with type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2005: CD004096.
60 Pinelli NR, Cha R, Brown MB, Jaber LA. Addition of thiazolidinedione or exenatide to oral agents in type 2 diabetes: a meta-analysis. *Ann Pharmacother* 2008; **42:** 1541–51.
61 Colagiuri S. Diabesity: therapeutic options. *Diabetes Obes Metab* 2010; **12:** 463–73.
62 Iaconelli A, Panunzi S, De Gaetano A *et al.* Effects of biliopancreatic diversion on diabetic complications: a 10-year follow-up. *Diabetes Care* 2011; **34:** 561–7.
63 Romeo S, Maglio C, Burza MA *et al.* Cardiovascular events after bariatric surgery in obese subjects with type 2 diabetes. *Diabetes Care* 2012; **35:** 2613–17.
64 Tuomiletho J, Lindström J, Eriksson JG *et al.* Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; **344:** 1343–50.
65 Knowler WC, Barrett-Connor E, Fowler SE *et al.* Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346:** 393–403.
66 Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. Xenical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004; **27:** 155–61.
67 Yamaoka K, Tango T. Efficacy of lifestyle education to prevent type 2 diabetes: a meta-analysis of randomized controlled trials. *Diabetes Care* 2005; **28:** 2780–6.
68 Orozco LJ, Buchleitner AM, Gimenez-Perez G, Roque IFM, Richter B, Mauricio D. Exercise or exercise and diet for preventing type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2008:CD003054.
69 Lindstrom J, Ilanne-Parikka P, Peltonen M *et al.* Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the finnish diabetes prevention study. *Lancet* 2006; **368:** 1673–9.
70 Knowler WC, Fowler SE, Hamman RF *et al.* 10-year follow-up of diabetes incidence and weight loss in the diabetes prevention program outcomes study. *Lancet* 2009; **374:** 1677–86.
71 Lauritzen T, Borch-Johnsen K, Sandbaek A. Is prevention of type-2 diabetes feasible and efficient in primary care? a systematic PubMed review. *Prim Care Diabetes* 2007; **1:** 5–11.
72 Dixon JB, Zimmet P, Alberti KG, Rubino F. Bariatric surgery: an IDF statement for obese type 2 diabetes. *Diabet Med* 2011; **28:** 628–42.
73 ADA: Executive summary: standards of medical care in diabetes – 2011. *Diabetes Care* 2011; **34 Suppl 1:** S4–10.
74 Rubino F, Kaplan LM, Schauer PR, Cummings DE. The diabetes surgery summit consensus conference: recommendations for the evaluation and use of gastrointestinal surgery to treat type 2 diabetes mellitus. *Ann Surg* 2010; **251:** 399–405.
75 Runkel N, Colombo-Benkmann M, Huttl TP *et al.* Evidence-based German guidelines for surgery for obesity. *Int J Colorectal Dis* 2011; **26:** 397–404.
76 Adams T, Stroup A, Gress R *et al.* Cancer incidence and mortality after gastric bypass surgery. *Obesity (Silver Spring)* 2009; **17:** 796–802.
77 McCawley GM, Ferriss JS, Geffel D, Northup CJ, Modesitt SC. Cancer in obese women: potential protective impact of bariatric surgery. *J Am Coll Surg* 2009; **208:** 1093–8.
78 Renehan AG. Bariatric surgery, weight reduction, and cancer prevention. *Lancet Oncology* 2009; **10:** 640–1.
79 Björntorp P, de Jounge K, Sjöström L, Sullivan L. The effect of physical training on insulin production in obesity. *Metabolism* 1970; **19:** 631–8.
80 Stevens VJ, Obarzanek E, Cook NR *et al.* Long-term weight loss and changes in blood pressure: results of the trials of hypertension prevention, phase II. *Ann Intern Med* 2001; **134:** 1–11.
81 Poobalan A, Aucott L, Smith WC *et al.* Effects of weight loss in overweight/obese individuals and long-term lipid outcomes–a systematic review. *Obes Rev* 2004; **5:** 43–50.

82 Aucott L, Poobalan A, Smith WC, Avenell A, Jung R, Broom J. Effects of weight loss in overweight/obese individuals and long-term hypertension outcomes: a systematic review. *Hypertension* 2005; **45:** 1035–41.
83 Sjöström CD, Lissner L, Wedel H, Sjöström L. Reduction in incidence of diabetes, hypertension and lipid disturbances after intentional weight loss induced by bariatric surgery: the SOS intervention study. *Obes Res* 1999; **7:** 477–84.
84 NIH conference. Gastrointestinal surgery for severe obesity. Consensus development conference panel. *Ann Intern Med* 1991;**115:**956–61.
85 Guidelines for laparoscopic and open surgical treatment of morbid obesity American Society for Bariatric Surgery. Society of American Gastrointestinal Endoscopic Surgeons. *Obes Surg* 2000; **10:** 378–9.
86 Fried M, Hainer V, Basdevant A *et al.* Interdisciplinary European guidelines on surgery of severe obesity. *Obesity facts* 2008; **1:** 52–9.
87 Rao RS, Kini S. Diabetic and bariatric surgery: a review of the recent trends. *Surg Endosc* 2012; **26:** 893–903.
88 Karason K, Wallentin I, Larsson B, Sjöström L. Effects of obesity and weight loss on left ventricular mass and relative wall thickness: survey and intervention study. *BMJ* 1997; **315:** 912–6.
89 Karason K, Wallentin I, Larsson B, Sjöström L. Effects of obesity and weight loss on cardiac function and valvular performance. *Obes Res* 1998; **6:** 422–9.
90 Kardassis D, Bech-Hanssen O, Schonander M, Sjöström L, Karason K. The influence of body composition, fat distribution, and sustained weight loss on left ventricular mass and geometry in obesity. *Obesity* 2012; **20:** 605–11.
91 Kardassis D, Bech-Hanssen O, Schonander M, Sjöström L, Petzold M, Karason K, Impact of body composition, fat distribution and sustained weight loss on cardiac function in obesity. *Int J Cardiol* 2012; **159:** 128–33.
92 Karason K, Lindroos AK, Stenlöf K, Sjöström L. Relief of cardiorespiratory symptoms and increased physical activity after surgically induced weight loss. Results from the SOS study. *Arch Int Med* 2000; **160:** 1797–802.
93 Karason K, Peltonen M, Lindroos A, Sjöström L, Lönn L, Torgerson J. Effort-related calf pain in the obese and long-term changes after surgical obesity treatment. *Obes Res* 2005; **13:** 137–45.
94 Grunstein RR, Stenlöf K, Hedner J, Sjöström L. Impact of obstructive sleep apnea and sleepiness on metabolic and cardiovascular risk factors in the Swedish Obese Subjects (SOS) Study. *Int J Obes Relat Metab Disord* 1995; **19:** 410–8.
95 Peltonen M, Lindroos A, Torgerson J. Musculosceletal pain in the obese: a comparison with a general population and long-term changes after conventional and surgical obesity treatment. *Pain* 2003; **104:** 549–57.
96 Temelkova-Kurktschiev T, Stefanov T. Lifestyle and genetics in obesity and type 2 diabetes. *Exp Clin Endocrinol Diabetes* 2012; **120:** 1–6.
97 Karlsson J, Taft C, Rydén A, Sjöström L, Sullivan M. Ten year trends in health related quality of life after surgical and conventional treatment for severe obesity: the SOS intervention study. *Int J Obes (Lond)* 2007; **31:** 1248–61.
98 Narbro K, Jonsson E, Larsson B, Waaler H, Wedel H, Sjöström L. Economic consequences of sick-leave and early retirement in obese Swedish women. *Int J Obes Relat Metab Disord* 1996; **20:** 895–903.
99 Narbro K, Ågren G, Jonsson E *et al.* Sick leave and disability pension before and after treatment for obesity: a report from the Swedish Obese Subjects (SOS) study. *Int J Obes Relat Metab Disord* 1999; **23:** 619–24.
100 Gripeteg L, Lindroos AK, Peltonen M, Sjöström L, Narbro K. Effects of bariatric surgery on disability pension in Swedish obese subjects. *Int J Obes* 2012; **36:** 356–62.
101 Neovius M, Narbro K, Keating C *et al.* Health care use during 20 years following bariatric surgery. *JAMA* 2012; **308:** 1132–41.

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