Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial

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Summary

Background **Obesity is a risk factor for cancer. Intentional weight loss in the obese might protect against malignancy, but evidence is limited. To our knowledge, the Swedish Obese Subjects (SOS) study is the first intervention trial in the obese population to provide prospective, controlled cancer-incidence data.**

Methods **The SOS study started in 1987 and involved 2010 obese patients (body-mass index [BMI] ≥34 kg/m² in men, and ≥38 kg/m² in women) who underwent bariatric surgery and 2037 contemporaneously matched obese controls, who received conventional treatment. While the main endpoint of SOS was overall mortality, the main outcome of this exploratory report was cancer incidence until Dec 31, 2005. Cancer follow-up rate was 99·9% and the median follow-up time was 10·9 years (range 0–18·1 years).**

Findings **Bariatric surgery resulted in a sustained mean weight reduction of 19·9 kg (SD 15·6 kg) over 10 years, whereas the mean weight change in controls was a gain of 1·3 kg (SD 13·7 kg). 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). The sex–treatment interaction p value 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; HR 0·58, 0·44–0·77; p=0·0001), whereas there was no effect of surgery in men (38 in the surgery group *vs* 39 in the control group; HR 0·97, 0·62–1·52; p=0·90). Similar results were obtained after exclusion of all cancer cases during the first 3 years of the intervention.**

Interpretation **Bariatric surgery was associated with reduced cancer incidence in obese women but not in obese men.**

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Introduction

A recent meta-analysis, including 282 000 incident cancer cases over more than 133 million person-years of follow-up, shows that high body-mass index (BMI) is associated with an increased incidence of many types of cancer.[1] Since obesity is increasingly common throughout the world, its effect on cancer occurrence is substantial. In the USA, where the prevalence of obesity was 32·9% among adults in 2003–04,[2] it has been estimated that being overweight or obese accounts for 14% of cancer deaths in men and 20% in women, making it the largest avoidable cause of cancer with the exception of smoking.[3]

In obese individuals, intentional weight loss might reduce cancer morbidity and mortality, particularly in women,[4,5] but the evidence for this is limited. Observational studies[4–10] are hard to interpret owing to the difficulty of separating intentional from unintentional weight loss, the latter often being caused by disease. Additionally, few obese people are successful in long-term weight reduction. So far, the best evidence that weight loss reduces cancer risk comes from two very recent, retrospective cohort studies of obese patients treated with bariatric surgery.[11,12] Both studies, which appeared after the current Swedish Obese Subjects (SOS) report was submitted, showed reductions in overall cancer incidence in patients who underwent surgery compared with those who did not.

The SOS Study, which to our knowledge is the first prospective, controlled intervention study that investigates the effect of long-term weight loss[13,14] on disease and death rates, recently showed that bariatric surgery is associated with reduced overall mortality.[15] However, although cancer was the most common cause of death, the study was not sufficiently powered to assess mortality due to specific causes.[15] Therefore, the aim of the present study is to investigate whether bariatric surgery is associated with reduced overall incidence of fatal and non-fatal cancer. As a secondary subgroup analysis, we also examined the effects of changed bodyweight and caloric intake on cancer incidence. Given the unexpectedly strong effect of cancer on mortality in the SOS Study, we consider this exploratory examination of importance, despite the fact that cancer incidence was not a predefined endpoint.

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Methods

Patients

Briefly, the ongoing SOS trial enrolled 4047 obese patients at 25 surgical departments and 480 primary health care centres in Sweden between Sept 1, 1987, and Jan 31, 2001.[13–15] The cutoff date for our current analysis was Dec 31, 2005. Seven regional ethics review boards approved the study protocol. Informed consent was obtained from all participants.

After recruitment campaigns in the mass media and at 480 primary health-care centres, a matching examination was completed by 6905 patients, 5335 of which were eligible (figure 1). Among them, 2010 individuals electing surgery constituted the surgery group, and a contemporaneously matched control group of 2037 individuals was created using 18 matching variables, indicated with M in table 1.[13] The remaining 1288 eligible patients were not used by the automatic matching system,[13] since they offered less optimal matches. Although a surgery patient and his or her conventionally treated control always started the study on the day of surgery, the matching was not based on individuals in the sense that a given surgery patient and his or her control should necessarily be as similar as possible. Instead the matching algorithm selected controls in such a way that the current mean values of the matching variables in the control group moved as much as possible in the direction of the current mean values in the surgery group.

Procedures

Baseline examinations in the surgery and control groups took place approximately 4 weeks before the start of the intervention. The two study groups had identical inclusion and exclusion criteria, and all controls were eligible for surgery. The inclusion criteria were age 37–60 years and a BMI of 34 kg/m² or more for men and 38 kg/m² or more for women. Young people were excluded to increase overall risk and thereby minimise the size of the study. The chosen BMI cutoffs correspond to a doubled mortality as compared with BMI 20–25 kg/m² according to the largest Nordic study available before the start of the study.[16] The exclusion criteria were: earlier 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; myocardial infarction during the past 6 months; bulimic eating pattern; drug or alcohol (>0·75 L 40% liquor per week or corresponding ethanol amount) abuse; psychiatric or cooperative problems contraindicating bariatric surgery; other contraindicating conditions (such as continuous glucocorticoid or antiphlogisitic treatment).

The primary endpoint of SOS was overall mortality, which was published in 2007.[15] Secondary endpoints were diabetes,[14] gall bladder disease,[17] and cardiovascular disease (not yet published). Cancer was not specified as a secondary endpoint.

All participants were examined at the matching and baseline examinations and after 0·5, 1, 2, 3, 4, 6, 8, 10, and 15 years. Centralised biochemical examinations were undertaken at the matching and baseline examinations and after 2, 10, and 15 years. Self-reported total energy intake was obtained from the validated SOS food questionnaire.[18]

In the surgery group, 376 patients underwent non-adjustable or adjustable banding, 1369 underwent vertical banded gastroplasty, and 265 underwent gastric bypass.[19] Omentectomy was not done in any of the operated cases. Control participants received the customary treatment for obesity at their centres of registration. The quality of treatment ranged from advanced life-style advice at some sites to no treatment at all in many practices. The treatment of controls started at baseline, varied in duration, and was interrupted and restarted in many cases.

Cancer incidence was obtained by cross-checking social security numbers from the SOS database with the Swedish National Cancer Registry, the Cause of Death Registry and the Registry of the Total Population (to trace the 24 emigrants). At record linkage (March 26, 2007), the Cancer Registry was complete up to Dec 31, 2005.

Statistical analysis

Mean values and standard deviations or 95% CI were used to describe the baseline characteristics and changes over time. Baseline characteristics between the treatment groups were compared with *t*-tests for continuous variables and Fisher's exact test for dichotomous variables. Time of progression to first malignant cancer after inclusion was compared between treatment groups with Kaplan–Meier estimates of cumulative incidence rates. Additionally, hazard ratios from a Cox proportional-hazards model[20] with a single covariate for treatment group were calculated. Calculations were done with and without cancer cases that occurred during the first 3 years of the intervention to account for undetected prevalent cancer at baseline.

Multiple Cox proportional-hazards models based on matching data or baseline data were also used to assess time to cancer (from baseline) while adjusting for significant confounders. These models were built using a forward stepwise procedure. At each step, all terms were required to be marginally significant at the 0·05 level. Each of the variables in table 1 (except BMI, waist–hip ratio, and pulse pressure, which were excluded for colinearity reasons) were entered in the model-selection procedure. No interaction terms were considered in the forward selection procedure. Missing values were replaced by time (matching and baseline) and group (control and surgery) specific medians. In this way all patients could be used for multiple adjustments. Since it was not obvious whether matching or baseline data should be used for the multivariable adjustments, we used both datasets to determine whether the resulting models gave similar

cancer incidence hazard ratio values with respect to treatment (surgery compared with controls).

Since a group match rather than individual matching was used in SOS, we did not use procedures for paired matched designs. Both when analysing the matching dataset and the baseline dataset, all variables in table 1 (except those that caused colinearity problems) were offered to the multivariable stepwise analyses. These variables included all matching variables (table 1).

To calculate hazard ratios for subtypes of cancers, the incidence of all other subtypes were censored at the time of incidence.

In secondary subgroup analyses with limited statistical power we also explored the relationships between

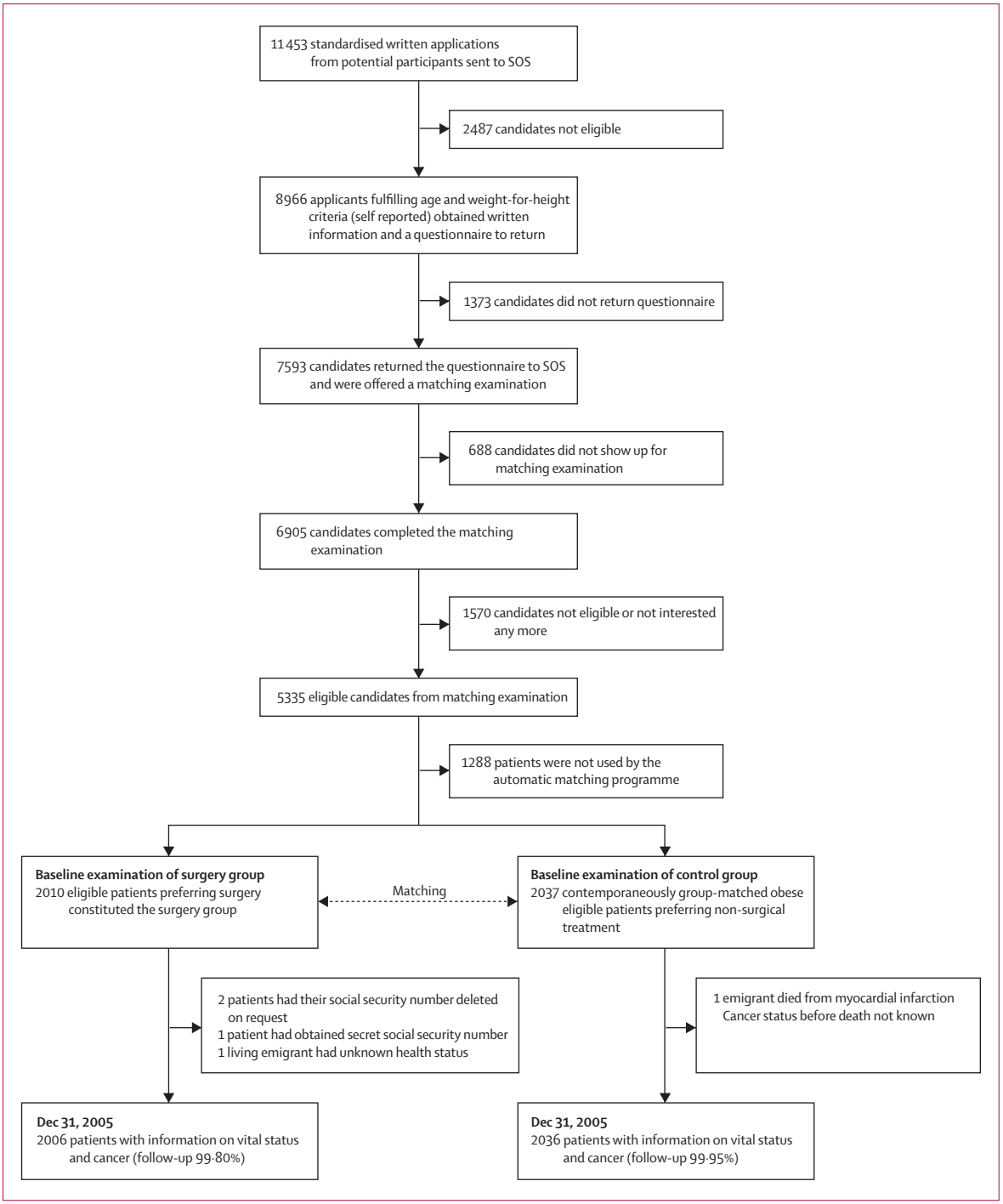

Figure 1: **Trial profile**

	Women					Men				
	Surgery		Control		p	Surgery		Control		p
	Mean (SD)	Number with missing data	Mean (SD)	Number with missing data		Mean (SD)	Number with missing data	Mean (SD)	Number with missing data	
Number of individuals	1420		1447			590		590		
Postmenopausal (n [%]); M	452 (31·8)	0	513 (35·5)	0	0·044	na	na	na	na	na
Age at exam (years); M	46·1 (5·9)	0	47·6 (6·2)	0	<0·001	46·0 (5·6)	0	46·8 (5·8)	0	0·015
Daily smokers (n [%]); M	393 (27·7)	0	272 (18·8)	0	<0·0001	167 (28·3)	0	140 (23·7)	0	0·084
Previous myocardial infarction (n[%])	8 (0·6)	0	8 (0·6)	0	1·000	21 (3·6)	0	14 (2·4)	0	0·30
Previous stroke (n [%])	8 (0·6)	0	12 (0·8)	0	0·502	7 (1·2)	0	7 (1·2)	0	1·000
Previous cancer (n [%])	18 (1·3)	0	19 (1·3)	0	1·000	5 (0·8)	0	1 (0·2)	0	0·22
Diabetes (n [%]); M	81 (5·7)	0	75 (5·2)	0	0·565	67 (11·4)	0	50 (8·5)	0	0·12
Sleep apnoea (n [%])	230 (16·3)	6	234 (16·5)	25	0·92	247 (42·0)	2	216 (37·0)	6	0·083
Lipid lowering medication (n [%])	13 (0·9)	0	4 (0·3)	0	0·029	9 (1·5)	0	11 (1·9)	0	0·82
NSAID therapy (n [%])	157 (11·1)	0	127 (8·8)	0	0·045	46 (7·8)	0	36 (6·1)	0	0·30
Antidepressive therapy (n [%])	96 (6·8)	0	92 (6·4)	0	0·71	25 (4·2)	0	12 (2·0)	0	0·147
Weight (kg); M	114·5 (13·30)	0	112·9 (13·9)	0	0·0017	130·5 (16·4)	0	126·8 (14·4)	0	<0·0001
Height (m); M	1·65 (0·06)	0	1·65 (0·06)	0	0·83	1·79 (0·07)	0	1·80 (0·07)	0	0·17
Body-mass index (kg/m^2)*	42·2 (4·1)	0	41·6 (4·2)	0	<0·0001	40·6 (4·7)	0	39·2 (4·1)	0	<0·0001
Waist circumference (cm); M	122·2 (10·0)	1	120·6 (10·4)	0	<0·0001	128·7 (10·8)	0	126·1 (8·2)	0	<0·0001
Hip circumference (cm); M	127·3 (9·1)	1	125·9 (9·1)	1	<0·0001	122·7 (10·1)	0	120·8 (8·7)	0	0·0007
Waist–hip ratio*	0·961 (0·066)	1	0·959 (0·069)	1	0·41	1·049 (0·051)	0	1·045 (0·047)	0	0·099
Sagittal diameter (cm)	27·7 (3·3)	2	27·4 (3·3)	1	0·022	30·2 (3·7)	0	29·2 (3·2)	0	<0·0001
Neck circumference (cm)	41·6 (2·9)	5	41·7 (3·2)	0	0·42	47·8 (3·6)	0	47·7 (3·3)	1	0·59
Upper arm circumference (cm)	39·6 (3·9)	1	39·3 (3·7)	0	0·020	39·4 (3·4)	1	39·2 (3·2)	0	0·36
Thigh circumference (cm)	76·0 (7·0)	1	75·4 (7·0)	0	0·017	72·2 (6·3)	0	70·8 (5·9)	2	<0·0001
Systolic blood pressure (mm Hg); M	139·6 (18·7)	1	139·1 (18·0)	0	0·41	143·0 (18·2)	1	142·1 (17·6)	0	0·40
Diastolic blood pressure (mm Hg)	86·2 (10·8)	2	85·8 (10·3)	3	0·39	90·6 (11·6)	1	90·3 (10·9)	0	0·61
Pulse pressure (mm Hg)*	53·4 (13·5)	2	53·3 (13·2)	3	0·76	52·4 (13·1)	3	51·8 (13·0)	0	0·41
Glucose (mmol/L)	5·2 (1·7)	0	5·2 (1·9)	2	0·38	5·7 (2·4)	0	5·6 (2·2)	1	0·30
Insulin (mU/L)	19·6 (12·7)	1	18·4 (11·3)	2	0·0049	25·6 (17·1)	5	24·1 (14·7)	1	0·12
Triglycerides (mmol/L); M	2·02 (1·07)	1	1·90 (1·09)	0	0·0037	2·73 (1·99)	1	2·75 (2·09)	0	0·85
Total cholesterol (mmol/L); M	5·79 (1·10)	1	5·70 (1·06)	0	0·016	5·97 (1·16)	1	5·87 (1·12)	0	0·13
HDL cholesterol (mmol/L)	1·25 (0·29)	37	1·25 (0·30)	18	0·43	1·09 (0·25)	32	1·07 (0·28)	21	0·25
Uric acid, mmol/L	332·3 (73·8)	1	328·3 (70·2)	1	0·14	401·1 (75·0)	1	404·8 (80·0)	1	0·41
ASAT, IU/L	22·7 (0·190)	0	22·8 (13·20)	1	0·77	30·2 (19·7)	0	29·9 (15·6)	1	0·75
ALAT, IU/L	30·5 (17·6)	0	31·0 (21·1)	1	0·66	48·5 (25·4)	0	48·4 (25·7)	1	0·98
ALP, IU/L	184 (52·8)	0	184 (54·0)	1	0·96	183 (48·3)	0	177 (45·0)	1	0·043
Bilirubin, µmol/L	8·70 (3·70)	0	9·09 (3·64)	1	0·0047	10·53 (4·61)	0	10·60 (4·49)	1	0·78
Energy intake, kcal/day	2831 (1180)	19	2727 (1152)	5	0·018	3426 (1347)	6	3229 (1196)	1	0·0083
Current health; M†	21·3 (6·1)	0	22·6 (6·1)	0	<0·0001	21·6 (6·0)	0	23·0 (6·2)	0	<0·0002
Monotony avoidance; M†	22·1 (5·1)	0	22·4 (5·1)	0	0·22	23·5 (4·9)	0	23·2 (4·8)	0	0·46
Psychasthenia; M†	24·0 (5·2)	0	23·2 (5·3)	0	<0·0001	23·9 (5·1)	0	23·1 (5·2)	0	0·015
Quantity of social support; M†	5·99 (2·38)	0	6·07 (2·46)	1	0·37	6·11 (2·53)	0	6·10 (2·44)	0	0·93
Quality of social support; M†	4·33 (1·27)	0	4·34 (1·26)	0	0·94	4·06 (1·41)	0	4·13 (1·39)	0	0·37
Stressful life events; M†	2·57 (1·31)	0	2·49 (1·27)	0	0·096	2·32 (1·28)	0	2·27 (1·31)	0	0·56

HDL=high-density lipoprotein. ASAT=aspartate aminotransferase. ALAT=alanine aminotransferase. ALP=alkaline phosphatase. na=not applicable. NSAID=non-steroidal anti-inflammatory drug. Values are means (SD) unless otherwise indicated. Sex and all variables indicated with M were matching variables. *This variable was not used in the multivariable stepwise regression analysis because it was derived from other variables in this table. †For psychosocial measurements, higher scores represent better current health (range 9–36), more of the personality traits; monotony avoidance (range 10–40) and psychasthenia (range 10–40), a higher quantity of social support (range 0–12), a better quality of social support (range 0–5), and a greater number of stressful life events (range 0–8).

Table 1: **Characteristics of the surgically treated and control patients at the matching examination shown separately for men and women**

changes in bodyweight or energy intake during the first year and the cancer incidence from start of year 4. In patients with missing information on weight or energy intake change during the first year, sex-specific and group-specific (surgery subtype and control) median 1-year values were imputed.

All p values are two-sided and p<0·05 was considered as statistically significant. Statistical analyses were done using the STATA statistical package 9.2.

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Results

The matching procedure created biologically similar surgery and control groups in both sexes, although some group differences reached significance owing to the comparatively large number of participants (table 1). 71% (2867 of 4047) of patients were women.

Because of long surgical waiting lists, the median waiting time between the matching and the baseline examination was 13 months (range 0–38 months), and during this time bodyweight and associated risk factors increased in the surgery group and decreased in controls (webappendix). The webappendix also shows measured weight changes from baseline separately for men and women over periods of up to 15 years. Over the first 10 years, the mean weight loss was 19·9 kg (SD 15·6 kg) in the surgery group, while a mean weight gain of 1·3 (SD 13·7 kg) was observed in the control group. The baseline-adjusted overall mean weight loss over 10 years after gastric bypass was larger in women (–35·2 kg [SD 17·9]) than in men (–23·9 kg [SD 15·4]) (p=0·024).

Information on cancer occurrence could be obtained for 4042 of 4047 patients, corresponding to a follow-up rate of 99·80% (2006 of 2010) in the surgery group and 99·95% (2036 of 2037) in the control group (figure 1). The median follow-up time was 10·9 years (range 0–18·1 years; mean [SD] 10·7 [3·6] years).

Of the 286 first-time cancers recorded during the follow-up period, 169 occurred in the control group and 117 in the surgery group. Compared with patients in the control group, patients in the surgery group had a hazard ratio (HR) for overall incident cancer of 0·67 (95% CI 0·53–0·85; p=0·0009; figure 2). After the exclusion of 45 cancers that occurred during the first 3 years, the HR was virtually unchanged (0·67; 0·52–0·86, p=0·002).

There were no covariate–treatment interactions with respect to menopausal, diabetic, BMI, age, or smoking status (figure 2). The p value for the sex–treatment interaction was 0·054 (figure 2). Figure 3 shows the unadjusted cumulative incidences for fatal plus non-fatal cancer separately for men and women. Although bariatric surgery was not related to cancer incidence in men (39 in the control group *vs* 38 in the surgery group [HR 0·97, 95% CI 0·62–1·52; p=0·90]), we observed a marked reduction of risk in women (130 *vs* 79 cases [HR 0·58; 0·44–0·77, p=0·0001]). Exclusion of all cancer events over the first 3 years of the intervention (two men in the control group, seven men in the surgery group, 25 women in the control group, and 11 women in the surgery group) did not affect these sex differences (events from start of year 4 in men: 37 cases in the control group and 31 cases in the surgery group [HR 0·84; 95% CI 0·52–1·34, p=0·46]; events from the start of year 4 in women: 105 cases in the control group, 68 cases in the surgery group [HR 0·61, 0·45–0·83, p=0·0016].

The treatment effect in the total study group (HR 0·70; 95% CI 0·55–0·89, p=0·0033) and in women (HR 0·58; 0·44–0·77, p=0·0002) remained highly significant after taking significant confounders into account (table 2). Similar multivariable-adjusted treatment effects were obtained with or without exclusion of cancer events during the first 3 years (HR for all: 0·72; 95% CI

See Online for webappendix

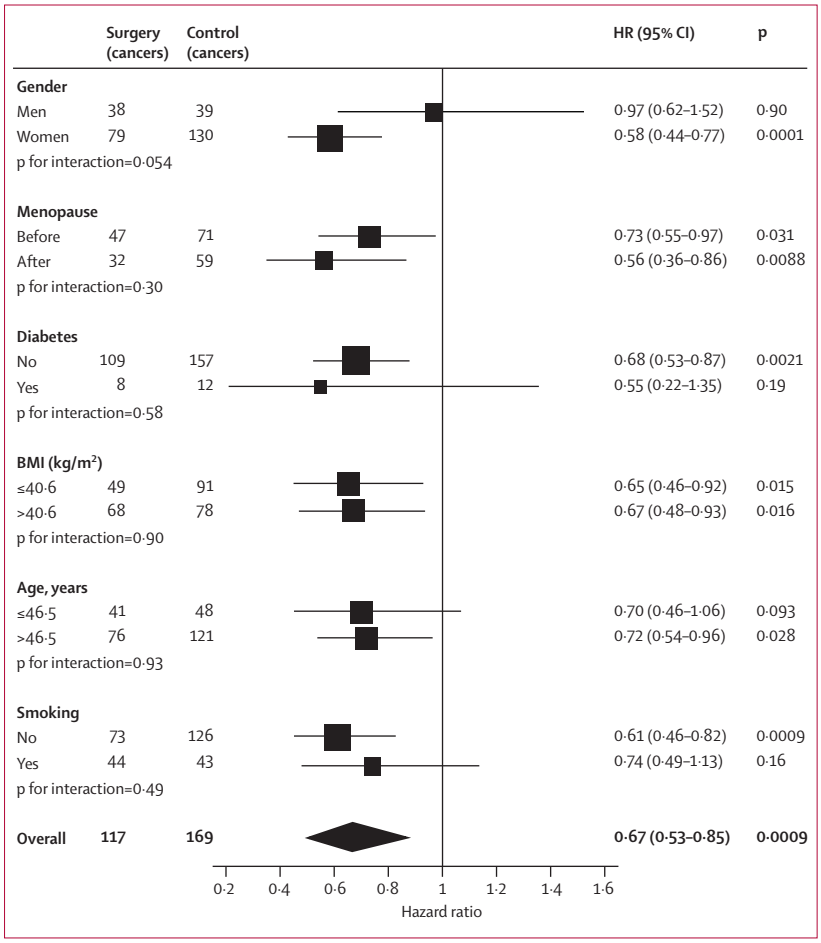


***Figure 2*: Unadjusted subgroup–treatment interactions with respect to overall fatal plus non-fatal cancer**
Dots with bars represent the hazard ratio (HR) and its 95% CI for subgroups. Areas of squares are proportional to the number of cancer cases within subgroups. The rhombus at the bottom of the figure illustrates the total treatment effect (HR and 95% CI) taking all patients into account. Results of this figure were based on matching data. For BMI and age, medians were used for the cutoffs.

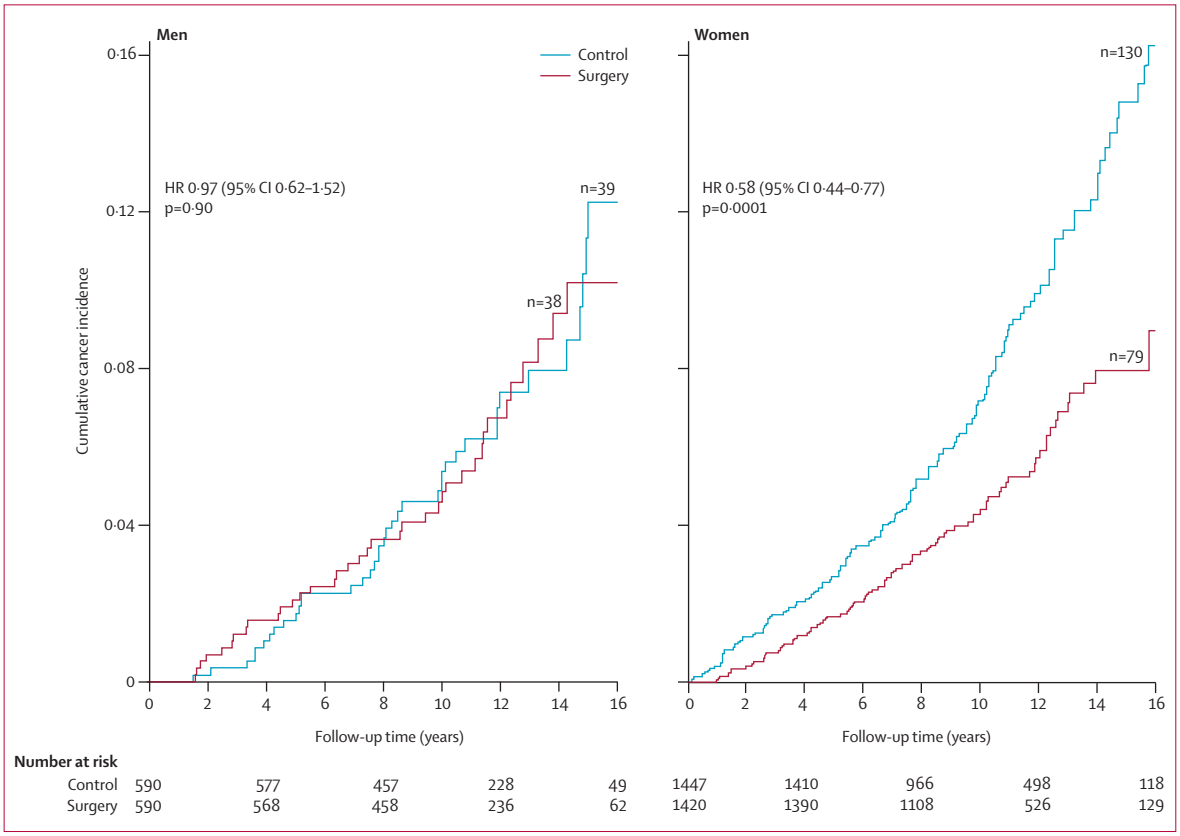


Figure 3: **The unadjusted cumulative fatal plus non-fatal cancer incidence from the start of the intervention by sex in surgically treated obese individuals and in obese control individuals**

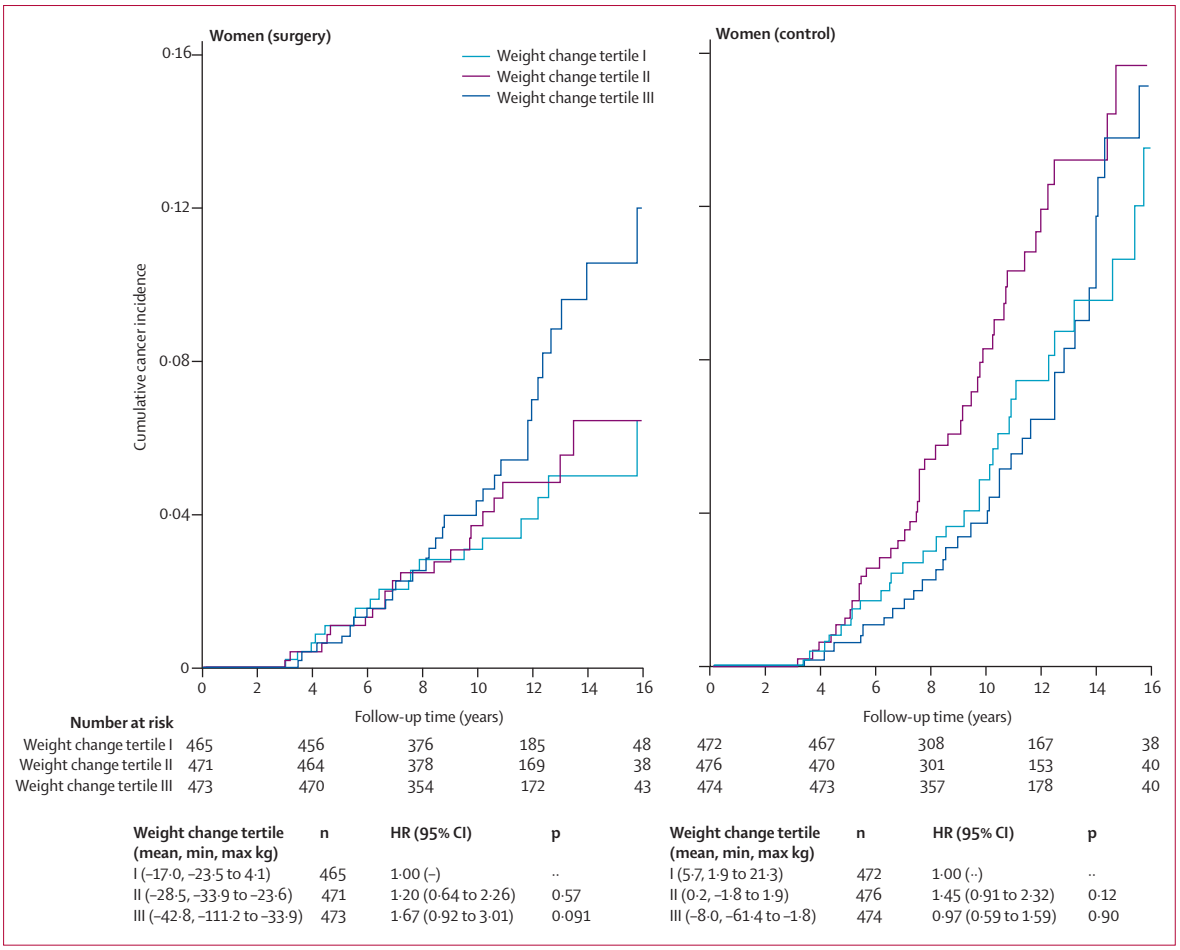
	All patients (N=4047)		Women (N=2867)		Men (N=1180)	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Treatment: surgery *vs* control	0·70 (0·55–0·89)	0·0033	0·58 (0·44–0·77)	0·0002	na	..
Age (per year)	1·08 (1·06–1·10)	<0·0001	1·07 (1·04–1·09)	<0·0001	1·10 (1·06–1·14)	<0·0001
Smoking (yes/no)	1·41 (1·08–1·83)	0·010	1·40 (1·03–1·91)	0·034	na	..
Sagittal diameter (per 10 cm)	1·46 (1·07–2·00)	0·017	1·99 (1·36–2·90)	0·0004	na	..
Quantity of social interaction* (per 5 units)	0·73 (0·57–0·94)	0·013	na	..	na	..
ASAT (per IU/L)	na	..	na	..	1·01 (1·00–1·03)	0·036

ASAT=aspartate aminotransferase. HR=hazard ratio. na=variables not entering the indicated multivariable model. Statistically significant predictors from a forward stepwise procedure: analyses based on prospectively collected information on cancer incidence from start of the intervention and on the baseline examination with respect to all variables in the webappendix except those with colinearity properties. Missing values were imputed by using group-specific and sex-specific median values. *A questionnaire-based, normally distributed variable ranging from 0–12, with the highest score for the most frequent contact with family and friends.

Table 2: **Multiple Cox proportional hazards models of fatal and nonfatal cancer events from the start of the trial done in all patients and separately for females and males**

0·55–0·93, p=0·0013; HR for women only: 0·60; 0·44–0·81, p=0·0009), with or without imputation for missing data (ie, after the exclusion of 202 women and 118 men with missing values regarding at least one potential covariate: HR for all: 0·73; 95% CI 0·57–0·93, p=0·011; HR for women: 0·59, 0·44–0·79, p=0·0004) and, with baseline and matching datasets (HR for all: 0·70; 0·55–0·89, p=0·0035; HR for women: 0·60, 0·45–0·80, p=0·0005). Additionally, age, sagittal trunk diameter (a proxy for intra-abdominal adiposity)[21] and smoking contributed to the explained variance in women (table 2).

First-time tumours of different origins in men and women over the first 3 years and over the entire observation period are given in the webappendix. In men, the incidence reduction did not reach significance for any type of cancer. In women, most cancer types were less common in the surgery group, but a significant treatment effect was seen only for malignant melanoma, haematopoietic cancers, and for cancers of an origin



Weight change tertile (mean, min, max kg)	n	HR (95% CI)	p
I (−17·0, −23·5 to 4·1)	465	1·00 (–)	..
II (−28·5, −33·9 to −23·6)	471	1·20 (0·64 to 2·26)	0·57
III (−42·8, −111·2 to −33·9)	473	1·67 (0·92 to 3·01)	0·091

Weight change tertile (mean, min, max kg)	n	HR (95% CI)	p
I (5·7, 1·9 to 21·3)	472	1·00 (··)	..
II (0·2, −1·8 to 1·9)	476	1·45 (0·91 to 2·32)	0·12
III (−8·0, −61·4 to −1·8)	474	0·97 (0·59 to 1·59)	0·90

Figure 4: **Unadjusted cumulative incidence of fatal plus non-fatal cancer from start of year 4 and onwards, stratified by weight-change tertiles (kg) during the first year**

Analyses were done separately for women who underwent surgery and controls. 36 cancer events that occurred during the first 3 years were excluded from the analyses. In individuals with missing information regarding bodyweight at 12 months, the 6-month weights were used. In 103 controls and 16 women who underwent surgery, both 6-month and 12-month weights were missing. In these cases group-specific (surgery subtype/control) median 1-year weight changes in women were imputed.

other than those specified in the figure (see webappendix).

In men, reduced cancer incidence was not seen for any of the three surgical techniques (p of 0·56–0·77) whereas in women HR was 0·54 for banding (95% CI 0·31–0·93, p=0·026), 0·60 for vertical banded gastroplasty (0·44–0·82, p=0·0012), and 0·54 for gastric bypass (0·26–1·15, p=0·11) (webappendix).

To examine whether weight changes were related to cancer incidence in patients with the same type of treatment, unadjusted analyses of cancer incidence from the start of year 4 by weight-change tertiles during the first year were done separately among women who underwent surgery and women in the control group. There were no significant relationships between cancer incidence and weight change in women in the surgery or control groups (figure 4).

The female cancer incidence from the start of year 4 was also analysed in a multivariable Cox-regression

	HR (95% CI)	p
Treatment	0·38 (0·20–0·73)	0·0036
Weight change (per 10 kg)	0·97 (0·75–1·26)	0·83
Treatment×weight change	0·88 (0·64–1·20)	0·41
Age (per year)	1·07 (1·04–1·09)	<0·0001
Smoking (yes or no)	1·49 (1·06–2·09)	0·022
Sagittal diameter (per 10 cm)	1·61 (1·05–2·51)	0·030

N=2831. Predictors include weight change during the first year after inclusion, treatment group (surgery or control), treatment×weight change interaction, and the significant variables of table 2. Hazard ratios and corresponding 95% CIs are shown. In women with missing information regarding bodyweight at 12 months, the 6-month weights were used. In 103 control women and 16 surgery women both 6-month and 12-month weights were missing. In these cases, group-specific (surgery subgroup or control) median 1-year weight changes were imputed. 36 cancer events occurring during the first 3 years after inclusion were excluded from the calculations. The effect of weight change and treatment×weight change interaction are the only non-significant variables shown.

Table 3: **Multiple Cox proportional hazards model for female cancer incidence from start of year 4**

model that included all significant variables indicated in table 2 and changes in bodyweight during the first year (table 3). Under these circumstances the treatment group (ie, surgery or control) was a significant predictor of cancer incidence (HR 0·38, 95% CI 0·20–0·73; p=0·0036), whereas changes in body weight was not (0·97, 0·75–1·26; p=0·83) (table 3). The treatment×weight change interaction was non-significant (p=0·41), suggesting that the direction of the weight-change effect on cancer incidence was no different in surgery and control women. Baseline age, smoking, and sagittal trunk diameter were also significantly related to female cancer incidence (table 3). When all patients who had missing baseline or missing weight-change information were excluded the results were very similar (data not shown).

When change in energy intake during the first year was assessed in the same way as weight change (figure 4 and table 3) no significant effects on the female cancer incidence were seen (HR per 500 kcal/day difference 0·98; 95% CI 0·87–1·11, p=0·77).

Within 90 days from the start of the study, five of 2010 patients (0·25%) in the surgery group and two of the 2037 (0·10%) patients in the control group died. As reported elsewhere for 1164 patients,[19] 151 (13%) patients had 193 postoperative complications (bleeding in 6 of 1164 patients [0·5%]; thrombosis and embolism in 9 patients [0·8%]; wound complications in 21 patients [1·8%]; deep infections in 24 patients [2·1%]; pulmonary complications in 71 patients [6·1%]; and other complications in 62 patients [5·3%]). In 26 patients (2·2%), the postoperative complications were serious enough to require reoperation.

Discussion

Only a small fraction of all cancers can be related to genetic factors, while most are influenced by lifestyle and environment[22] and might therefore be preventable. Cancer incidence is clearly increased in obese individuals,[1] although it has been less clear whether obesity treatment decreases cancer incidence. In this Article, bariatric surgery was associated with a significant reduction in cancer incidence in the entire study group. Unexpectedly, however, cancer incidence was only reduced in women (HR 0·58; 95% CI 0·44–0·77, p=0·0001). Since cancer incidence was not a predefined endpoint of the SOS Study it is not possible to assess the robustness of our findings in any way other than by means of observed CI and p value. However, to put this risk reduction into perspective, it might be helpful to compare it with statin treatment, where the HR for reduction in incidence of fatal plus non-fatal myocardial infarction (*vs* placebo) has been in the order of 0·80.[23]

The main limitation of the SOS Study was that the intervention could not be randomised for ethical reasons. At baseline, the prevalence of previous cancer was similar in the surgery and control groups. At both matching and baseline examinations, BMI and some risk factors were slightly higher in the surgery group than in the control group, indicating that the unadjusted risk reduction reported for the surgery group is conservative. Over the first 15 years of follow-up, there were ten pre-defined visits in both surgery and control groups, suggesting that the chance for cancer detection was similar in both groups. If anything, the weight reduction in the surgery group would facilitate cancer detection,[24] but the cancer incidence was still lower in this group.

Another limitation is that cancer incidence was not specified as a secondary endpoint in the study protocol. When SOS was planned in 1985–87, available literature indicated that fatal plus non-fatal myocardial infarction would become the most common endpoint, and we wanted to limit the number of secondary endpoints as much as possible. In reality, it turned out that the incidence of myocardial infarction in the control group was only about 70% of that for cancer. Since the current report is exploratory, new controlled, and preferably randomised bariatric surgery interventions for cancer are needed. These studies need to be about three times larger than SOS so that the statistical power permits a proper examination of the relationships between weight loss and cancer. These studies would be very expensive, and it would be very difficult to find patients willing to accept randomisation over prolonged periods of time. Such studies might also be difficult to do because of ethical concerns, since several studies now show that bariatric surgery reduces overall mortality[15,25] and has many other positive effects in obese individuals.[26]

Epidemiological studies suggest that the beneficial effect of weight loss on cancer is greater in women than in men.[4,5] Two reports[11,12] from retrospective cohort studies on bariatric surgery and cancer incidence have recently been published. In one of them, the cancer incidence was not reported by sex.[11] In the other,[12] bariatric surgery had a significant effect on cancer incidence in women (HR 0·73; p=0·0004) but not in men (HR 1·02; p=0·91), thus supporting our prospective results.

It has been claimed that bariatric surgery mainly affects obesity-related cancers,[12] but whether a clear-cut distinction can be made between obesity-related and non-obesity-related cancers is uncertain. In Renehan's extensive meta-analysis,[1] the risk ratios (RR) per 5 BMI units difference at baseline showed a continuum, and 80% of examined cancer types had a RR above 1·0. Furthermore, in the meta-analysis of women, the RR of endometrial (1·59) and kidney (1·34) cancers were high,[1] while the effect of bariatric surgery on the incidences of these conditions seemed to be low in our study. Conversely, malignant melanoma was negatively related to BMI in the meta-analysis of women,[1] while bariatric surgery had a favourable effect on this condition. In other words, the sex-specific incidences of different cancer types in obesity are not necessarily proportional to their responses to bariatric surgery. In our study, the significant

reduction in overall cancer incidence in the female surgery group emanated from a variety of cancer types, indicating a broad effect of bariatric surgery.

Increased cancer risk in obese patients might be related to central obesity and metabolic deregulation. Exposure to endocrine disruptors (food contaminants, stress, others) affecting the normal regulation of oestrogens, androgens, and insulin might also affect the development of obesity and cancer.[27] Abdominal obesity is linked to alterations in the levels or activities of three suggested mediators of increased cancer incidence in obese individuals: insulin and the insulin-like growth factor-1 (IGF-1);[28] sex steroids;[29] and adipokines.[30] We investigated various baseline variables of body composition and metabolism as predictors of cancer occurrence. In addition to treatment, the baseline sagittal trunk diameter[21] came out as a strong multiple cancer predictor, whereas bodyweight and BMI did not, indicating that visceral adiposity is a stronger risk factor for cancer than obesity per se, at least in women. Some studies have reported that gastric bypass has a weight-loss-independent effect on insulin, mediated via changed gastrointestinal hormone signalling.[31] In a previous report, the reduction in insulin was twice as large after gastric bypass as after restrictive bariatric procedures.[14] If hyperinsulinaemia mediates cancer development, one could therefore expect gastric bypass to be associated with more pronounced cancer protection than restrictive techniques. However, this was not the case in our study. Also, insulin and anthropometric proxies for visceral obesity[21] were higher in men than women but the beneficial effect of bariatric surgery on cancer was seen only in women. Future studies are needed to clarify which endocrine disruptors or other cancer mechanisms that can be more easily influenced in a favourable direction by bariatric surgery in women.

Although the range of weight changes were large in both study arms, the mean 10-year weight change was close to zero (a gain of 1·3 kg) in the control group. The large difference in weight change between the surgery group and the control group was anticipated, since even during specialised care, non-surgical treatment of obesity was and is associated with small long-term weight losses.[32–34] Additionally, many patients do not obtain advice from their primary health-care physicians on how to lose weight efficiently.[35] In line with this, the prevalence of obesity is increasing in many countries,[2] and we saw no weight loss in the SOS controls.

The primary aim of SOS was to assess whether weight loss, achieved by means of bariatric surgery, was associated with reduced overall mortality. Although we showed that bariatric surgery was associated with decreased mortality, we were unable to show an association between weight loss and overall mortality.[15] Similarly, in the current report, secondary subgroup analyses of the female surgery and control groups did not detect associations between cancer incidence and weight loss or reduced energy intake. In fact, in the female surgery group, weight loss showed a non-significant association with increased cancer incidence. The absence of a favourable weight loss effect on cancer might well be a chance finding explained by limited statistical power when the surgery and control groups were further divided in weight-loss tertiles. In the multivariable analyses, the colinearity between treatment group and degree of weight loss might have obstructed the detection of a weight-loss effect. The relation between weight change and cancer deserves further exploration after longer follow-up or in larger controlled intervention trials.

Although food questionnaires have very limited precision on the individual level, the SOS questionnaire is validated against 24-h energy expenditure and gives reliable energy intake levels both in lean and obese weight-stable study groups,[18] as well as reasonable energy intake levels in the SOS surgery and control groups over 10 years of observation.[14] Using this questionnaire, we were unable to find significant associations between changed energy intake and cancer incidence. Again, this absence of an effect might be due to limited statistical power.

Energy reduction is associated with decreased breast-cancer incidence in mice.[36] However, a prospective randomised nutrition trial in 48 835 postmenopausal women showed no association between a reduced fat intake and incidence of breast[37] or colon[38] cancer, and no effects of fat reduction on the incidence of benign proliferative breast disease,[39] a condition that is thought to be precancerous. Published information is difficult to interpret because of interactions between energy and macronutrient intake, physical activity, body mass, and metabolic efficiency,[40] and the relationships between reduced energy and fat intake and cancer need to be explored further.

Earlier reports from SOS show that bariatric surgery is associated with reduced overall mortality, and has beneficial effects on diabetes, other cardiovascular risk factors, intima-media progression rate, cardiovascular symptoms, sleep apnoea, joint pain, and health-related quality of life.[26] The current exploratory report on cancer further underlines the favourable effects of bariatric surgery, particularly in women. The intriguing but unproven possibility that the beneficial effects of bariatric surgery on cancer are mediated by mechanisms other than weight loss or reduced energy intake needs to be further explored.

Contributors

The study was initiated by LS and designed by LS, HW, CBe, CBo, SD, BL, and IN, done by the steering committee and supervised by the safety monitoring committee. The steering committee consists of LS (chairman), KN, CBe, CBo, JK, HL, IN, JT, and LMSC. The safety monitoring committee consists of HW (chairman), SD and BL. Surgical expertise was provided by SD, HL, IN, and TO, and CBe was an important link to the Swedish primary health-care system. CBo, BC, PJ, and LMSC provided genetic expertise. KN cross-checked the SOS database against public registers and KN, CDS, and AG checked that all diagnoses were correct. CDS traced and interviewed emigrants. LS, AG, CDS, KN, HW, and PJ did initial calculations, and MP independently checked all data and did all statistical analyses. LS and AG wrote the first version of the manuscript, and all co-authors critically revised the manuscript. LS, AG, CDS, PJ, and LMSC compiled the final manuscript, which was approved by all authors.

Conflicts of interest

SOS has previously been supported by grants to LS from Hoffmann-La Roche, AstraZeneca and Cederroths. From 2007 LS is also obtaining SOS grants from Sanofi-Aventis and Ethicon. LS has obtained lecture and consulting fees from AstraZeneca, Biovitrum, BMS, GlaxoSmithKline, Johnson and Johnson, Lenimen, Merck, Novo Nordisk, Hoffmann-La Roche, Sanofi-Aventis, and Servier, and holds stocks in Lenimen and is chairman of its board. BC is employed by AstraZeneca and holds stocks in the same company. IN has obtained lecture fees from Johnson and Johnson. A-KL has served as a consultant for Abbott. DS has obtained consulting and lecture fees from Sanofi-Aventis and Ethicon. PJ has obtained research grants from Hoffmann-La Roche. JK has served as consultant for Pfizer. KS has served as consultant for AstraZeneca, Janssen-Cilag, GlaxoSmithKline, BMS, MSD, Novo Nordisk and SanofiAventis. JT obtained lecture grants from AstraZeneca, Johnson and Johnson, and Roche, and consulting fees from Roche. LMSC has served as a consultant for AstraZeneca and holds stocks in Sahltech. All other authors declared no conflicts of interest.

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