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ORIGINAL ARTICLE

Impact of weight change, secular trends and ageing on cardiovascular risk factors: 10-year experiences from the SOS study

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Objective: Many short-term studies indicate that 5% weight loss in the obese is enough to induce significant improvements of cardiovascular risk factors. However, it is not known what degree of weight loss is required to improve risk factors over a more extended period of time or how ageing and secular trends *per se* are influencing risk factors during long-term follow-up.
Methods: Patients examined after 10 years in the intervention study Swedish Obese Subjects were used for the current analysis. Surgically treated subjects ($n = 959$) and conventionally treated obese controls ($n = 842$) were pooled to obtain a study group with a large range of weight changes. The patients were divided in 11 groups based on the amount of weight change. Analysis of covariance was used to determine the necessary weight change over 10 years for a significant alteration of a risk factor. In a linear regression of risk factor change by weight change, the *y* intercept was interpreted as the effect of 10 years ageing and secular trends on a given risk factor in the absence of weight change.
Results: The necessary weight loss for significant improvement of risk factors ranged from 10 to 44 kg. At zero weight change, 10 years of ageing was associated with significant increases in systolic blood pressure, pulse pressure, high-density lipoprotein cholesterol and glucose, and with significant decreases in diastolic blood pressure, total cholesterol, triglycerides and insulin.
Conclusions: The necessary weight loss to maintain a favourable effect on risk factors in an obese population is larger than previously indicated by short-term studies. Treatment effects are influenced by non-weight change-dependant shifts in risk factor levels.
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Keywords: weight loss; ageing; long-term effects; risk factors; bariatric surgery

Introduction

The beneficial effects of modest weight loss have been widely accepted since the Goldstein review was published in 1992.[1] Goldstein's conclusions have been backed up by several other studies.[2,3] In the World Health Organization (WHO) report on obesity, published in year 2000, it was estimated that a 10 kg weight loss was associated with reductions of 10 and 20 mm Hg in systolic and diastolic blood pressure, respectively, 10–15% reductions in total and low-density lipoprotein cholesterol, 30% reduction in triglycerides and with an 8% increase in high-density lipoprotein (HDL) cholesterol.[4]

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However, the WHO estimates were mainly based on studies with durations shorter than 2 years. Recent meta-analyses based on studies with at least 2 years follow-up have resulted in more modest expectations.[5–7] According to some of these analyses, 10 kg weight loss is associated with 5–6 mm Hg reductions in systolic and diastolic blood pressure, and in 0.23 mmol l^{-1} reduction in cholesterol.[5,6] It is also noted that even in studies with $\geqslant 5\%$ weight loss after at least 2 years, the weight loss does not uniformly improve cardiovascular risk factors.[7] Given the difficulties in maintaining weight losses over time, it is not surprising that the majority of included studies in the meta-analyses have observation periods of less than 5 years.

The current report is based on 10-year data from the intervention study Swedish Obese Subjects (SOS).[8–11] Risk factor changes were analyzed as a function of weight change over a wide range of body weight changes in severely obese subjects. Our hypothesis was that over prolonged periods of time much larger weight losses than previously believed are required to produce significant improvements of

cardiovascular risk factors. Furthermore, we hypothesized that ageing and secular trends (taken together, designated as total time effect in this paper) may influence the interpretation of risk factor changes in long-term observational studies. Therefore, we wanted to separate the effect of weight change from the total time effect on risk factors.

Subjects and methods

Study design

SOS is a prospective, intervention trial of 4047 obese subjects. The outcomes in a surgically treated group are compared with those in a contemporaneously matched, conventionally treated obese control group. A computerized matching programme produced two comparable study groups.[8–11]

The intervention study for a surgically treated patient and his or her matched control began on the day of the surgically treated subject's operation. The SOS study enroled patients between 1987 and 2001. The dates of all subsequent examinations for both subjects were calculated in relation to the date of surgery. The examinations were conducted at 25 surgical departments and 480 primary health-care centres in Sweden.

Inclusion criteria for the intervention study were a body mass index of 34 or more (for men) and 38 or more (for women), and an age of 37–60 years. Exclusion criteria were minimal and were aimed at ensuring that the subjects in the surgical group could tolerate the operation. Identical inclusion and exclusion criteria were used in the two study groups. Subjects with diabetes, hypertension or lipid disturbances were not excluded nor were patients with myocardial infarction or stroke having occurred more than 6 months before inclusion. The study design has been described in detail elsewhere.[8–11]

The Ethics Review Board at each of the seven involved participating universities in Sweden approved the protocol, and all participants gave their written informed consent.

Participants of this report

For the purposes of this report, the first 1801 patients who had been enroled for at least 10 years were included. This corresponded to a 71% participation rate at the 10-year examination. The surgically ($n=959$) and non-surgically ($n=842$) treated patients were pooled to create a study group with as broad range of weight changes as possible.

Three types of surgical interventions were performed at inclusion. These were vertical banded gastroplasty ($n=685$, 71.4%), banding ($n=227$, 23.7%) and gastric bypass ($n=47$, 4.9%).[12] Also, 38 of the control patients had undergone surgical treatment within 10 years from inclusion. Owing to conversions from other types of surgery and new operations in controls, a total of 171 patients had received a gastric bypass during the observation period.

The conventional, non-surgical treatments were the same as those usually offered at each patient's primary health-care centre. No attempt was made to standardize the non-surgical treatment, which ranged from sophisticated lifestyle intervention and behaviour modification to, in some practices, no treatment whatsoever. No anti-obesity drugs were approved in Sweden until 1998.

At baseline, 25% of the 1801 patients were taking anti-hypertensive drugs (ATC codes: C02, C03, C07, C08 and C09). At 10 years, this figure was 44%. Corresponding figures for anti-diabetic medication (ATC code A10) were 6 and 17%, for drugs against dyslipidemia (ATC code C10) 1 and 12%, and for weight-reducing drugs (ATC code A08) 0 and 5%, respectively.

Clinical and biochemical assessments

Body weight was measured to the nearest 0.1 kg and height to the nearest 0.01 m. Body mass index was calculated as weight divided by height squared ($kg\,m^{-2}$). Waist circumference was measured in the supine position halfway between the lower rib margin and the iliac crest. Systolic and phase 5 diastolic blood pressure readings were made after 15 min in the supine position. Cuff width and upper arm circumference were recorded in each individual case.

All blood samples, which were obtained in the morning after a 10- to 12-h fast, were analyzed at the Central Laboratory of Sahlgrenska University Hospital (accredited according to the European norm 45001). Apart from glucose, which was analysed in whole blood, all risk factors were analysed in serum. Risk factor values have been adjusted for all changes in laboratory techniques that have occurred over the study period.

Dietary intake was measured by the validated SOS Dietary Questionnaire.[13,14] From the questionnaire, total energy intake in kilocalories and alcohol in grams per day were calculated. Subjects were also asked to rate their physical activity during leisure time on a scale from 1 to 4, where 1 denotes sedentary activity and 4 regular strenuous exercise.[13,15] In the current report, ratings were dichotomized; a rating of 1 corresponded to physically inactive and ratings of 2, 3 or 4 to physically active. In addition, self-reported information on regular medication and smoking habits was obtained from the subjects through questionnaires.

Statistical methods

Unless otherwise specified, data are presented as mean ± s.d. For the determination of the minimum weight loss needed for a significant reduction in risk factor levels, the study group was divided into 11 weight change classes. Patients were ranked in weight change order and then allocated to the classes in such way that the mean weight changes became −30 kg (range −32.5 to −27.5 kg), −25 kg (−27.4 to −22.4 kg), −20 kg (−22.3 to −17.7 kg), −15 kg (−17.6 to

−12.4 kg), −10 kg (−12.3 to −7.4 kg), −5 kg (−7.3 to −2.7 kg), ±0 (−2.6 to +2.5 kg), +5 (+2.6 to 8.0 kg) and +10 (+8.1 to +12.3 kg) kg. Each one of these classes contained 95–212 subjects (see Figures 1–3). Outside each extreme of this interval of weight changes, the remaining patients were added as one large weight loss group and one large weight-gain group with weight change means of −43.7 kg ($n=182$, range −105.7 to −33.0 kg) and +20.5 kg ($n=172$, range +12.4 to +60.6 kg), respectively. The group with a mean weight change of ±0 kg served as reference.

Analysis of covariance was used to estimate changes in risk factors, with adjustment for covariates. Covariates used for all risk factors included treatment group (surgical or conventional), gender, age at baseline, height at baseline, weight at baseline, waist circumference at baseline, kilocalories

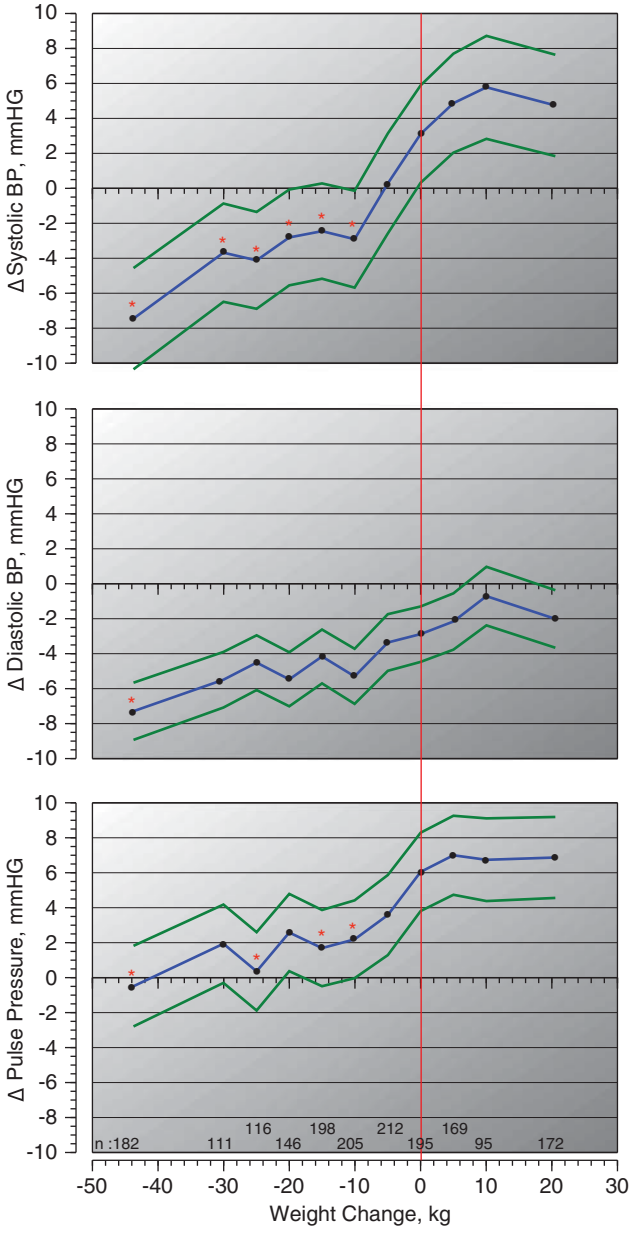

Figure 1 Adjusted means (±95% confidence interval) for 10-year changes in systolic-, diastolic- and pulse pressure in 1801 obese patients. Study population divided into 11 delta weight classes. *Denotes a significant ($P<0.05$) difference in the level of risk factor change as compared with reference (red vertical line).

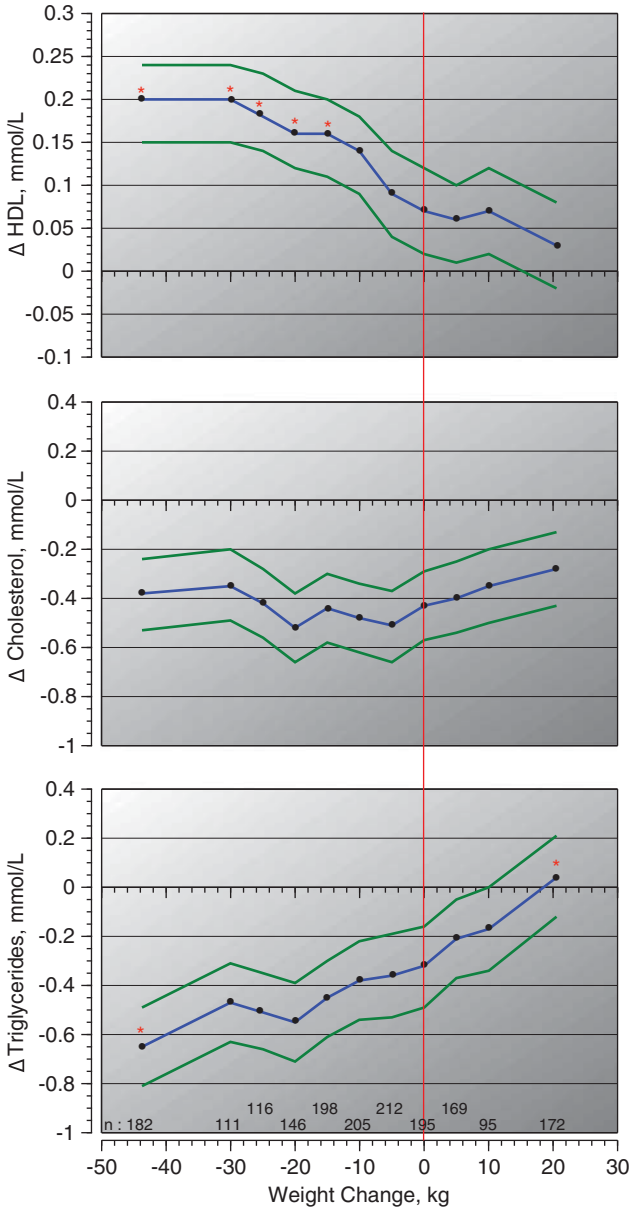

Figure 2 Adjusted means (±95% confidence interval) for 10-year changes in cholesterol, HDL cholesterol and triglycerides in 1801 obese patients. Study population divided into 11 delta weight classes. *Denotes a significant ($P<0.05$) difference in the level of risk factor change as compared with reference (red vertical line).

consumed at year 10, physical activity at year 10, alcohol consumption at year 10, smoking status at year 10, and use of ongoing anti-obesity medication. Each model for estimating changes in a specific risk factor was further adjusted for baseline levels of the risk factor in question. Finally, the blood pressure change models were all adjusted for use of blood pressure medication; cholesterol, HDL and triglyceride change models were adjusted for use of lipid moderating medication; the glucose and insulin change models were adjusted for use of medication for diabetes.

With all of the separate models for changes in risk factors, the adjusted means were obtained by multiplying the estimated model coefficients by the observed values of the relevant covariates for all subjects within a given delta weight class and averaging. The necessary weight change for a statistically significant alteration of a risk factor was defined as the smallest possible x distance between two non-overlapping 95% confidence intervals, one of which being located at zero change in body weight.

To evaluate the non-weight change-dependant shift in risk factor levels over the study period, a linear regression model was used. Change in a risk factor was regressed by change in body weight. The y intercept was the risk factor change in the absence of weight change. We interpreted this risk factor shift as the effect of 10-year ageing and secular trends.

As these were exploratory analyses, all hypotheses were tested at a marginal significance level of 0.05, without correction for multiple testing.

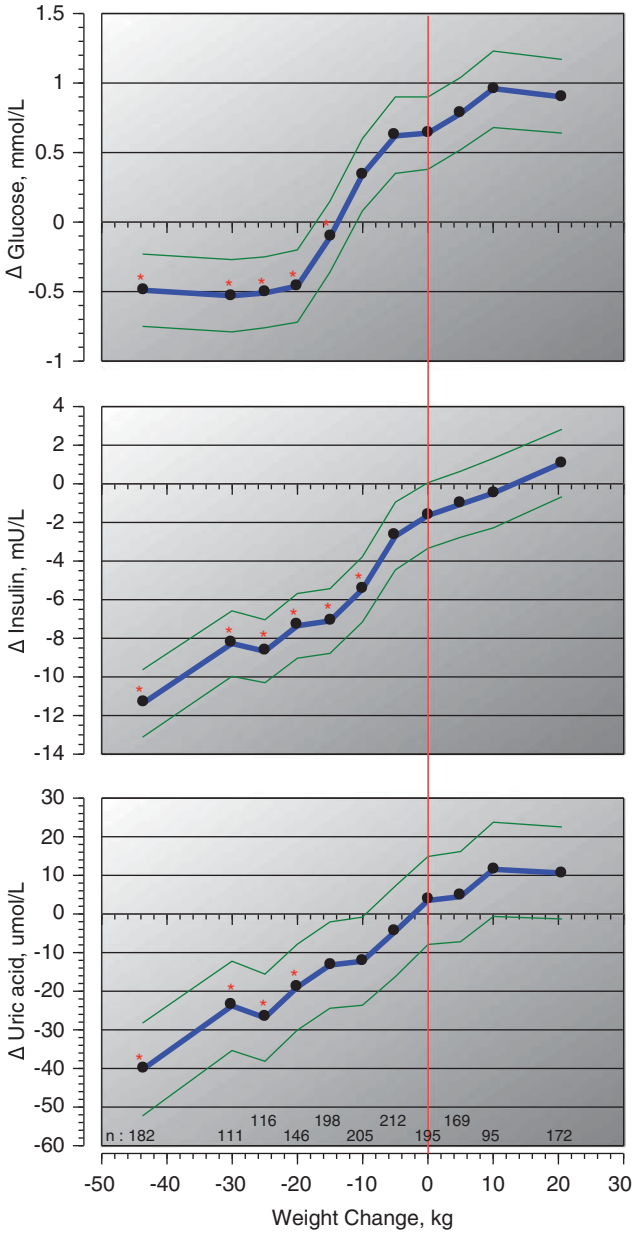

Figure 3 Adjusted means (±95% confidence interval) for 10-year changes in glucose, insulin and uric acid in 1801 obese patients. Study population divided into 11 delta weight classes. *Denotes a significant ($P<0.05$) difference in the level of risk factor change as compared with reference (red vertical line).

Results

Risk factor changes in relation to their baseline values

Baseline characteristics of the study group as well as changes over 10 years are summarized in Table 1. The mean age at baseline was 47.8 ± 6.0 years and the mean body mass index was 40.9 ± 4.6 kg m^{-2}. During the 10-year observation period, the weight change was on average −9.9 kg and ranged from −106 to +61 kg. After 10 years, there was a significant change from baseline values in every cardiovascular risk factor ($P<0.0001$), except for systolic blood pressure ($P=0.40$).

Table 1 Patient characteristics at inclusion and 10-year changes in 1801 surgically and conventionally treated patients (mean ± s.d.)

	Inclusion	*10-year changes*
Number of patients	1801	
Age (yr)	47.8 ± 6.0	
Male sex (%)	31.0	
Smoker (%)	21.8	−3.0
Weight (kg)	117.3 ± 16.7	−9.9 ± 18.2
BMI (kg m^{-2})	40.9 ± 4.6	−3.5 ± 6.3
Waist (cm)	122.1 ± 11.3	−5.8 ± 14.7
Systolic BP (mm Hg)	142.5 ± 18.9	−0.4 ± 20.6
Diastolic BP (mm Hg)	88.6 ± 11.5	−4.0 ± 12.6
Pulse pressure (mm Hg)	53.9 ± 13.7	3.5 ± 16.4
Glucose (mmol l^{-1})	5.2 ± 1.9	0.2 ± 2.2
Insulin (mU l^{-1})	19.7 ± 12.3	−4.7 ± 14.2
Uric acid (μmol l^{-1})	358.1 ± 78.9	−9.8 ± 81.5
Triglycerides (mmol l^{-1})	2.18 ± 1.43	−0.37 ± 1.26
Total cholesterol (mmol l^{-1})	5.86 ± 1.10	−0.42 ± 1.09
HDL cholesterol (mmol l^{-1})	1.19 ± 0.29	0.12 ± 0.31

Abbreviations: BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein.

Risk factor changes in relation to level of weight change
Instead of comparing risk factor changes with baseline values, Figures 1–3 compare risk factor changes at different body weight changes with the risk factor change at no body weight deviation from baseline. Significant differences are indicated with asterisks. A 5 kg weight loss was not associated with any significant risk factor changes over 10 years. A 10 kg average weight loss (or more) was related to significant 10-year improvements in systolic blood pressure (−6.0 mm Hg, 95% confidence interval: −10.66 to −1.38), pulse pressure (−3.9 mm Hg, −7.56 to −0.14) and insulin ($-3.8\,mU\,ml^{-1}$, −6.67 to −0.99). A 15 kg weight loss was required to detect significant 10-year improvements of HDL cholesterol ($+0.09\,mmol\,l^{-1}$, 95% confidence interval: 0.01 to 0.17) and glucose ($-0.75\,mmol\,l^{-1}$, −1.18 to −0.31), whereas a significant reduction in uric acid ($-22.4\,umol\,l^{-1}$, −44.04 to −0.83) required a maintained weight loss of 20 kg. Significant improvements in diastolic blood pressure (−4.4 mm Hg, −7.13 to −1.68) and triglycerides ($-0.33\,mmol\,l^{-1}$, −0.61 to −0.05) as compared with the weight-stable reference group were only seen in the weight change class with the largest weight loss, 44 kg. Total cholesterol was not significantly improved in any of the studied weight change classes.

Risk factor changes in relation to ageing and secular trends
The *y* intercept of a linear regression model was used to estimate the shift in risk factor levels over 10 study years at no body weight change (Table 2). This time effect was associated with elevations of systolic blood pressure, pulse pressure, glucose, HDL cholesterol and uric acid but with decreases of diastolic blood pressure, insulin, triglycerides and total cholesterol. All effects were significant at $P<0.001$, except for insulin ($P=0.003$). As illustrated by Figures 1–3, the relationships between weight change and risk factor change were not always perfectly linear, but the risk factor changes at no weight change in the figures agree well with the *y* intercepts of Table 2.

Table 2 Risk factor changes in response to 10 years of ageing with no weight change (mean and 95% CI)

	10 years of ageing[a]
Systolic BP (mm Hg)	2.5 (1.4, 3.5)
Diastolic BP (mm Hg)	−2.4 (−3.0, −1.7)
Pulse pressure (mm Hg)	4.8 (3.9, 5.6)
Glucose ($mmol\,l^{-1}$)	0.6 (0.5, 0.7)
Insulin ($mU\,l^{-1}$)	−1.0 (−1.6, −0.3)
Uric acid ($\mu mol\,l^{-1}$)	7.6 (3.7, 11.6)
Triglycerides ($mmol\,l^{-1}$)	−0.18 (−0.24, −0.12)
Total cholesterol ($mmol\,l^{-1}$)	−0.37 (−0.42, −0.31)
HDL cholesterol ($mmol\,l^{-1}$)	0.06 (0.04, 0.07)

Abbreviations: BP, blood pressure; CI, confidence interval; HDL, high-density lipoprotein.
All values are significant at $P<0.001$, except for insulin ($P=0.003$). [a]*y* intercept, in a linear regression model, at weight change = 0 kg.

Sensitivity analyses
Owing to a limited number of observations, the effects of large weight increases and decreases on risk factors could not be analyzed separately for surgically and non-surgically treated subjects. However, a reasonable number of observations of both treatment groups were available for 10 and 15 kg weight loss. Controls that had undergone bariatric surgery during the study period were excluded from these calculations. As shown in Table 3, a given weight loss resulted in similar risk factor changes in both treatment groups. However, for glucose, there were significant differences between the groups in favour of surgery both at 10 and 15 kg weight loss.

We also repeated all calculations for Figures 1–3 after exclusion of 171 gastric bypass patients. Our conclusions were not changed by this exclusion (data not shown). If anything, even larger weight losses in the remaining patients were needed to achieve significant changes in HDL cholesterol, triglycerides and uric acid.

Discussion

This paper demonstrates that larger weight losses than previously believed are needed to achieve effects on risk factors over 10 years in the severely obese. Weight changes in the order of 10–45 kg (9–38%) were required to achieve significant risk factor changes. A 5 kg (4%) weight reduction did not influence any of the measured risk factors significantly.

Previous reports from the SOS trial comparing surgical and conventional treatment have demonstrated that bariatric surgery is an effective strategy for treating and preventing diabetes, for improving hypertension and various lipid disturbances.[9,16–19] However, these papers have not explored what degree of weight loss is actually required to achieve significant long-term improvements in risk factors. Our current results are at variance with short-term studies with less than 2 years of mean follow-up in which 5–10% weight loss was enough to improve risk factors substantially.[1,3,4,20] This does not imply that short-term data are not reliable, just that results are not to be extrapolated to longer periods of time or to other degrees of obesity than the studies originally comprise. Weight loss data from prospective clinical trials with follow-up periods longer than a few years are very scarce. This is mainly because of relatively small weight changes over time and large dropout rates. In this perspective, the current analyses might help to increase our knowledge about the long-term effects of weight loss.

In the current report, we tried to separate effects of weight loss *per se* from effects of ageing and potential time trends. These shifts in risk factor levels are making the interpretation of weight change effects even harder. Sometimes a beneficial weight loss-dependant change in a risk factor will act in the same direction as a non-beneficial time/age-dependant shift

Table 3 Comparisons regarding effects on risk factor changes between surgically and non-surgically treated subjects who experienced 10 and 15 kg weight loss over 10 years (mean ± s.d.)

	10 kg weight loss			*15 kg weight loss*		
	Surgery	*Conventional*	P	*Surgery*	*Conventional*	P
Number of patients	128	74		146	45	
Baseline age (year)	47.4 ± 5.6	49.5 ± 6.4	0.015	47.6 ± 5.8	49.2 ± 6.2	0.10
Baseline body weight (kg)	115.6 ± 14.8	115.2 ± 14.5	0.85	117.1 ± 13.5	118.3 ± 16.7	0.62
10-year weight change (kg)	−10.1 ± 1.5	−9.9 ± 1.4	0.41	−15.1 ± 1.6	−14.8 ± 1.7	0.23
10-year risk factor changes						
Systolic BP (mm Hg)	−2.1 ± 23.4	−0.1 ± 19.0	0.53	−1.8 ± 19.4	0.6 ± 19.8	0.48
Diastolic BP (mm Hg)	−4.8 ± 14.7	−4.9 ± 12.1	0.98	−3.9 ± 11.9	−3.0 ± 11.9	0.65
Pulse pressure (mm Hg)	2.7 ± 19.1	4.8 ± 14.4	0.42	2.2 ± 15.5	3.6 ± 17.8	0.60
Glucose (mmol l^{-1})	0.2 ± 1.2	0.8 ± 2.4	0.015	−0.5 ± 1.8	0.8 ± 2.2	0.0001
Insulin (mU l^{-1})	−5.0 ± 10.8	−6.2 ± 7.0	0.39	−7.7 ± 11.0	−9.3 ± 10.8	0.40
Uric acid (μmol l^{-1})	−4.8 ± 74.0	−13.4 ± 88.5	0.46	−15.7 ± 68.6	−21.9 ± 101.5	0.64
Triglycerides (mmol l^{-1})	−0.19 ± 1.92	−0.34 ± 0.79	0.50	−0.46 ± 0.97	−0.39 ± 0.76	0.70
Total cholesterol (mmol l^{-1})	−0.22 ± 1.23	−0.64 ± 1.11	0.017	−0.32 ± 1.05	−0.68 ± 1.21	0.05
HDL cholesterol (mmol l^{-1})	0.12 ± 0.23	0.01 ± 0.24	0.001	0.18 ± 0.30	0.11 ± 0.30	0.20

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein.

in the same risk factor. In the current study, this was evident concerning insulin and diastolic blood pressure.

As expected, 10 years of ageing in an obese body will deteriorate the status of glucose metabolism. The current study showed a significant upward shift in glucose levels and a decrease in insulin output over 10 years. A 15 kg weight loss over 10 years neutralized the effect of the time-dependant upward shift in glucose, and a 20 kg weight loss yielded a decrease in glucose from baseline levels.

The time effect was also associated with a worsening in blood pressure status with decreasing diastolic blood pressure and increasing systolic and pulse pressure, whereas weight loss was related to improvements in all three variables. Increasing pulse pressure is caused by increasing, age-dependent stiffness in large elastic arteries.[21] As compared with a normal weight population,[22] the obese patients of the current report seemed to develop their age-dependent decline in diastolic blood pressure 10 years prematurely. It is encouraging that weight loss can prevent this premature ageing of the arteries in obese subjects.

As judged form cross-sectional cohort studies, cholesterol is generally expected to increase with age.[23] Surprisingly, the lipid profile in our study displayed a weight change-independent significant improvement over 10 years. Similar decreases in total cholesterol, but not for triglycerides and HDL, were observed in a 9-year follow-up of weight-stable obese participants in the ARIC study.[24] In that study, it was also noted that the 9-year changes in lipids were more favourable among obese than among normal weight participants. The shift in lipid levels also corresponded to time trends over the last decades with decreasing total cholesterol in normal weight as well as obese populations.[23,25] In Sweden, data from the MONICA project suggest that the general impact from lipid-lowering drugs between 1986 and 2004 has been very modest.[23] Instead, a reduced consumption of saturated fats has been proposed as the most probable reason for this decrease.[26] Whereas both triglycerides and HDL cholesterol were improved by large weight losses, no relationship between weight loss and total cholesterol was evident in the current analyses. The reason for this is not clear.

The main limitation of the SOS trial as such is that, for ethical reasons, it was a matched and not a randomized study. The most important weakness of the current report is that we had to pool surgically and non-surgically treated subjects to obtain a study group with a very wide range of weight changes. To minimize this potential bias, we adjusted for treatment (surgery, non-surgery) in the main analysis. Furthermore, in unadjusted sensitivity analyses at 10 and 15 kg weight loss, the effects on risk factors were very similar in surgically and non-surgically treated subjects. As the changes for glucose were in favour for surgical treatment in these analyses, it might be argued that even larger weight losses would have been needed to achieve the same results from only non-surgical treatment. In other words, the interpretation of the main findings of this study is, if anything, on the conservative side.

Including patients who have undergone gastric bypass might also have confounded the results. After gastric bypass, several gastrointestinal signal peptides are changed in a partly weight loss-independent way.[27,28] In the current report, 171 out of 1801 participants were treated with gastric bypass. However, excluding these patients from the calculations did not change our conclusions.

In summary, our report has illustrated that only large 10-year weight losses are associated with improved risk factors. It is important to take the effects of ageing and secular trends into account when evaluating long-term

changes in risk factor levels. These effects are acting in different directions for different risk factors and are often as large as those of considerable long-term weight changes.

Furthermore, this study lays stress on the urgent need for a broader therapeutic arsenal in the treatment of obesity. Currently, bariatric surgery is the only treatment resulting in large enough weight losses that are sustained over time.

Conflict of interest

CD Sjöström is a current employee of AstraZeneca and has received lecture and/or consulting fees from Sanofi-aventis, Ethicon and MSD. T Lystig is a current employee of Boehringer Ingelheim Pharmaceuticals, a former employee of AstraZeneca, and has stock ownership in Affymetrix, Amgen, AstraZeneca, Medco Health Solutions, Merck and Oncogenex Pharmaceuticals (no individual stock holding worth more than $10 000). AK Lindroos declares no potential conflict of interest.

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Disclaimer

The sponsors of the SOS study had no role in the study design, data collection, data analysis, data interpretation or writing the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication.

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