Effects of Bariatric Surgery in Early- and Adult-Onset Obesity in the Prospective Controlled Swedish Obese Subjects Study

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CARDIOVASCULAR AND METABOLIC RISK

OBJECTIVE

Bariatric surgery is an effective treatment for obesity, but it is unknown if outcomes differ between adults with early- versus adult-onset obesity. We investigated how obesity status at 20 years of age affects outcomes after bariatric surgery later in life.

RESEARCH DESIGN AND METHODS

The Swedish Obese Subjects study is a prospective matched study performed at 25 surgical departments and 480 primary health care centers. Participants aged 37–60 years with BMI ≥34 kg/m^2 (men) or ≥38 kg/m^2 (women) were recruited between 1987 and 2001; 2,007 participants received bariatric surgery and 2,040 usual care. Self-reported body weight at 20 years of age was used to stratify patients into subgroups with normal BMI (<25 kg/m^2), overweight (BMI 25–29.9 kg/m^2), or obesity (BMI ≥30 kg/m^2). Body weight, energy intake, and type 2 diabetes status were examined over 10 years, and incidence of cardiovascular and microvascular disease was determined over up to 26 years using data from health registers.

RESULTS

There were small but statistically significant differences in reduction of body weight among the subgroups after bariatric surgery (interaction $P = 0.032$), with the largest reductions among those with obesity aged 20 years. Bariatric surgery increased type 2 diabetes remission (odds ratios 4.51, 4.90, and 5.58 in subgroups with normal BMI, overweight, or obesity at 20 years of age, respectively; interaction $P = 0.951$), reduced type 2 diabetes incidence (odds ratios 0.15, 0.13, and 0.15, respectively; interaction $P = 0.972$), and reduced microvascular complications independent of obesity status at 20 years of age (interaction $P = 0.650$). The association between bariatric surgery and cardiovascular disease was similar in the subgroups (interaction $P = 0.674$). Surgical complications were similar in the subgroups.

CONCLUSIONS

The treatment benefits of bariatric surgery in adults are similar regardless of obesity status at 20 years of age.

Bariatric surgery is currently the most effective treatment to achieve substantial and long-term weight loss in patients with severe obesity, and it also has beneficial effects on obesity-associated comorbidities such as type 2 diabetes, cardiovascular disease, and cancer (1–6). Despite its effectiveness and establishment as a treatment of obesity, there is still debate regarding in which patients bariatric surgery should be used (7,8).

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The current guidelines for bariatric surgery are based on categorization of BMI together with obesity-related comorbidities, based on the assumption that those with already established obesity-related risk factors and comorbidities would benefit the most from the operation. For patients with obesity and type 2 diabetes, it has been reported that short diabetes duration is associated with better treatment effects of bariatric surgery (9), while less is known about the importance of obesity duration. Early-onset obesity often persists into adulthood and is associated with higher rates of mortality and comorbidities (10–12). When 3-year weight losses in subgroups of patients with obesity were compared in the Longitudinal Assessment of Bariatric Surgery (LABORATORIES) study, those with extreme obesity of early onset had the smallest weight losses (13). However, no studies have evaluated how early obesity onset influences the effects of bariatric surgery on outcomes other than weight loss in adults.

Because patients with early-onset obesity have had prolonged exposure to obesity and the associated risk factors, it is possible that some of the positive effects of bariatric surgery on obesity comorbidities might be reduced. In addition, the group with early onset of obesity may include rare cases of genetic obesity with alterations in the signaling system controlling appetite and energy expenditure, and it is possible that the weight loss after bariatric surgery is reduced or less durable in such patients. We therefore hypothesize that the effectiveness of bariatric surgery, both in terms of weight loss and prevention of obesity comorbidities, may be reduced in patients with early-onset obesity compared with in those with adult-onset obesity. To test this hypothesis, in this study, we examine how self-reported obesity status at 20 years of age affects outcomes after bariatric surgery, including weight loss, type 2 diabetes remission, incidence of major obesity comorbidities, and lifestyle changes in the Swedish Obese Subjects (SOS) study.

RESEARCH DESIGN AND METHODS

Study Design and Treatment

The SOS study is an ongoing, prospective, nonrandomized intervention study comparing the effects of bariatric surgery and conventional obesity treatment (2,5,14,15). In brief, after recruitment campaigns in mass media and at 480 primary health care centers, a matching examination was completed by 6,905 patients, 5,335 of whom were eligible (15). Between 1 September 1987 and 31 January 2001, a total of 4,047 individuals with obesity were enrolled. Patients electing surgery constituted the surgery group, and a matched control group was created using 18 matching variables (14). The surgery and control group had identical inclusion and exclusion criteria. Inclusion criteria were age between 37 and 60 years and a BMI of $\geq$34 kg/m^2 for men and $\geq$38 kg/m^2 for women. Exclusion criteria were earlier surgery for gastric or duodenal ulcer, earlier bariatric surgery, gastric ulcer in the past 6 months, ongoing malignancy, active malignancy in the past 5 years, myocardial infarction in the past 6 months, bulimic eating pattern, drug or alcohol abuse, psychiatric or cooperative problems contraindicating bariatric surgery, and other contraindicating conditions (e.g., chronic glucocorticoid or anti-inflammatory treatment). Seven regional ethics review boards approved the study, and written or oral informed consent was obtained. The SOS study is registered at ClinicalTrials.gov (NCT01479452).

At study start, 2,010 patients were recruited in the surgery group and 2,037 in the control group. The intended surgical intervention was not performed in three patients initially recruited to the surgery group, and thus 2,007 patients were included in the surgery group (266 of whom underwent gastric bypass, 376 banding, and 1,365 vertical-banded gastroplasty) and 2,040 in the control group. In this study, the surgery group consists of all individuals treated by bariatric surgery, regardless of surgical procedure type.

Each surgery patient was matched to a control patient who also started the study on the day of surgery, and baseline examinations in both groups took place 4 weeks before surgery. Follow-up examinations were performed after 0.5, 1, 2, 3, 4, 6, 8, and 10 years. Biochemical variables were measured at baseline and after 2 and 10 years at the Central Laboratory, Sahlgrenska University Hospital (Gothenburg, Sweden; accredited according to ISO/IEC 15 189).

Stratification of Participants Into Subgroups Defined by Self-Reported BMI at 20 Years of Age

To identify those who had early-onset overweight and obesity, we calculated BMI based on self-reported weight at 20 years of age together with baseline height measurements. Information on self-reported weight was collected from the questionnaire that all potential participants completed before the matching examination (on average ~1 year before inclusion). Subgroups were defined as having normal BMI (BMI $<$25 kg/m^2), overweight (BMI 25–29.9 kg/m^2), or obesity (BMI $\geq$30 kg/m^2) at 20 years of age. Ten patients in the per-protocol surgery group were excluded from the analysis due to missing data. Of the remaining 1,997 patients, 725 (36.3%) had normal BMI, 744 (37.3%) were overweight, and 528 (26.4%) had obesity at 20 years old. Eleven patients in the per-protocol control group were excluded from the analysis due to missing data. Of the remaining 2,029 patients, 869 (42.8%) had normal BMI, 721 (35.6%) were overweight, and 439 (21.6%) had obesity at 20 years old.

Stratification and analysis of the study participants according to obesity status at 20 years of age were performed post hoc.

Outcomes

On the date of analysis (31 December 2013), the follow-up time was up to 26 years with a median of 19 years (interquartile range 17–22 years). Data on death and emigration status were obtained by cross-checking social security numbers from the SOS database with the Swedish Cause of Death Register and the Registry of the Total Population.

Patients were considered to have type 2 diabetes if they reported use of glucose-lowering medication or if there was documentation of a fasting blood glucose level of $\geq$110 mg/dL (6.1 mmol/L) or a fasting plasma glucose level of $\geq$126 mg/dL (7.0 mmol/L) (2). Type 2 diabetes status was determined at baseline and at follow-up examinations 2 and 10 years after study start.

Cardiovascular or microvascular disease that was diagnosed in hospital or hospital-based outpatient care or that was associated with death was identified by searching the Swedish Cause of Death Register and the National Patient Register using ICD-9 and ICD-10 codes.

The National Patient Register has 99% coverage of inpatient care and ~80% coverage of specialist outpatient care for somatic diseases (16). Cardiovascular events were defined as fatal and nonfatal acute myocardial infarction or stroke, whichever happened first (6). Microvascular disease was defined as microvascular vascular events affecting eyes, kidneys, and nerves, whichever happened first, as previously described (17). Data on cancer incidence were obtained from the Swedish National Cancer Registry, which has 95% coverage for malignancies (18).

Total energy intake was calculated based on dietary data collected using a semiquantative diet questionnaire (19) completed 4 weeks before inclusion and at all follow-up visits. Leisure-time physical activity was calculated based on questionnaires completed 4 weeks before inclusion and at all follow-up visits.

Statistical Analysis

Baseline characteristics are reported as mean values (with SDs) and percentages. Multilevel mixed-effects models were used to analyze differences in changes in body weight and in self-reported energy intake and physical activity by treatment and BMI category at 20 years of age. The analyses were adjusted for age, sex, and BMI. The observations over time were considered nested within the individuals, and the statistic tests and CIs were therefore calculated controlling for repeated measurements. Tests for treatment by BMI-category interactions were conducted to evaluate between-group differences in changes.

Incidence of and remission from type 2 diabetes were analyzed with logistic regression models for 2- and 10-year follow-up. The results are adjusted for age, sex, and BMI at baseline and expressed as odds ratios (ORs) with 95% CIs. For other diseases, Kaplan-Meier estimates of cumulative incidence were used to analyze time from baseline to the first event. Differences in cumulative incidence between patients who underwent bariatric surgery and control subjects and BMI categories were analyzed with log-rank tests in unadjusted analyses, and Cox proportional hazard regression models were used adjusted for age, sex, and BMI at baseline. The results are presented as adjusted hazard ratios (HRs) with 95% CIs.

A per-protocol approach was used in all analyses; all participants were included in their original study group until any bariatric surgery was performed in the control group or there was a removal of the bariatric surgical procedure in the surgery group resulting in normal anatomy, after which they were censored from the analysis. All *P* values are two-tailed, and $P < 0.05$ was considered statistically significant. Statistical analyses were carried out using the Stata statistical package 15-1 (Stata Statistical Software: Release 15; StataCorp LLC, College Station, TX).

RESULTS

Baseline Characteristics

Baseline characteristics (i.e., at the start of the SOS study) of surgery and control patients divided by self-reported BMI at 20 years of age are shown in Table 1. In both the surgery and control groups, patients with obesity at 20 years of age were younger, were heavier, and had higher BMI at baseline compared with those with normal body weight at the age of 20 years ($P < 0.001$ for all). Most risk factors were less favorable in the subgroups defined by self-reported BMI at 20 years of age of the surgery group compared with the subgroups of the control group, while the differences between subgroups within the surgery and control arms were small.

Changes in Body Weight, Energy Intake, and Physical Activity

Body weight changes over 10 years in the SOS study are shown in Fig. 1. All surgery subgroups experienced an average maximal weight loss of ~25% after 1 year. This was followed by a gradual increase

Table 1—Baseline characteristics of surgery and control patients divided by self-reported BMI at 20 years of age

Variable	Surgery group			Control group		
	BMI <25 (*n* = 725)	BMI 25–29.99 (*n* = 744)	BMI ≥30 (*n* = 528)	BMI <25 (*n* = 869)	BMI 25–29.99 (*n* = 721)	BMI ≥30 (*n* = 439)
Men (0 missing), *n* (%)	190 (26.2)	227 (30.5)	166 (31.4)	233 (26.8)	224 (31.1)	131 (29.8)
Age, years (0 missing)	49.0 (5.7)	47.0 (5.9)	44.9 (5.4)	50.0 (6.0)	48.7 (6.3)	46.1 (5.9)
Weight, kg (0 missing)	117.5 (14.9)	120.3 (15.9)	126.7 (18.4)	112.3 (14.8)	115.0 (16.6)	118.9 (18.5)
BMI, kg/m^2 (0 missing)	41.5 (4.1)	42.1 (4.1)	44.0 (5.0)	39.4 (4.2)	40.1 (4.7)	41.7 (5.3)
Waist-to-hip ratio (6 missing)	0.99 (0.07)	0.99 (0.08)	1.00 (0.08)	0.98 (0.07)	0.98 (0.07)	0.98 (0.08)
Fasting blood glucose, mmol/L (12 missing)	5.21 (2.02)	5.07 (1.88)	5.26 (2.12)	4.90 (1.66)	4.93 (1.88)	5.02 (2.04)
Fasting serum insulin, mU/L (12 missing)	21.55 (11.90)	21.02 (12.96)	22.28 (16.83)	18.23 (10.56)	17.84 (12.18)	17.85 (11.64)
Systolic BP, mmHg (9 missing)	145.7 (18.9)	144.8 (18.7)	144.5 (18.8)	138.5 (17.7)	138.3 (18.4)	136.2 (17.8)
Diastolic BP, mmHg (13 missing)	89.8 (11.0)	90.2 (11.1)	89.6 (11.3)	85.3 (10.2)	85.1 (11.0)	84.7 (11.0)
Total cholesterol, mmol/L (6 missing)	5.95 (1.12)	5.84 (1.12)	5.77 (1.14)	5.74 (1.07)	5.59 (1.05)	5.42 (1.02)
HDL cholesterol, mmol/L (147 missing)	1.38 (0.31)	1.33 (0.32)	1.33 (0.32)	1.36 (0.34)	1.34 (0.32)	1.34 (0.32)
Triglycerides, mmol/L (6 missing)	2.25 (1.20)	2.23 (1.63)	2.28 (1.73)	2.09 (1.60)	1.99 (1.32)	1.94 (1.32)
Type 2 diabetes (11 missing)	134 (18.5)	109 (14.7)	98 (18.6)	106 (12.2)	93 (12.9)	63 (14.4)
Hypertension (1 missing)	216 (29.8)	208 (28.0)	138 (26.1)	245 (28.2)	206 (28.6)	99 (22.6)
Current daily smokers (12 missing), *n* (%)	150 (20.7)	176 (23.7)	188 (35.6)	183 (21.1)	126 (17.5)	111 (25.3)
Ever smokers (0 missing), *n* (%)	486 (67.0)	502 (67.5)	379 (71.8)	496 (57.1)	414 (57.4)	281 (64.0)
Caloric intake/day, kcal (1 missing)	2,927 (1,276)	2,905 (1,182)	2,972 (1,302)	2,616 (1,059)	2,606 (1,007)	2,527 (1,089)

Data are mean (SD) unless otherwise stated. BMI units are kg/m^2. BP, blood pressure.

in body weight, which stabilized at 15–20% weight loss after 8–10 years. There was a small difference in weight loss among the subgroups based on BMI at 20 years old of the surgery group (test of interaction between obesity onset subgroup and treatment on body weight change, $P = 0.032$), in whom the relative weight loss was largest among those with obesity at 20 years old. For example, the relative weight changes at the 1-year follow-up in the surgery group were −24.5% (95% CI −25.3 to −23.8), −24.3% (95% CI −25.0 to −23.6), and −26.7% (95% CI −27.5 to −25.8) in subgroups with normal BMI, overweight, or obesity at 20 years of age, respectively (Fig. 1). In all control subgroups, mean weight changes were small and never exceeded 3%.

During follow-up, energy intake was reduced in all subgroups, but the decreases were larger after surgical treatment (Supplementary Fig. 1*A*). There were small but statistically significant differences in changes in energy intake over time in the subgroups (test of interaction between subgroups and treatment, $P < 0.001$) with the largest relative decrease in energy intake among those with obesity at 20 years of age.

The proportion of patients who were physically active at leisure time increased in all subgroups after bariatric surgery (Supplementary Fig. 1*B*). Test of interaction between treatment and obesity-onset subgroups was not statistically significant ($P = 0.071$).

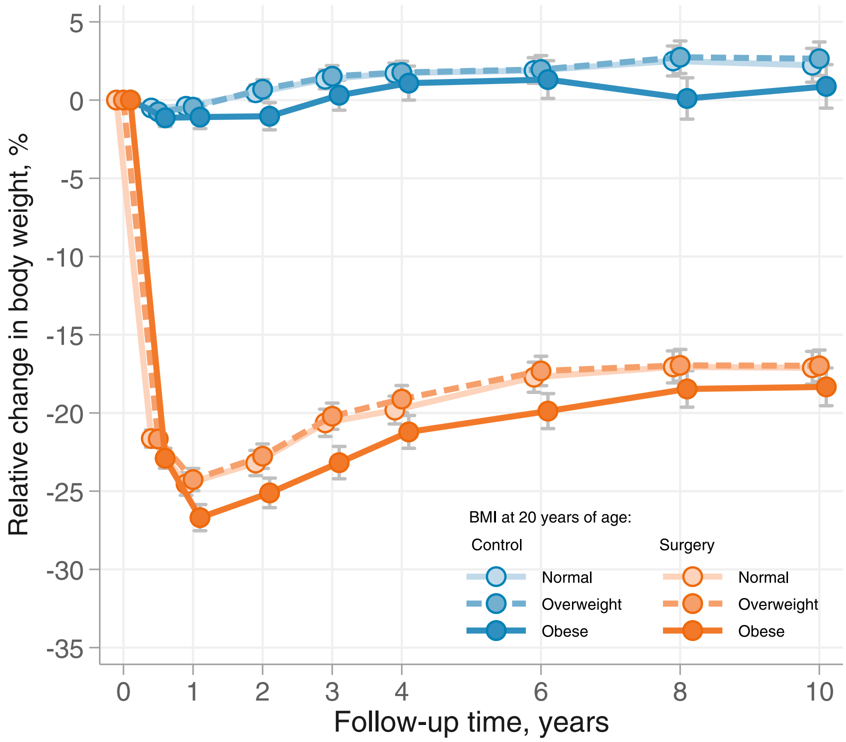

Figure 1—Body weight changes over 10 years after bariatric surgery or usual care in subgroups with normal BMI, overweight, or obesity at 20 years of age. Error bars represent 95% CIs. $P = 0.032$ for interaction between the treatment (bariatric surgery vs. control) and the three subgroups based on self-reported BMI at 20 years old on body weight changes.

Type 2 Diabetes Incidence and Remission

Among patients without type 2 diabetes at baseline, type 2 diabetes incidence was significantly lower in the surgery subgroups compared with the corresponding control subgroups after both 2 and 10 years (Fig. 2*A*). At the 10-year follow-up, the ORs for type 2 diabetes incidence comparing surgery versus control subjects were 0.15 (95% CI 0.09–0.24; $P = 0.000$), 0.13 (0.08–0.22; $P = 0.000$), and 0.13 (0.07–0.025; $P = 0.000$) for subgroups with normal BMI, overweight, or obesity at 20 years old, respectively. There were no differences in treatment benefit by bariatric surgery among the subgroups at 2 or 10 years of follow-up (interaction $P = 0.905$ and 0.972 at the 2- and 10-year examinations, respectively).

At baseline, 339 patients in the surgery group and 229 patients in the control group had type 2 diabetes. Figure 2*B* shows remission of type 2 diabetes in these patients at the 2- and 10-year examinations. The surgery group as a whole had a significantly larger proportion of patients in remission at both the 2- and 10-year follow-up, compared with the control group, and there were no significant differences among subgroups with normal BMI, overweight, or obesity at 20 years of age (interaction $P = 0.201$ and 0.951 at the 2- and 10-year examinations, respectively). At the 10-year follow-up, ORs for remission comparing surgery versus control subjects were 4.51 (95% CI 1.58–12.86; $P = 0.005$), 4.90 (1.69–14.17; $P = 0.003$), and 5.58 (1.11–27.96; $P = 0.037$) in the subgroups with normal BMI, overweight, or obesity at 20 years of age, respectively.

Microvascular Complications

The cumulative incidence of microvascular complications (eyes, kidneys, and peripheral nerves—whichever came first) in subgroups with normal BMI, overweight, or obesity at 20 years old is shown in Fig. 3. In patients without type 2 diabetes at baseline (Fig. 3*A*), incidence of microvascular complications was lower in all subgroups in the surgery group compared with the control group, with adjusted HRs of 0.52 (95% CI 0.35–0.78; $P < 0.001$), 0.38 (0.25–0.56; $P < 0.001$), and 0.39 (0.23–0.66; $P < 0.001$) for subgroups with normal BMI, overweight, or obesity, respectively. In patients with type 2 diabetes at baseline (Fig. 3*B*), the incidence of microvascular complications was lower in the bariatric surgery group compared with the control group, with adjusted HRs of 0.49 (95% CI 0.32–0.77; $P = 0.002$), 0.58 (0.37–0.90; $P = 0.016$), and 0.40 (0.22–0.73; $P = 0.003$) for subgroups with normal BMI, overweight, or obesity at 20 years of age, respectively. Test of interaction indicated that there were no differences in treatment benefit in the subgroups with normal BMI, overweight, or obesity at 20 years old in individuals with and without type 2 diabetes at baseline ($P = 0.698$ and $P = 0.682$, respectively).

Cardiovascular Disease and Cancer

There were no differences in the treatment benefit of bariatric surgery among subgroups with normal BMI, overweight,

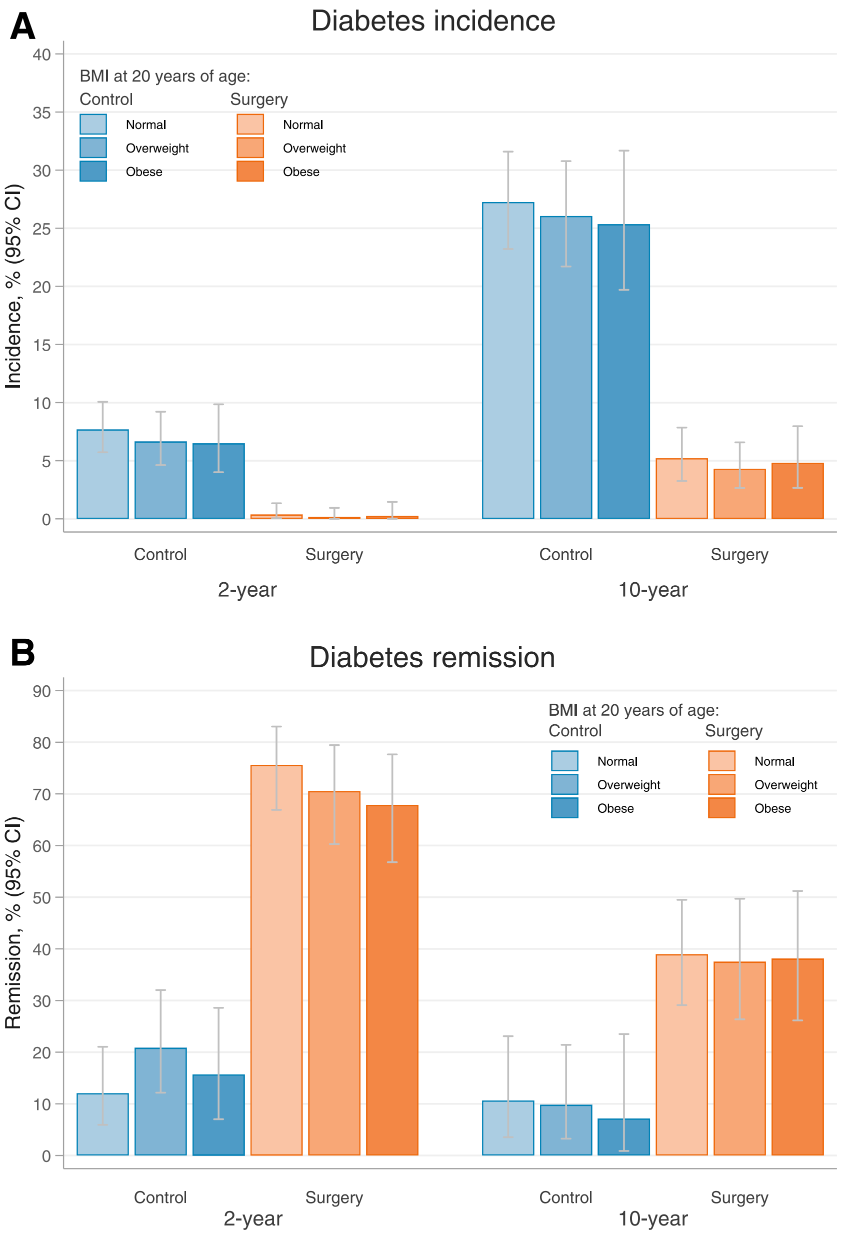

Figure 2—Type 2 diabetes incidence (*A*) and type 2 diabetes remission (*B*) after bariatric surgery or usual care after 2 and 10 years in subgroups with normal BMI, overweight, or obesity at 20 years of age. Type 2 diabetes was defined as fasting blood glucose >6.1 mmol/L or plasma fasting glucose >7.0 mmol/L or self-reported glucose-lowering medication. $P = 0.905$ and $P = 0.972$ for test of interaction between the treatment (bariatric surgery vs. control) and the three subgroups based on self-reported BMI at 20 years of age on type 2 diabetes incidence over 2 and 10 years, respectively. $P = 0.201$ and $P = 0.951$ for test of interaction between the treatment (bariatric surgery vs. control) and the three subgroups based on self-reported BMI at 20 years old on type 2 diabetes remission over 2 and 10 years, respectively.

or obesity at 20 years of age with respect to cardiovascular disease, myocardial infarction, or stroke (Supplementary Fig. 2) (interaction $P = 0.674$, 0.781, and 0.927, respectively). The treatment benefit of bariatric surgery with respect to cancer did not differ among subgroups with normal BMI, overweight, or obesity at 20 years old (Supplementary Fig. 2) (interaction $P = 0.810$).

Postoperative Surgical Complications

Postoperative complications occurred in 14.5% of the patients in the SOS surgery group, and the proportions were similar in subgroups with normal BMI, overweight, or obesity at 20 years of age (13.7, 15.6, and 14.2%, respectively; $P = 0.568$). The types of complications were also similar in the subgroups, with the exception of increased rate of hemorrhage in the subgroup with overweight at 20 years of age and thromboembolism in the subgroup of obesity at 20 years old (Supplementary Table 1).

CONCLUSIONS

Although it is known that there is variability in the effects of bariatric surgery (20,21), to our knowledge, no studies have previously explored the potential influence of obesity onset on the very long-term outcomes of bariatric surgery. For the first time in the SOS study, we compared the effects of bariatric surgery in patients who became obese as adults to those with obesity or overweight before 20 years of age. Our results show that weight loss and reduction of energy intake after bariatric surgery were slightly greater in patients with obesity already at 20 years old, while the effects on obesity comorbidities were similar in subgroups with normal BMI, overweight, or obesity at 20 years of age.

The response to weight loss therapies, including lifestyle modifications, antiobesity drugs, and bariatric surgery, varies among individuals, and it is likely that this variation is partly caused by genetic differences affecting the regulation of food intake and energy expenditure (22–26). In patients with a very strong genetic component, obesity usually manifests at an early age (27,28), and it is therefore likely that the subgroup with obesity at 20 years of age in the SOS cohort includes some individuals with a strong genetic susceptibility to gain weight. In these patients, it is possible that a genetically impaired regulation of food intake could hamper the response to bariatric surgery. However, information on weight loss after bariatric surgery in patients with genetic obesity is limited, and the results have been inconsistent, suggesting that the weight loss may be reduced or show no difference compared with patients with common obesity (23,29–31). Because obesity is the result of a complex interplay between genetic and environmental factors, early-onset obesity in those without a strong genetic cause may reflect an unhealthy lifestyle. The result of surgical treatment of obesity is dependent on adherence to lifestyle advice, including dietary changes, and it is therefore possible that unhealthy eating patterns established in childhood could make it more difficult to

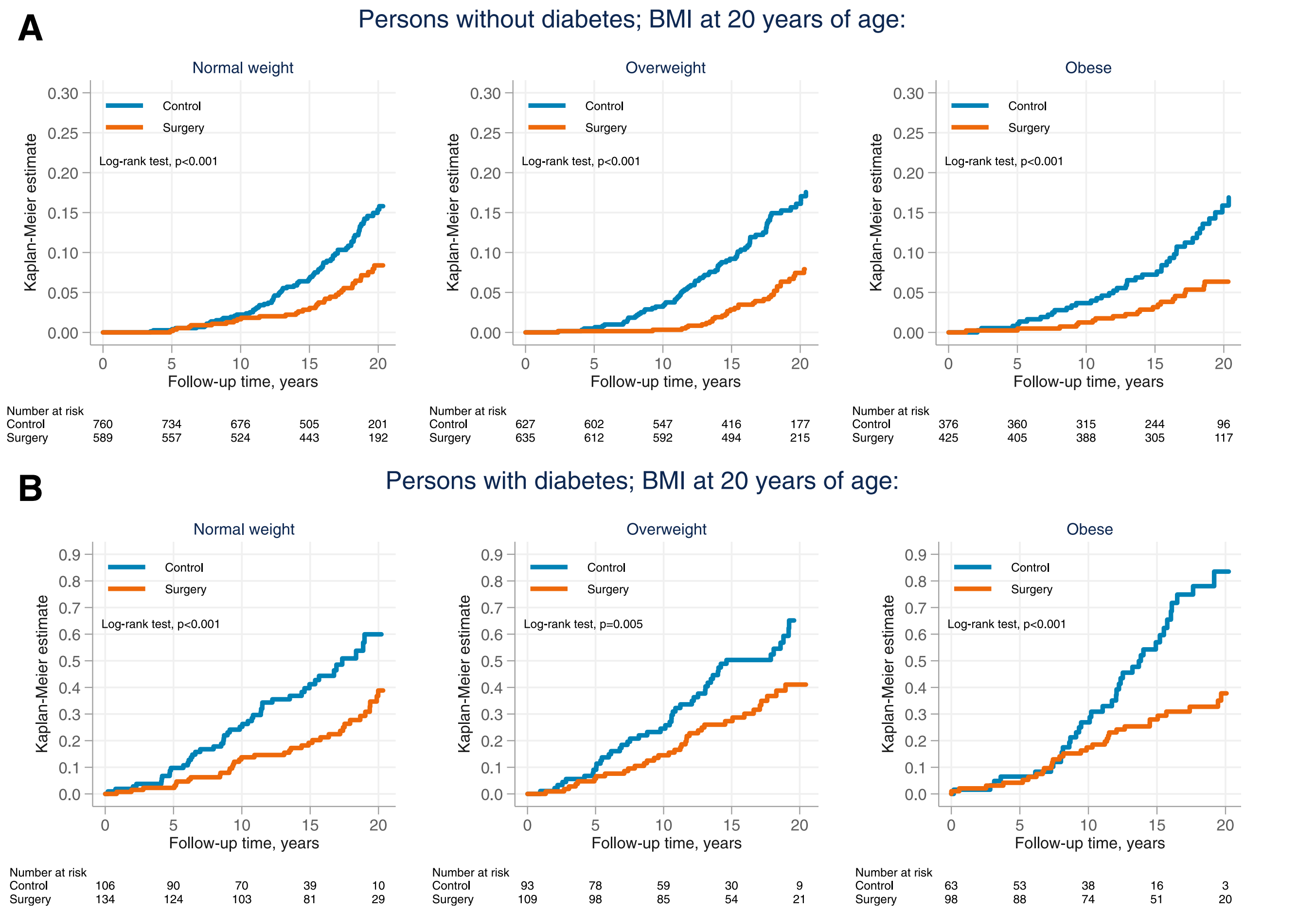

Figure 3—Cumulative incidence of microvascular type 2 diabetes complications after bariatric surgery or usual care in subgroups with normal BMI, overweight, or obesity at 20 years of age. *A* shows patients without type 2 diabetes at baseline, and *B* shows patients with type 2 diabetes at baseline. $P = 0.682$ and $P = 0.698$ for test of interaction between treatment (bariatric surgery vs. control) and the three subgroups based on self-reported BMI at 20 years of age on incidence of microvascular complications in individuals without and with type 2 diabetes at baseline, respectively.

adhere to dietary changes after bariatric surgery. However, our results show that, if anything, the reductions in energy intake and body weight were slightly larger in patients with obesity that was established before 20 years of age compared with those who developed obesity later in life.

In addition to weight loss, the goal of bariatric surgery is also to prevent or ameliorate obesity comorbidities. Patients who develop obesity in childhood will have a longer exposure to the disease, possibly affecting the response to treatment. However, our results demonstrate that bariatric surgery had similar long-term effects on major obesity-related diseases, such as type 2 diabetes and its complications, cardiovascular disease, and cancer, when performed in subgroups of adults with normal BMI, overweight, or obesity at 20 years old. Importantly, the risk of surgical complications was also similar in the subgroups, suggesting that candidates for bariatric surgery with obesity of early or adult onset do not differ from a safety perspective.

A limitation of the SOS study is that the intervention was not randomized. A randomized design was not approved due to ethical reasons because of the high postoperative mortality rate during the 1980s (32). Another limitation is the lack of information on body weight during childhood. Instead, we used self-reported weight at 20 years of age from questionnaires answered before the matching examination to estimate BMI at 20 years of age. Because mean age at inclusion was ∼40 years, a substantial time has passed, which may affect the precision of the answers. All analyses reported in this study should be regarded as exploratory, as the subgroup analyses were not predefined, and the power for tests of interaction could be limited. A strength of the SOS study is that the large number of participants and the wealth of very long-term follow-up data allow examination of the impact of early- and adult-onset obesity on a wide range of outcomes of bariatric surgery.

In conclusion, our results demonstrate that the long-term positive effects of bariatric surgery in adults on obesity comorbidities as well as the surgical complications are similar in patients with early- and adult-onset obesity, while the reductions in body weight and energy intake are slightly larger in those with early-onset obesity. Thus, the longer exposure to obesity and the presumed greater genetic influence or early established unhealthy lifestyle in those with early-onset obesity does not appear to reduce the positive effects of bariatric surgery in adults.

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Author Contributions. F.M.K., M.P., and L.M.S.C. were responsible for study concept and design. F.M.K., J.C.A.-A., P.-A.S., B.C., M.P., and L.M.S.C. were responsible for acquisition, analysis, or interpretation of data. F.M.K., J.C.A.-A., and L.M.S.C. were responsible for drafting of the manuscript. F.M.K., J.C.A.-A., P.-A.S., B.C., M.P., and L.M.S.C. performed critical revision of the manuscript for important intellectual content. F.M.K. and M.P. performed statistical analysis. L.M.S.C. obtained funding. M.P. and L.M.S.C. are the guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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