


Bariatric Surgery and the Incidence of Psoriasis and Psoriatic Arthritis in the Swedish Obese Subjects Study

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Objective: The aim of this study was to assess the effect of bariatric surgery (vertical gastropasty, gastric banding, or gastric bypass) compared with usual care on the incidence of psoriasis and psoriatic arthritis (PsA) in the Swedish Obese Subjects study.

Methods: This report includes 1,991 subjects who underwent bariatric surgery and 2,018 controls with obesity from the SOS study; none of them had psoriasis or PsA at baseline. Information about psoriasis and PsA diagnosis was retrieved through the Swedish National Patient Register and questionnaires.

Results: During follow-up for up to 26 years, bariatric surgery was associated with a lower incidence of psoriasis compared with usual care (number of events = 174; hazard ratio 0.65; 95% CI: 0.47-0.89; $P = 0.008$). Both smoking and a longer duration of obesity were independently associated with a higher risk for psoriasis. No significant difference was detected among the three surgical procedures in terms of lowering the risk of developing psoriasis. The association between bariatric surgery and psoriasis incidence was not influenced by baseline confounders. No significant difference in the risk of developing PsA (number of events = 46) was detected when comparing the surgery and the control groups.

Conclusions: This study shows that bariatric surgery is associated with a lower risk of developing psoriasis compared with usual care.

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Introduction

Psoriasis is a complex, primarily cutaneous inflammatory disease mediated by the activation of specific innate and adaptive immune pathways (1,2). The most common form of psoriasis, psoriasis vulgaris, is characterized by well-demarcated papulosquamous plaques, which are often located at sites of trauma (1). Up to one-third of subjects with psoriasis are affected by psoriatic arthritis (PsA), which is characterized by chronic joint and soft tissue inflammation (3-5).

Obesity is a risk factor for both psoriasis and PsA (6-10). A high body mass index (BMI) also has a negative impact on the response to treatment in patients with psoriasis or PsA (11-13). Diet-induced weight loss as well as bariatric surgery seem to have positive effects on the severity of psoriasis (14,15). Response to treatment is also improved after low-calorie diet-induced weight loss in subjects with psoriasis (16,17) as well as in those with PsA (18).

Recently, the effect of gastric bypass and gastric banding on psoriasis and PsA has been retrospectively investigated in the Danish population

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Author contributions: CM performed the main analysis of the data, interpreted the results, drafted and revised the manuscript, and approved the final version; CM also has full access to the data in the study and takes final responsibility for the decision to submit the manuscript for publication. MP helped with the data analysis, interpreted the results, revised the manuscript, and approved the final version; AR interpreted the results, revised the manuscript, and approved the final version; LMSC interpreted the results, revised the manuscript, and approved the final version.

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(19). By using the data from the Danish National Patient Registry, the authors identified a population of subjects who underwent bariatric surgery during a 15-year period. In this cohort, the risk of psoriasis and PsA was lower after undergoing gastric bypass but not after gastric banding.

Here, we aim to study the effect of bariatric surgery compared with usual care on the incidence of psoriasis and PsA in the prospective Swedish Obese Subjects (SOS) study (20). The SOS study is a longitudinal, nonrandomized intervention trial designed to determine the effect of bariatric surgery on overall mortality and obesity-related comorbidities, and it includes a bariatric surgery arm and a matched control arm.

Methods

SOS study design

The ongoing SOS trial includes 4,047 subjects with obesity who were recruited in Sweden from 25 surgical departments and 480 primary health care centers between 1987 and 2001 (20). The surgery group included 2,010 subjects who electively chose to undergo bariatric surgery, whereas 2,037 subjects formed the control group. Both study groups had identical inclusion and exclusion criteria, and all the participants from the control group were, in principle, eligible for surgery. Further details about the matching method and the inclusion and exclusion criteria are shown in the Supporting Information. The primary end point of the SOS study was overall mortality (21). Secondary end points included type 2 diabetes and cardiovascular disease. The incidence of psoriasis and PsA was not a predefined end point.

Subjects in the surgery group underwent gastric banding ($n = 376$), vertical banded gastroplasty ($n = 1,369$), or gastric bypass ($n = 265$). The control group received conventional nonsurgical obesity treatment at the centers of registration, ranging from advanced lifestyle modifications with the help of professional guidance (including recommendations regarding eating behavior, food selection, energy intake, and physical activity) to no treatment whatsoever. No attempt was made to standardize the nonsurgical treatment. Study participants were examined at matching, at baseline, at 6 months, and at 1, 2, 3, 4, 6, 8, 10, 15, and 20 years. At the same time points, questionnaires about patients' health state were collected. Biochemical parameters were measured in a centralized laboratory at matching, at baseline, and at 2, 10, 15, and 20 years. Type 2 diabetes was defined as fasting blood glucose ≥ 110 mg/dL and/or self-reported therapy with glucose-lowering medications. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or self-reported treatment with antihypertensive medication. The variable called "obesity duration" was created based on patients' self-reported weight at different ages and age at baseline. The first reported BMI (calculated from self-reported weight) higher or equal to 30 after 20 years of age was considered as obesity debut. Obesity duration was defined as the time period from obesity debut to baseline age.

Seven local ethics review boards approved the SOS study protocol. Written or oral informed consent was obtained from all the study participants. The study is registered at ClinicalTrials.gov with identifier NCT01479452.

Psoriasis and PsA

The Swedish National Patient Register was searched for the diagnoses of psoriasis and PsA. The National Patient Register comprises medical records from inpatient and nonprimary care outpatient visits in Sweden. Inpatient care visits have been documented since 1964, and the

register reached national coverage in 1987. Recording of nonprimary outpatient care, including visits to hospital-based medical specialists, was started nationwide in 2001. The National Patient Register was searched for the following International Classification of Diseases (ICD) codes for the diagnosis of psoriasis and PsA: 696.0, 696.10, and 696.19 (ICD-8); 696.0 and 696.1 (ICD-9); L40.0-9, M07.0-3, and M09.0 (ICD-10). Moreover, subjects with a diagnosis of psoriasis or PsA were detected through patients' questionnaires based on the following questions: "Since the last questionnaire, have you been regularly followed up for other diseases?" and "Please list the two most important reasons that caused your sickness absence."

A total of 38 subjects had a diagnosis of psoriasis or PsA before baseline and were excluded from the main analyses of this report, which includes 4,009 subjects: 1,991 from the surgery group and 2,018 from the control group. In the surgery group, 375 subjects underwent gastric banding, 1,354 underwent vertical banded gastroplasty, and 262 underwent gastric bypass. In the control group, according to questionnaires administered to study participants at 6 months, 1 year, and 2 years, about 50% (1,017 subjects) had tried to lose weight with professional guidance. The end points of this report were the first diagnosis of psoriasis or PsA; the occurrence of the end point psoriasis did not result in censoring in the analysis on the incidence of PsA. During a follow-up for up to 26 years, 174 subjects developed psoriasis, including 46 subjects who developed PsA. Patients were followed up until diagnosis of psoriasis or PsA, death, migration, or the end of follow-up. Information on death or migration was obtained from the Cause of Death Register and the Register of the Total Population (22). The cutoff date for the current analyses was December 31, 2013.

Statistical analysis

Baseline characteristics are shown as mean \pm standard deviation (SD) or number (%). Baseline continuous variables were compared by general linear model tests, whereas categorical variables were compared by χ^2 tests.

The time of progression to incident psoriasis or PsA after inclusion was assessed by Kaplan-Meier estimates of cumulative incidence rates and compared between the control and the surgery group, as well as among the three different surgical procedures by log-rank test. Cox proportional hazard models were used to assess the hazard ratios (HR) for the risk of psoriasis and PsA. HRs were also adjusted for preselected baseline risk factors (sex, age, BMI, obesity duration, serum insulin, metabolic syndrome, smoking, and alcohol intake). The association between baseline risk factors and the effect of bariatric surgery on the incidence of psoriasis or PsA was assessed using a risk factor-treatment interaction analysis. For continuous variables, the interaction test used the original variable. A total of 18 post hoc subgroup analyses were executed and reported for both psoriasis and PsA; no adjustment for multiple testing was performed. One out of twenty interaction tests would be expected to be statistically significant because of chance alone. The number of surgery procedures needed to be performed (number needed to treat) to prevent one incident diagnosis of psoriasis or PsA over 15 years was calculated as the reciprocal of the absolute risk difference (obtained from Kaplan-Meier risk estimates) between subjects from the surgery and control groups.

Two-sided $P < 0.05$ was considered statistically significant. The intention-to-treat principle was used in all analyses, unless otherwise

TABLE 1 Baseline characteristics of study participants

	Control group (n = 2,018)	Surgery group (n = 1,991)	P value
Age, y	49 ± 6	47 ± 6	< 0.001
Sex, n men (%)	583 (29)	582 (29)	0.81
BMI	40 ± 5	42 ± 5	< 0.001
Obesity duration, y	16 ± 8	16 ± 8	0.72
Hypertension, n (%)	1,286 (64)	1,556 (78)	< 0.001
Creatinine, mg/dL	0.8 ± 0.1	0.8 ± 0.1	0.22
Insulin, mU/L	18 ± 11	22 ± 14	< 0.001
Diabetes, n (%)	259 (13)	338 (17)	< 0.001
Metabolic syndrome, n (%)	1,251 (62)	1,468 (74)	< 0.001
Alcohol intake, g/d	5.3 ± 8.1	5.2 ± 7.3	0.70
Smoking, n (%)	420 (21)	511 (26)	< 0.001

Plus-minus values are mean ± SD.

specified. Statistical analyses were performed with SPSS Statistics (version 24.0; IBM Corp., Armonk, New York).

Results

Baseline characteristics and BMI changes during follow-up

In Supporting Information Table S1, we show the baseline characteristics of the SOS study participants who had a diagnosis of psoriasis or PsA at baseline compared with subjects who did not have such diagnoses before inclusion. No significant differences were observed in the clinical characteristics at baseline between the two groups, with the exception of a higher prevalence of type 2 diabetes in subjects who had a diagnosis of psoriasis or PsA at baseline.

Baseline characteristics of the 1,991 surgically treated subjects and the 2,018 matched controls included in the current report are shown in Table 1. None of them were affected by psoriasis or PsA at baseline. As previously reported (20), participants from the surgery group at baseline were slightly younger and had higher BMI and serum insulin levels as well as a higher prevalence of hypertension, type 2 diabetes, metabolic syndrome, and smoking habit compared with the control group. During follow-up, BMI decreased significantly in the surgery group (−23%; 95% confidence interval [CI]: −24 to −23 at a 2-year follow-up; −17%; 95% CI: −17 to −16 at a 10-year follow-up), whereas virtually no change in BMI was observed in the control group (+0.1%; 95% CI: −0.3 to 0.5 at a 2-year follow-up; +1.7%; 95% CI: −1.0 to 2.4 at a 10-year follow-up). A significant although marginal decrease in BMI was observed at 1 year among subjects from the control group who attempted to lose weight with professional help compared with those who did not (−0.6% with 95% CI: −1.1 to −0.04 vs. +0.9% with 95% CI: 0.5 to 1.5, respectively; $P < 0.001$); however, this difference in BMI change disappeared at 10, 15, and 20 years ($P = 0.86, 0.77, \text{ and } 0.16$, respectively).

Incidence of psoriasis

We examined the risk of developing psoriasis in the surgery and control groups. A total of 174 subjects developed psoriasis during

follow-up. The median follow-up was 18.1 (range: 0-26) years for the control group and 18.7 (range: 0-26) years for the surgery group. Bariatric surgery was associated with a lower incidence of psoriasis during follow-up (103 events occurred in the control group [5.1%] and 71 in the surgery group [3.6%]; log-rank $P = 0.013$; unadjusted HR 0.68; 95% CI: 0.50-0.92; $P = 0.013$; Figure 1A). After adjustment for risk factors, the HR was 0.65 with a 95% CI: 0.47-0.89 ($P = 0.008$; Table 2). Smoking (HR 1.75; 95% CI: 1.26-2.42; $P = 0.001$) and a longer duration of obesity at baseline (HR 1.28; 95% CI: 1.05-1.55; $P = 0.014$) were both independently associated with a greater risk of developing psoriasis independently of bariatric surgery (Table 2). The difference in absolute risk for psoriasis between the control and the surgery group was 1.3 percentage points at 15 years, and the number needed to treat to prevent one event was 77 (Supporting Information Table S2). After stratifying the population according to the surgical procedure, only vertical banded gastroplasty was significantly associated with a lower incidence of psoriasis compared with conventional treatment (Figure 2). However, when comparing the three procedures among each other, they did not differ in terms of prevention of psoriasis (log-rank $P = 0.374$; having gastric banding as a reference, HR for vertical banded gastroplasty 0.80; 95% CI: 0.46-1.39; $P = 0.418$; HR for gastric bypass 0.71; 95% CI: 0.29-1.71; $P = 0.439$). After excluding those who switched treatment group during follow-up, such as subjects from the control group who underwent bariatric surgery later on (per-protocol analysis), we could confirm that bariatric surgery prevented the incidence of psoriasis in subjects with obesity (log-rank $P = 0.006$; unadjusted HR 0.61; 95% CI: 0.43-0.87; $P = 0.007$).

Incidence of PsA

The median follow-up for the incidence of PsA was 18.3 (range: 0-26) years for the control group and 18.7 (range: 0-26) years for the surgery group. A total of 46 subjects was diagnosed with PsA during follow-up: 26 subjects from the control group (1.3%) and 20 from the surgery group (1.0%). No significant difference in the risk of developing PsA was observed in comparing the surgery and the control group (log-rank $P = 0.368$; unadjusted HR 0.77; 95% CI: 0.43-1.37; $P = 0.370$; Figure 1B), even after adjusting for confounders (HR 0.71; 95% CI: 0.38-1.33; $P = 0.287$). A per-protocol analysis did not detect any difference in the incidence of PsA between the

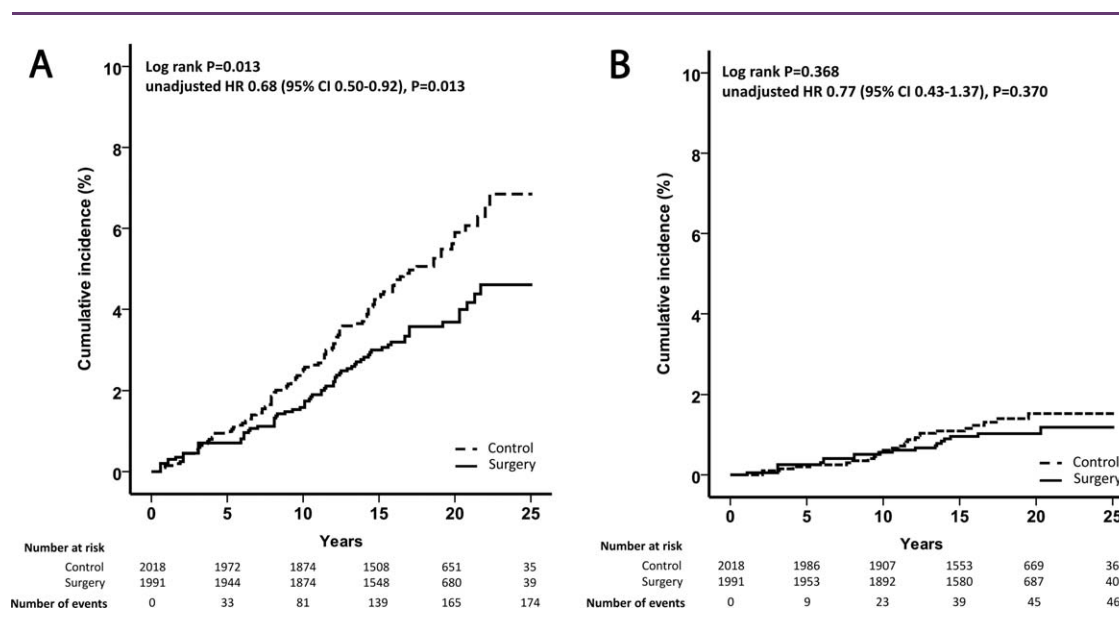


Figure 1 Cumulative incidence of psoriasis and psoriatic arthritis (PsA) in the Swedish Obese Subjects study. **(A)** Incidence of psoriasis. A total of 103 events occurred in the control group compared with 71 events in the surgery group. **(B)** Incidence of PsA. A total of 26 events occurred in the control group compared with 20 events in the surgery group.

surgery and control groups (log-rank $P = 0.153$; unadjusted HR 0.57; 95% CI: 0.27-1.21; $P = 0.141$).

Risk factor-treatment interaction

We then analyzed the interaction between risk factors and bariatric surgery on the incidence of psoriasis and PsA. Specifically, the relative treatment effect and the treatment interactions for the incidence of the end points were assessed after stratifying the population by sex, type 2 diabetes, metabolic syndrome, and smoking habit and by the median of baseline age, BMI, obesity duration, serum insulin levels, and alcohol intake.

In our cohort, no significant interactions between risk factors at baseline and bariatric surgery were found with respect to the

development of psoriasis or PsA (Figure 3, Supporting Information Figure S1, and Supporting Information Table S2). Study participants who were older at baseline had a slightly better, although not significant, response to bariatric surgery in terms of lower incidence of psoriasis compared with those who were younger (Figure 3 and Supporting Information Table S2). No significant interactions between surgical treatment and BMI or obesity duration were detected.

Discussion

This study showed that bariatric surgery in subjects with obesity prevents the incidence of psoriasis compared with usual care. Our study could not confirm that bariatric surgery is associated with a lower risk for PsA.

TABLE 2 Hazard ratios for the incidence of psoriasis

	Univariate analysis		Multivariate analysis	
	Adjusted hazard ratio (95% CI)	P value	Adjusted hazard ratio (95% CI)	P value
Surgery vs. control group	0.68 (0.50-0.92)	0.01	0.65 (0.47-0.89)	0.008
Men vs. women	0.93 (0.67-1.30)	0.67	0.84 (0.57-1.23)	0.36
Age, per 10 y	1.09 (0.86-1.40)	0.47	0.99 (0.76-1.29)	0.93
BMI, per 10 kg/m ²	0.87 (0.63-1.21)	0.42	0.87 (0.61-1.23)	0.43
Obesity duration, per 10 y	1.25 (1.05-1.49)	0.012	1.28 (1.05-1.55)	0.01
Insulin, per 10 mU/L	1.04 (0.94-1.16)	0.42	1.08 (0.99-1.18)	0.09
Metabolic syndrome, yes vs. no	1.03 (0.75-1.41)	0.87	1.02 (0.73-1.42)	0.93
Smoking, yes vs. no	1.69 (1.23-2.32)	0.001	1.75 (1.26-2.42)	0.001
Alcohol intake, per 1 g/d	1.00 (0.98-1.02)	0.88	1.00 (0.98-1.02)	0.96

Hazard ratios calculated by using Cox proportional hazards model based on baseline data.

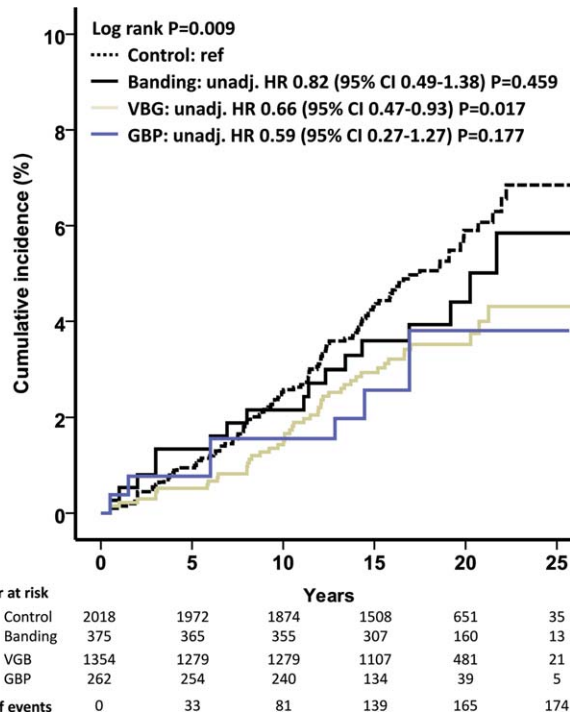


Figure 2 Cumulative incidence of psoriasis stratified by surgical procedure. A total of 103 events occurred in the control group (5.1%) as compared with 17 in the banding group (4.5%), 47 in the vertical banded gastroplasty (VBG) group (3.5%), and 7 in the gastric bypass (GBP) group (2.7%). Survival distributions in the control and the surgery groups were compared by using a log rank test. Cox proportional hazard ratios (HR) and confidence intervals (CI) are unadjusted.

Obesity is a known risk factor for both psoriasis and PsA. Bariatric surgery is the most effective way to achieve and maintain weight loss (20,23); it also reduces the risk and improves the prognosis of several obesity-associated disorders, such as type 2 diabetes and cardiovascular diseases (23-26). We recently showed that bariatric surgery is also effective in reducing the incidence of gouty arthritis in participants of the SOS study (27).

Recently, a retrospective study including 13,435 subjects who underwent bariatric surgery in Denmark between 1997 and 2013 showed that gastric bypass, but not gastric banding, was associated with a reduced risk of developing psoriasis and PsA (19). The study did not have a separate control group, but the authors compared the risk of developing psoriasis and PsA in the same group of individuals before and after bariatric surgery. In this report, we answered the same research question in the prospective SOS cohort, which included a bariatric surgery and a control group, and we demonstrated a beneficial effect of bariatric surgery on the incidence of psoriasis up to a 26-year follow-up. In our cohort of patients with obesity and no previous diagnosis of psoriasis or PsA, bariatric surgery was associated with a 32% lower risk of developing psoriasis compared with usual care. Although we saw a similar trend, we could not detect a significant reduction in the incidence of PsA in subjects undergoing bariatric surgery. This may be due to a lack of statistical power, because only 46 cases of incident PsA were observed in our cohort of more than 4,000 individuals. Another possible explanation is that the role of obesity in

modulating the risk of PsA is not as strong as for psoriasis. In fact, psoriasis and PsA are two related but different conditions that share many, but not all, risk factors. For example, smoking is a known risk factor for psoriasis (28), but its role in the development of PsA is still controversial (29-31). Moreover, although genetics plays a significant role in the susceptibility to both psoriasis and PsA, the genetic background behind these two diseases seems to be at least partially different (32).

In recent years, a few reports in small cohorts have suggested an improvement in the severity of psoriasis after gastric bypass (33-35). Romero-Talamás et al. reported that in a cohort of 33 patients, gastric bypass predicted improvement of psoriasis compared with other procedures (36). It has been hypothesized that gastric bypass induces remission of psoriasis because of an anti-inflammatory effect mediated by a rapid increase in glucagon-like peptide-1 levels after surgery. In the study from Egeberg et al., gastric bypass, but not gastric banding, was associated with a lower risk for psoriasis (19); however, the difference between the surgery types was not formally tested. In the SOS cohort, about 13% of the participants from the surgery group underwent gastric bypass, whereas 68% underwent vertical banded gastroplasty and 19% underwent gastric banding. In our report, only vertical banded gastroplasty was significantly associated with a lower incidence of psoriasis among subjects with obesity; however, when formally tested, the three procedures did not significantly differ in terms of prevention of psoriasis. Therefore, we can only state that bariatric surgery was effective in reducing the risk of psoriasis in our cohort, but we cannot point out which bariatric procedure was the most effective.

A long obesity duration has been associated with a higher risk for diabetes, cancer, and even impaired lung function (37-39). In our cohort,

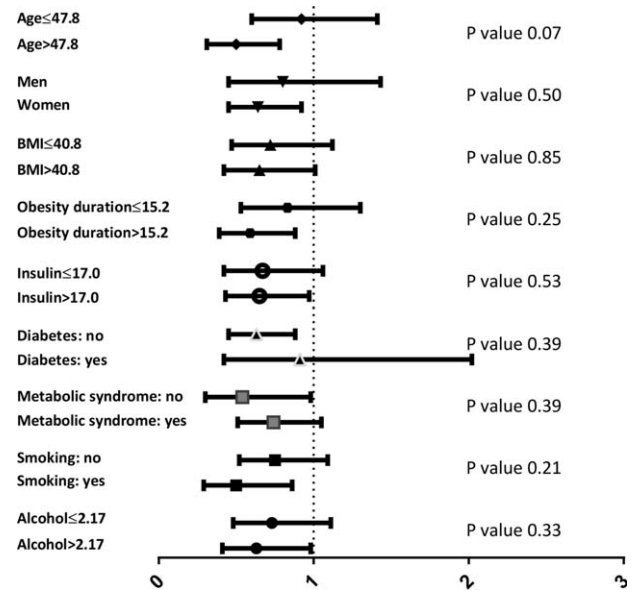


Figure 3 Risk factor-treatment interaction analyses for the incidence of psoriasis in high- and low-risk subgroups. For continuous variables, subgrouping is based on median baseline values. Hazard ratios and corresponding 95% confidence intervals are shown. P value refers to the interaction. P values between the indicated subgroups and bariatric surgery. For each continuous variable, the test of interaction was calculated by using the original continuous variable. Dichotomous variables could have one of two values (e.g., men/women).

the duration of obesity was a risk factor for developing psoriasis independently of bariatric surgery. However, no significant interaction between obesity treatment and obesity duration was detected. In this population, baseline BMI was neither an independent risk factor for psoriasis or PsA nor showed any interaction with bariatric surgery in terms of prevention of both conditions.

This study had some limitations. Neither psoriasis nor PsA was a predefined end point for the SOS trial, and the diagnoses were retrieved through the Swedish National Patient Register and the questionnaires that SOS participants fill in regularly. Since the National Patient Register does not include data from primary care, we might have missed some cases of mild psoriasis followed up by general practitioners unless the information was present in the SOS questionnaires. On the other hand, the medical records from inpatient and nonprimary care outpatient visits included in the National Patient Register gave us a full account of PsA diagnoses because PsA is always diagnosed by rheumatologists in Sweden.

This study showed that bariatric surgery is associated with a lower incidence of psoriasis compared with usual obesity care. The preventive role of bariatric surgery on the risk of psoriasis has been recently highlighted by a retrospective Danish study. However, we lent strength to the previous results by confirming this association in a large prospective intervention trial designed to examine the effect of bariatric surgery on obesity-related comorbidities in comparison with usual obesity care. **O**

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