



## The associations between bariatric surgery and hip or knee arthroplasty, and hip or knee osteoarthritis: Propensity score-matched cohort studies

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### ABSTRACT

**Objective:** To investigate the associations between bariatric surgery and hip or knee arthroplasty, and secondary care hip or knee osteoarthritis (OA).

**Methods:** We performed cohort studies using data from Swedish nationwide healthcare registries. Patients aged 18–79 years who underwent bariatric surgery between 2006 and 2019 were matched on their propensity score (PS) to up to 2 obese patients (“unexposed episodes”) in risk-set sampling. After a 1-year run-in period, episodes were followed in an “as-treated” approach. Using Cox proportional hazard regression, we calculated hazard ratios (HR) with 95% confidence intervals (CIs) of hip or knee arthroplasty overall and in subgroups of age, sex, joint location, arthroplasty type, bariatric surgery type, and by duration of follow-up if proportional hazard assumptions were violated. In a secondary cohort, we assessed the outcome incident secondary care hip or knee osteoarthritis (OA).

**Results:** Among 39'392 bariatric surgery episodes when compared to 61'085 PS-matched unexposed episodes (47'594 unique patients), the risk of hip or knee arthroplasty was strongest increased within the first three years of follow-up (HR 1.79, 95% CI 1.56–2.07), decreased thereafter, but remained elevated throughout follow-up. In a secondary cohort of 37'929 exposed when compared to 58'600 PS-matched unexposed episodes, the risk of hip or knee osteoarthritis was decreased (HR 0.84, 95% CI 0.79–0.90).

**Conclusion:** Bariatric surgery is associated with increased risks of hip or knee arthroplasty, but also with decreased risks of secondary care OA. This contradiction supports the hypothesis that bariatric surgery may act as an enabler for hip or knee arthroplasty.

### 1. Introduction

Osteoarthritis (OA) is a slowly developing chronic joint disease mainly characterized by joint pain which may lead to physical disability [1]. In primary care in the United Kingdom (UK), the prevalence of hip or knee OA in patients aged 45–64 years is 30% in women and 20% in men, and increasing with age [2]. OA is caused by metabolic and genetic factors, and additionally by mechanical factors in weight bearing joints such as the knee [3]. Since there is no disease-modifying treatment available, OA is treated symptomatically with analgesics, exercise, or

walking aids in case of OA in a lower limb joint [3]. In end-stage disease, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) conditionally recommend arthroplasty [4].

In Sweden, the incidence of OA-related hip or knee arthroplasty procedures among patients aged  $\geq 65$  years was 36/10,000 persons in 2011 (abstract) [5]. In total hip or knee arthroplasty, all components are replaced and it is a larger surgery than partial hip or knee arthroplasty in which only one component is replaced [6]. However, all surgeries carry inherent risks of short- and long-term complications, particularly in obese patients [7]. Yet, mechanical aspects, low-grade inflammation, as

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well as a higher risk of chronic pain and lower pain threshold, may increase the risk of OA and arthroplasty for obese patients [8,9].

Lifestyle interventions are often ineffective to reduce excess body weight [10,11]. Thus, obese patients may undergo bariatric surgery and typically lose up to 50–70% of excess body weight within the first 2 years post-surgery [12]. Most patients sustain this weight loss 10 years post-surgery [13]. The benefit of bariatric surgery in relation to improvement or resolution of cardiovascular disease [14,15], type2 diabetes [15], metabolic syndrome [16], sleep apnea [16], cancer [15, 17], depression [18], psoriasis [19], rheumatoid arthritis [20], quality of life [15], and mortality [15,21] has been previously demonstrated. In most studies performed to date which assessed the impact of bariatric surgery or weight loss on hip or knee pain or function as proxies for OA, reported decreased pain and increased functionality of the joint [8, 22–27]. However, the impact of weight loss through bariatric surgery on elective hip or knee arthroplasty (as a proxy for end-stage OA) has not been studied to date.

Thus, we aimed to assess whether bariatric surgery was associated with primary hip or knee arthroplasty. As a secondary aim, we assessed whether bariatric surgery was associated with secondary care hip or knee OA.

## 2. Patients and methods

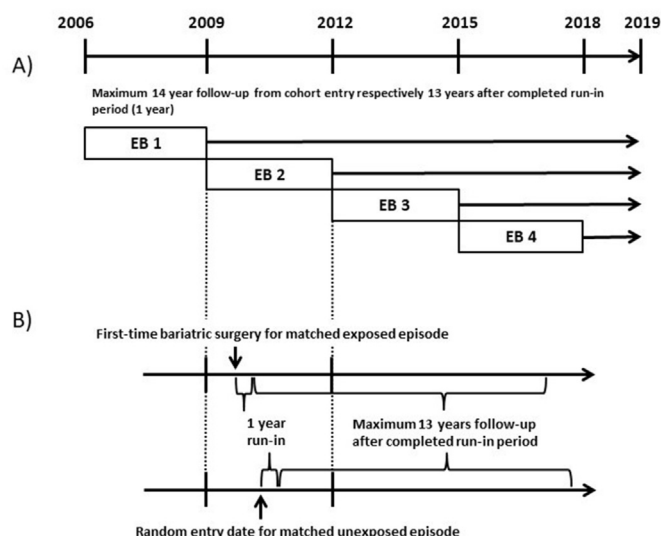
### 2.1. Study design and data source

We conducted a propensity score (PS)-matched sequential cohort study using data from the nationwide Swedish healthcare registries including the Patient Registry (in- and outpatient information) [28], Cause of Death Registry [29], Prescribed Drug Registry [30], Cancer Registry, and the Swedish section of the Scandinavian Obesity Surgery Registry (SOREg) [31]. All individuals born or permanently residing in Sweden are assigned a 10-digit personal code which is used for identification in healthcare registries and allowed for linkage. The quality of the data on surgery in general is excellent in the Swedish patient registry, with a previous study showing the validity of bariatric surgery captured in the Swedish Patient Registry when compared with SOReg. [32] We therefore used the Swedish patient registry to identify bariatric surgery patients and SOReg to obtain details on the type of surgery codes and body mass index (BMI) measurements.

### 2.2. Study population

We identified all individuals diagnosed with obesity (ICD10 E66, ICD9 278 A/B, ICD8 287,0, ICD7 277,99) aged 18–79 years at any time between January 1, 2006 and December 31, 2019 in the Swedish Patient Registry. Patients without an obesity record before bariatric surgery but with an obesity record after bariatric surgery were also eligible. From experience, a record of obesity in the Swedish Patient Registry may be entered for any obese individual, but more likely for morbid obese patients. We categorized patients who underwent bariatric surgery into 1 of 4 3-to-4-year cohort entry blocks according to the date of surgery (referred to as cohort entry) [Fig. 1A]. Selection of unexposed patients happened as follows: Unexposed patients were assigned a random entry date. If this date was during the period during which the patient was unexposed to bariatric surgery (i.e. from  $\geq 18$  years until bariatric surgery, exclusion criteria, or loss to follow-up), and after an obesity record, then the patient was considered for the matching process [Fig. 1B]. For simplicity reasons, we further refer to all contributing patients as episodes because patients could contribute only 1 episode as an exposed patient but multiple episodes as an unexposed patient throughout the study period, if eligibility criteria were fulfilled.

We excluded all episodes with a record of other weight-reducing surgery prior to cohort entry (e.g. jejunioleal bypass). Furthermore, we excluded episodes with prior primary and/or revision of hip or knee



**Fig. 1. A) Study overview.** Each entry block (EB) represented one cohort. The cohorts contained all eligible bariatric surgery episodes and their propensity score-matched unexposed episodes (matched of up to 2 unexposed per exposed episode). We followed all episodes for a maximum of 14 years after their entry in an EB, respectively 13 years after completed run-in period until they had a record of hip/knee arthroplasty or they were censored. **B) Entry block in detail.** Matched bariatric surgery episodes entered on the date of their surgery; matched unexposed episodes entered on a random date.

arthroplasty. We excluded episodes with prior osteotomy (partially joint-unspecified code) because it may delay the need for joint replacement. We also excluded episodes with differential indications for hip or knee arthroplasty such as rheumatoid arthritis, septic arthritis, avascular necrosis of head of femur, osteoporotic fracture (i.e. mainly hip fractures), knee trauma, or other surgical treatment on the hip or knee (e.g. replacement of joint surface of femoral head). In a secondary cohort, when assessing secondary care hip, knee, and generalized OA, respectively, patients with a previous record of any OA prior to cohort entry were additionally excluded.

### 2.3. PS matching

We estimated a PS (probability of undergoing bariatric surgery) for each bariatric surgery episode and unexposed episode using multivariable logistic regression. We included medical diagnoses recorded at any time before cohort entry and prescriptions recorded within 6-months before cohort entry. Selected diagnoses and prescriptions were either associated with obesity (e.g. type2 diabetes, hypertension, ischemic heart disease), associated with undergoing surgery in general (e.g. Royal College of Surgeons Charlson comorbidity score [33], sleep apnea), the risk of developing/recording severe OA (e.g. menopause, or fibromyalgia and depression [9] which lead to reduced pain thresholds), or potential confounders of the association between bariatric surgery and hip or knee arthroplasty or OA (e.g. age, sex). Covariates further included proxies for patient frailty (e.g. pneumonia) and engagement with the healthcare system (e.g. number of in- or outpatient encounters  $\leq 1$  year prior to cohort entry). All covariates were selected *a priori* based on clinical knowledge (Table 1) [34]. To maximize comparability between matched episodes, we matched bariatric surgery episodes and unexposed episodes separately within each of the 4 cohort entry blocks (to account for time trend bias of exposure and outcomes). A greedy 8-1 digit matching algorithm without replacement was applied, excluding those who could not be matched [35]. In a sensitivity analysis, we trimmed our study population asymmetrically at the extreme ends of the PS tail (bariatric surgery episodes below the 5th and unexposed episodes above the 95th

**Table 1**

Baseline characteristics of bariatric surgery episodes and unexposed episodes (follow-up >365 days) before and after PS-matching when assessing hip/knee arthroplasty.

|  | Before PS-matching   |                         | PS-matched           |                        |
|--|----------------------|-------------------------|----------------------|------------------------|
|  | Exposed (N = 51,261) | Unexposed (N = 341,962) | Exposed (N = 39,392) | Unexposed (N = 61,085) |
| Mean age [years] (SD)  | 40.8 (11.1)          | 47.7 (16.8)             | 41.5 (11.5)          | 41.8 (11.9)            |
| Mean follow-up [years] (SD)  | 6.5 (3.1)            | 5.7 (3.3)               | 6.7 (3.2)            | 6.1 (3.2)              |
| Women  | 38,746 (75.6%)       | 216,986 (63.5%)         | 28,619 (72.7%)       | 44,194 (72.4%)         |
| Men  | 12,515 (24.4%)       | 124,976 (36.6%)         | 10,773 (27.4%)       | 16,891 (27.7%)         |
| Alcohol proxy  | 353 (0.7%)           | 8536 (2.5%)             | 346 (0.9%)           | 648 (1.1%)             |
| Smoking  | 994 (1.9%)           | 10,833 (3.2%)           | 878 (2.2%)           | 1420 (2.3%)            |
| Median number of hospital contacts ≤1 year before cohort entry (IQR) | 2 (2–4)              | 0 (0–2)                 | 2 (2–4)              | 2 (0–5)                |
| <b>Comorbidities before cohort entry:</b>                            |                      |                         |                      |                        |
| Median Royal College of Surgeon Charlson comorbidity score (IQR)     | 0 (0–1)              | 1 (0–2)                 | 0 (0–1)              | 0 (0–1)                |
| Cholelithiasis/Cholecystitis   | 1780 (3.5%)          | 18,346 (5.4%)           | 1626 (4.1%)          | 2704 (4.4%)            |
| Diabetes Type 2 <sup>a</sup>   | 2819 (5.5%)          | 87,041 (25.5%)          | 7021 (17.8%)         | 11,279 (18.5%)         |
| Fibromyalgia   | 1035 (2.0%)          | 4194 (1.2%)             | 815 (2.1%)           | 1157 (1.9%)            |
| Hyperlipidemia <sup>a</sup>  | 5277 (10.3%)         | 81,485 (23.8%)          | 4798 (12.2%)         | 7991 (13.1%)           |
| Hypertension <sup>a</sup>  | 10,717 (20.9%)       | 107,553 (31.5%)         | 9093 (23.1%)         | 14,114 (23.1%)         |
| Hyperparathyroidism  | 238 (0.5%)           | 10,521 (3.1%)           | 227 (0.6%)           | 472 (0.8%)             |
| GERD <sup>a</sup>  | 24,666 (48.1%)       | 61,678 (18.0%)          | 14,950 (38.0%)       | 21,031 (34.4%)         |
| Gout   | 230 (0.5%)           | 5123 (1.5%)             | 216 (0.6%)           | 408 (0.7%)             |
| Ischemic heart disease <sup>b</sup>                                  | 558 (1.1%)           | 26,147 (7.7%)           | 544 (1.4%)           | 1098 (1.8%)            |
| Menopause  | 885 (1.7%)           | 20,105 (5.9%)           | 845 (2.2%)           | 1558 (2.6%)            |
| Migraine <sup>a</sup>  | 1673 (3.3%)          | 8910 (2.6%)             | 1427 (3.6%)          | 2150 (3.5%)            |
| Non-alcoholic fatty liver disease                                    | 159 (0.3%)           | 1763 (0.5%)             | 145 (0.4%)           | 229 (0.4%)             |
| Pneumonia  | 563 (1.1%)           | 12,041 (3.5%)           | 532 (1.4%)           | 976 (1.6%)             |
| Pregnancy/Delivery   | 4734 (9.2%)          | 72,946 (21.3%)          | 4578 (11.6%)         | 7047 (11.5%)           |
| Sleep apnea  | 5120 (10.0%)         | 44,189 (12.9%)          | 4358 (11.1%)         | 6734 (11.0%)           |
| Stroke/Transient ischemic attack                                     | 169 (0.3%)           | 9531 (2.8%)             | 165 (0.4%)           | 359 (0.6%)             |
| Hip osteoarthritis <sup>c</sup>                                      | 146 (0.3%)           | 2319 (0.7%)             | 120 (0.3%)           | 248 (0.4%)             |
| Knee osteoarthritis <sup>c</sup>                                     | 901 (1.8%)           | 10,676 (3.1%)           | 740 (1.9%)           | 1503 (2.5%)            |
| Generalized osteoarthritis <sup>c</sup>                              | 26 (0.1%)            | 1007 (0.3%)             | 24 (0.1%)            | 150 (0.3%)             |
| <b>Medications at the cohort entry:</b>                              |                      |                         |                      |                        |
| Analgesics/anti-inflammatory drugs <sup>c</sup>                      | 35,262 (68.8%)       | 105,376 (30.8%)         | 25,948 (65.9%)       | 23,421 (38.3%)         |
| Antibiotics  | 1029 (2.0%)          | 5333 (1.6%)             | 781 (2.0%)           | 1046 (1.7%)            |
| Antipsychotics   | 1018 (2.0%)          | 11,583 (3.4%)           | 960 (2.4%)           | 1688 (2.8%)            |
| Antidepressants  | 9340 (18.2%)         | 55,366 (16.2%)          | 7776 (19.7%)         | 11,815 (19.3%)         |
| Anxiolytics  | 3107 (6.1%)          | 28,038 (8.2%)           | 2820 (7.2%)          | 4512 (7.4%)            |
| Cardiovascular drugs   | 14,180 (27.7%)       | 149,121 (43.6%)         | 12,225 (31.0%)       | 19,157 (31.4%)         |
| Hypnotics/Sedatives  | 4982 (9.7%)          | 41,244 (12.1%)          | 4352 (11.1%)         | 6870 (11.3%)           |
| Local anaesthetics   | 216 (0.4%)           | 1902 (0.6%)             | 193 (0.5%)           | 365 (0.6%)             |
| <b>Cohort entry date</b>   |                      |                         |                      |                        |
| 2006–2008  | 5107 (10.0%)         | 45,287 (13.2%)          | 4620 (11.7%)         | 7373 (12.1%)           |
| 2009–2011  | 14,517 (28.3%)       | 70,248 (20.5%)          | 10,768 (27.3%)       | 15,997 (26.2%)         |
| 2012–2014  | 16,087 (31.4%)       | 105,215 (30.8%)         | 12,694 (32.2%)       | 19,331 (31.7%)         |
| 2015–2018  | 15,550 (30.3%)       | 121,212 (35.5%)         | 11,310 (28.7%)       | 18,384 (30.1%)         |
| <b>c-statistics</b>  | 0.90                 |                         | 0.57                 |                        |

c-statistics: concordance statistics; GERD: gastroesophageal reflux disease; IQR: interquartile range; OA: osteoarthritis; NA: not available; PS: propensity score; SD: standard deviation.

<sup>a</sup> Diagnosis or medication.

<sup>b</sup> Includes myocardial infarctions and angina pectoris.

<sup>c</sup> These variables were not used to estimate propensity scores.

percentile before matching) to exclude bariatric surgery and unexposed episodes treated contrary to prediction (those episodes are subject to highest confounding).

#### 2.4. Follow-up

Follow-up started after a run-in period on day 365 after cohort entry for all patients (Fig. 1B) because no earlier effect of bariatric surgery was expected. This means that (prior to matching) all patients with less than 1 year of follow-up were excluded. Episodes with hip or knee replacements within the first 365-days may have had arthroplasty already pre-planned prior to the bariatric surgery. We followed bariatric surgery and unexposed episodes in an “as-treated” approach until the first occurrence of hip or knee arthroplasty or censoring due to onset of an exclusion criterion described above, change of exposure status, loss to follow-up, or end of study period (December 2019). We performed two sensitivity analyses, starting follow-up at day 1 and day 720 after index date to assess the influence of the run-in periods.

#### 2.5. Exposure ascertainment

Our exposure was bariatric surgery identified from the Swedish Patient Registry using the following NOMESCO codes [36] as of 1997: gastric bypass: JDF10–11; duodenal switch: JFD03–04; others (93.4% sleeve gastrectomy according to SOReg, thus, we further referred to this group as sleeve gastrectomy): JDF00–01, JDF20–21, JDF96–97. When comparing information from the Swedish Patient Registry with SOReg, we observed that 92.6%, and 87.2% of patients categorized as having undergone gastric bypass, and duodenal switch, respectively, were categorized correctly. Change of exposure status happened if an exposed episode had a reversal code (NOMESCO code JFD23) or if an unexposed episode had a bariatric surgery code.

#### 2.6. Outcome

We defined hip or knee arthroplasty as the first recorded NOMESCO code of NFB09/19/29/39/49 (hip) or NGB09/19/29/39/49 (knee) in

the Swedish Patient Registry. In a secondary cohort, we assessed secondary care records of hip or knee OA (hip: ICD10 M16, knee: ICD10 M17) as the outcomes of interest, and in a sensitivity analysis, we used secondary care generalized OA (ICD10 M15) as the outcome. These additional analyses were performed to help frame results obtained in primary analyses.

In the Swedish Patient Registry, any prevailing OA is recorded when patients are referred to specialized healthcare (i.e. an orthopedist). Thus, secondary care OA reflects moderate to severe, but not mild OA. In patients with both secondary care hip or knee OA and hip or knee arthroplasty records, we observed a median duration between a first secondary care OA record and a first arthroplasty record of 78 days (interquartile range: 0–303 days). A total of 97% of patients with a hip or knee arthroplasty surgery had a record of hip or knee OA during the same hospital episode, for 26% of episodes it was the first secondary care hip or knee OA record.

## 2.7. Statistical analysis

After combining all sequential cohorts into 1 cohort, we compared covariate distribution between treatment groups before and after PS-matching through estimation of standardized mean differences. We further estimated pre- and post-matching c-statistics using a logistic regression model including all covariates included into the PS to assess covariate balance. To assess the association of bariatric surgery and hip or knee arthroplasty, we applied Cox proportional hazard regression and estimated hazard ratios (HR) with 95% confidence intervals (CI). We performed subgroup analyses by joint location (hip, knee), arthroplasty type (partial, total), combination of joint location and arthroplasty type, sex, age (18–39 years, 40–59 years, 60–79 years), bariatric surgery type (sleeve gastrectomy, gastric bypass, duodenal switch) for which we re-matched within subgroups. The proportional hazard assumption was tested using the martingale residual method. It did not hold overall or when assessing the outcome hip arthroplasty, knee arthroplasty, or total arthroplasty, and when assessing the subgroups women and episodes with gastric bypass surgery. Thus, we performed subgroup analyses by tertiles of follow-up (>1–3 years, >3–6 years, >6–13 years) overall and in aforementioned strata for which hazards were not proportional. For comparative reasons, in further sensitivity analyses, we also conducted all analyses using multivariable Cox regression in the unmatched cohort, adjusting for all covariates included in the PS. We repeated all analyses when assessing the secondary outcome hip or knee OA (hazards were not proportional when assessing knee OA, and in subgroups of women, episodes aged 40–59 years at cohort entry, and episodes with either sleeve gastrectomy or gastric bypass). Since patients may contribute several episodes, we requested robust sandwich estimates for the covariate matrix in overall analyses only due to computational power (results remained unchanged).

In post-hoc analyses, stratified by exposure, we compared cumulative incidences of hip and knee arthroplasty with those of hip and knee OA and further those of hip versus knee arthroplasty. All analyses were performed using SAS statistical software version 9.4 (NC, USA).

## 3. Results

### 3.1. Study populations

In the primary cohort, of the 51,261 eligible bariatric surgery episodes, 39,392 (76.8%) were matched with up to 2 unexposed episodes (i.e. 61,085 unexposed episodes), resulting in 100,477 PS-matched episodes, including 84,246 unique patients (83.8%) and 47,594 unique unexposed patients (77.9%) [Fig. 2].

The patient characteristics before and after PS-matching of the primary cohort are available in Table 1. Before PS-matching, the mean age of bariatric surgery episodes was lower, the proportion of women was higher, they had more hospital contacts, and were less frequently

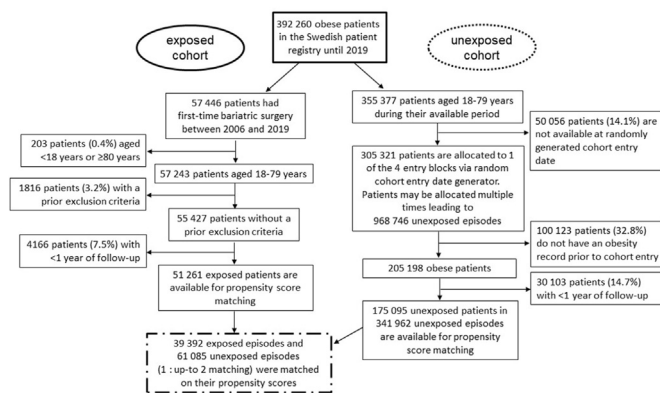


Fig. 2. Flow-chart of the study composition when assessing hip and knee arthroplasty.

diagnosed with hypertension, type2 diabetes, ischemic heart diseases, or OA, but more frequently diagnosed with GERD, when compared to unexposed episodes (Table 1). After PS-matching, the mean age was around 42 years and around 72% of patients were women. Covariate balance was achieved with a post-matching c-statistic of  $c = 0.57$ . Furthermore, all covariates yielded  $<10\%$  of standardized mean differences between bariatric surgery and unexposed episodes after PS-matching (Supplementary Figure 1). Moreover, censoring was comparable between groups after PS-matching (Supplementary Table 2). Mean BMI of exposed episodes (data obtained from SOReg) at the time of bariatric surgery was  $42.4 \text{ kg/m}^2$  (Supplementary Table 3). Gastric bypass was the most performed bariatric surgery (around 85%). Episodes with duodenal switch (only 1% of cases) had the highest mean preoperative BMI ( $55.3 \text{ kg/m}^2$ ).

The secondary cohort included 37,929 exposed episodes and 58,600 unexposed episodes (Flowchart in Supplementary Figure 2). The study population had no record of OA at cohort entry but was otherwise highly similar to that of the primary analysis. The characteristics of bariatric surgery and unexposed episodes can be found in Supplementary Table 4. Standardized mean differences of covariates can be found in Supplementary Figure3, censoring distribution in Supplementary Table 5, and BMI distribution among bariatric surgery episodes in Supplementary Table 6.

### 3.2. Risk of hip or knee arthroplasty and of hip or knee osteoarthritis following bariatric surgery

In the primary analyses, we observed 402 hip and 736 knee arthroplasties among bariatric surgery episodes and 460 hip and 648 knee arthroplasties among unexposed episodes. Hazard ratios of hip or knee arthroplasty in bariatric surgery episodes when compared to unexposed episodes in the PS-matched analysis overall and in subgroups can be seen in Table 2. The risk of hip or knee arthroplasty was highest within the first three years of follow-up (HR of 1.79, 95% CI 1.56–2.07) and decreased thereafter to a HR of 1.22, 95% CI 1.05–1.41 after 6 years of follow-up. By joint location, risks of knee arthroplasty were slightly higher than those of hip arthroplasty, however, confidence intervals overlapped. Results from sensitivity analyses (Table 2) and multivariable adjusted analyses (Supplementary Table 7) confirmed our findings. In post-hoc analyses, we obtained cumulative incidences of hip and knee arthroplasty stratified by exposure status (Fig. 3). Hazards of hip arthroplasty in bariatric versus unexposed episodes seemed to be proportional after an initial discrepancy whereas hazards of knee arthroplasty in bariatric versus unexposed episodes seemed to increase faster than those of unexposed episodes.

In secondary analyses, we observed 445 hip and 1279 knee OA records in secondary care among bariatric surgery episodes and 680 hip and 2137 knee OA records in secondary care among unexposed episodes. The risk of hip or knee OA was decreased among bariatric surgery



**Table 2**

Results of the associations between bariatric surgery (exposure) and hip/knee arthroplasty (outcome) overall and in subgroups after propensity score-matching.

|   | Events in exposed | Obs.-time <sup>a</sup> in exposed | Events in unexposed | Obs.-time <sup>a</sup> in unexposed | HR matched <sup>b</sup> (95% CI) |
|---|-------------------|-----------------------------------|---------------------|-------------------------------------|----------------------------------|
| <b>Overall<sup>c</sup></b>              |                   |                                   |                     |                                     |                                  |
| >1–3 years <sup>d</sup>                 | 423               | 112.1                             | 352                 | 169.2                               | 1.79 (1.56–2.07)                 |
| >3–6 years                              | 379               | 84.4                              | 399                 | 116.7                               | 1.31 (1.14–1.51)                 |
| >6–13 years                             | 336               | 65.5                              | 357                 | 84.7                                | 1.22 (1.05–1.41)                 |
| <b>Arthroplasty location</b>            |                   |                                   |                     |                                     |                                  |
| <b>Hip<sup>c</sup></b>                  |                   |                                   |                     |                                     |                                  |
| >1–3 years <sup>d</sup>                 | 148               | 112.1                             | 141                 | 169.2                               | 1.57 (1.25–1.97)                 |
| >3–6 years                              | 134               | 84.4                              | 161                 | 116.7                               | 1.15 (0.92–1.45)                 |
| >6–13 years                             | 120               | 65.5                              | 158                 | 84.7                                | 0.98 (0.78–1.25)                 |
| <b>Knee<sup>c</sup></b>                 |                   |                                   |                     |                                     |                                  |
| >1–3 years <sup>d</sup>                 | 275               | 112.1                             | 211                 | 169.2                               | 1.94 (1.62–2.32)                 |
| >3–6 years                              | 245               | 84.4                              | 238                 | 116.7                               | 1.42 (1.19–1.70)                 |
| >6–13 years                             | 216               | 65.5                              | 199                 | 84.7                                | 1.41 (1.16–1.70)                 |
| <b>Combination of location and type</b> |                   |                                   |                     |                                     |                                  |
| Partial arthroplasty                    | 43                | 262.0                             | 47                  | 370.6                               | 1.27 (0.84–1.93)                 |
| <b>Total arthroplasty<sup>c</sup></b>   |                   |                                   |                     |                                     |                                  |
| >1–3 years <sup>d</sup>                 | 411               | 112.1                             | 333                 | 169.2                               | 1.84 (1.59–2.13)                 |
| >3–6 years                              | 364               | 84.4                              | 381                 | 116.7                               | 1.32 (1.14–1.52)                 |
| >6–13 years                             | 321               | 65.5                              | 347                 | 84.7                                | 1.20 (1.03–1.39)                 |
| <b>Combination of location and type</b> |                   |                                   |                     |                                     |                                  |
| Partial hip                             | 0                 | 262.0                             | 4                   | 370.6                               | NA                               |
| Total hip                               | 402               | 262.0                             | 456                 | 370.6                               | 1.22 (1.07–1.40)                 |
| Partial knee                            | 43                | 262.0                             | 43                  | 370.6                               | 1.39 (0.91–2.12)                 |
| Total knee                              | 694               | 262.0                             | 605                 | 370.6                               | 1.60 (1.43–1.78)                 |
| <b>Sex</b>                              |                   |                                   |                     |                                     |                                  |
| <b>Women<sup>c</sup></b>                |                   |                                   |                     |                                     |                                  |
| >1–3 years <sup>d</sup>                 | 304               | 81.6                              | 278                 | 120.0                               | 1.59 (1.35–1.87)                 |
| >3–6 years                              | 290               | 61.1                              | 300                 | 82.4                                | 1.30 (1.11–1.53)                 |
| >6–13 years                             | 247               | 47.6                              | 242                 | 59.8                                | 1.28 (1.07–1.53)                 |
| <b>Men</b>                              | 298               | 68.8                              | 315                 | 103.1                               | 1.40 (1.20–1.64)                 |
| <b>Age in years</b>                     |                   |                                   |                     |                                     |                                  |
| 18–39                                   | 48                | 108.4                             | 44                  | 146.5                               | 1.41 (0.93–2.12)                 |
| 40–59                                   | 869               | 132.5                             | 807                 | 190.4                               | 1.52 (1.38–1.68)                 |
| 60–79                                   | 202               | 12.0                              | 240                 | 22.5                                | 1.58 (1.31–1.91)                 |
| <b>Bariatric surgery type</b>           |                   |                                   |                     |                                     |                                  |
| Sleeve gastrectomy                      | 103               | 23.3                              | 106                 | 41.7                                | 1.74 (1.33–2.28)                 |
| <b>Gastric bypass<sup>c</sup></b>       |                   |                                   |                     |                                     |                                  |
| >1–3 years <sup>d</sup>                 | 377               | 101.5                             | 340                 | 154.8                               | 1.67 (1.44–1.93)                 |
| >3–6 years                              | 356               | 80.3                              | 361                 | 111.2                               | 1.37 (1.18–1.58)                 |
| >6–13 years                             | 334               | 63.3                              | 339                 | 82.6                                | 1.29 (1.11–1.50)                 |
| Duodenal switch                         | 12                | 3.2                               | 6                   | 5.8                                 | 3.58 (1.34–9.54)                 |
| <b>Sensitivity analyses</b>             |                   |                                   |                     |                                     |                                  |
| <b>No run-in period<sup>c</sup></b>     |                   |                                   |                     |                                     |                                  |
| 0–3 years <sup>e</sup>                  | 472               | 79.94                             | 448                 | 114.4                               | 1.51 (1.32–1.71)                 |
| 2-year run-in period                    | 888               | 253.2                             | 923                 | 363.4                               | 1.34 (1.22–1.47)                 |
| <b>Trimmed PS<sup>c</sup></b>           |                   |                                   |                     |                                     |                                  |
| >1–3 years <sup>d</sup>                 | 227               | 59.4                              | 204                 | 108.3                               | 2.00 (1.66–2.42)                 |
| >3–6 years                              | 212               | 44.5                              | 244                 | 75.2                                | 1.47 (1.22–1.76)                 |
| >6–13 years                             | 174               | 34.7                              | 222                 | 55.0                                | 1.25 (1.02–1.52)                 |

CI: confidence interval; HR: hazard ratio; NA: not applicable; obs.-time: observation-time; PS: propensity score.

<sup>a</sup> Observation-time in 1000 person-years.<sup>b</sup> Adjusted for/PS estimation with covariates see Table 1.<sup>c</sup> Results shown stratified by tertiles of follow-up because proportional hazard assumption violated in entire follow-up.<sup>d</sup> Follow-up started after a 1-year run-in period only.<sup>e</sup> Follow-up started at day 1 (no run-in period), patients were followed up until the end of the first tertile.

episodes versus unexposed episodes (HR of 0.84, 95% CI 0.79–0.90) [Table 3]. Subgroup analyses did not yield any trends (Table 3). Our findings were confirmed by sensitivity analyses (Table 3) and multivariable adjusted analyses (Supplementary Table 8). In post-hoc analyses, we estimated cumulative incidences of hip or knee arthroplasty and of hip or knee OA stratified by exposure status which are provided in Fig. 4. While hazards of OA seemed to be identical in the first year of follow-up and only separated later between bariatric and unexposed episodes, hazards of arthroplasty separated immediately.

#### 4. Discussion

In this large cohort study with a maximum follow-up of 14 years among 84,246 obese patients in the Swedish Patient Registry, we observed a 79% increased risk of hip or knee arthroplasty >1–3 years

after bariatric surgery. This increase was mainly accounted for by knee arthroplasties with a 94% increased risk over hip arthroplasties which was associated with a 57% increased risk. Furthermore, the increased risk of hip arthroplasty among bariatric surgery patients was attenuated after 3 years of follow-up whereas those of knee arthroplasty remained elevated throughout the entire follow-up. In the secondary cohort (free from secondary care OA at follow-up start), we observed a 16% decreased risk of secondary care hip or knee OA following bariatric surgery.

Post-bariatric surgery, the increased risk of hip or knee arthroplasty seems to stand in contrast with the observed decreased risk of secondary care hip or knee OA. Several reasons are plausible. For example, chronic pain can persist because not only nociceptive pain trigger that decrease with weight loss are involved in pain perception, but also nociplastic (central) pain mechanisms steering pain memory [37]. Furthermore,

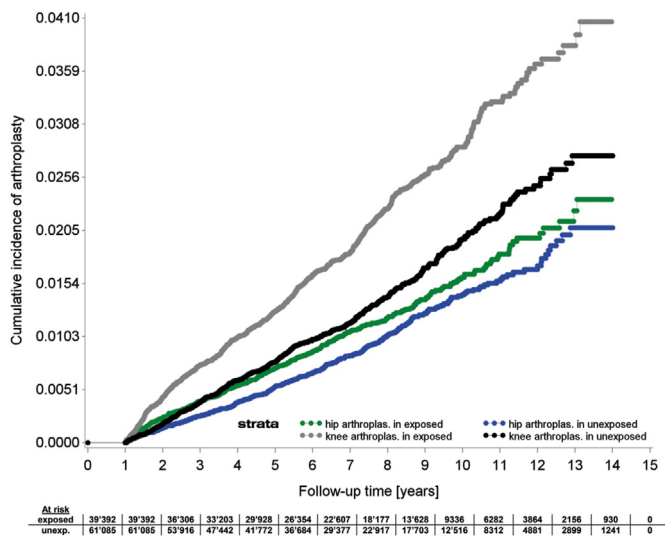


Fig. 3. Cumulative incidences of hip or knee arthroplasty in bariatric surgery episodes and unexposed episodes.

Table 3

Results of the associations between bariatric surgery (exposure) and incident hip/knee osteoarthritis (outcome) overall and in subgroups after propensity score-matching.

|                                 | Events in exposed | Obs.-time <sup>a</sup> in exposed | Events in unexposed | Obs.-time <sup>a</sup> in unexposed | HR matched <sup>b</sup> (95% CI) |
|---------------------------------|-------------------|-----------------------------------|---------------------|-------------------------------------|----------------------------------|
| Overall                         | 1701              | 249.9                             | 2761                | 349.9                               | 0.84 (0.79–0.90)                 |
| <b>OA location</b>              |                   |                                   |                     |                                     |                                  |
| Hip                             | 445               | 249.9                             | 680                 | 349.9                               | 0.90 (0.79–1.01)                 |
| Knee <sup>c</sup>               |                   |                                   |                     |                                     |                                  |
| >1–3 years <sup>d</sup>         | 372               | 107.8                             | 734                 | 161.7                               | 0.75 (0.66–0.85)                 |
| >3–6 years                      | 471               | 80.6                              | 766                 | 110.0                               | 0.84 (0.75–0.94)                 |
| >6–13 years                     | 436               | 61.5                              | 637                 | 78.2                                | 0.87 (0.77–0.98)                 |
| <b>Sex</b>                      |                   |                                   |                     |                                     |                                  |
| Women <sup>c</sup>              |                   |                                   |                     |                                     |                                  |
| >1–3 years <sup>d</sup>         | 362               | 78.8                              | 694                 | 115.4                               | 0.75 (0.66–0.86)                 |
| >3–6 years                      | 485               | 58.5                              | 728                 | 77.8                                | 0.89 (0.79–0.99)                 |
| >6–13 years                     | 442               | 44.5                              | 623                 | 54.7                                | 0.87 (0.77–0.98)                 |
| Men                             | 408               | 65.4                              | 703                 | 98.0                                | 0.86 (0.76–0.97)                 |
| <b>Age in years</b>             |                   |                                   |                     |                                     |                                  |
| 18–39                           | 175               | 107.8                             | 252                 | 144.3                               | 0.89 (0.73–1.07)                 |
| 40–59 <sup>c</sup>              |                   |                                   |                     |                                     |                                  |
| >1–3 years <sup>d</sup>         | 359               | 54.5                              | 728                 | 81.8                                | 0.73 (0.64–0.83)                 |
| >3–6 years                      | 491               | 40.3                              | 728                 | 55.0                                | 0.92 (0.82–1.03)                 |
| >6–13 years                     | 442               | 29.5                              | 620                 | 38.5                                | 0.93 (0.83–1.06)                 |
| 60–79                           | 217               | 10.4                              | 366                 | 18.9                                | 1.07 (0.91–1.27)                 |
| <b>Bariatric surgery type</b>   |                   |                                   |                     |                                     |                                  |
| Sleeve gastrectomy <sup>c</sup> |                   |                                   |                     |                                     |                                  |
| >1–3 years <sup>d</sup>         | 56                | 14.6                              | 153                 | 25.7                                | 0.64 (0.47–0.87)                 |
| >3–6 years                      | 50                | 5.4                               | 95                  | 10.0                                | 0.98 (0.70–1.38)                 |
| >6–13 years                     | 31                | 2.2                               | 41                  | 4.0                                 | 1.38 (0.87–2.21)                 |
| Gastric bypass <sup>c</sup>     |                   |                                   |                     |                                     |                                  |
| >1–3 years <sup>d</sup>         | 450               | 97.5                              | 892                 | 148.9                               | 0.76 (0.68–0.85)                 |
| >3–6 years                      | 583               | 76.6                              | 950                 | 105.2                               | 0.84 (0.76–0.93)                 |
| >6–13 years                     | 541               | 59.6                              | 808                 | 75.7                                | 0.85 (0.76–0.95)                 |
| Duodenal switch                 | 23                | 3.0                               | 484                 | 5.7                                 | 1.30 (0.76–2.21)                 |
| <b>Sensitivity analyses</b>     |                   |                                   |                     |                                     |                                  |
| No run-in period <sup>c</sup>   |                   |                                   |                     |                                     |                                  |
| 0–3 years <sup>e</sup>          | 911               | 111.2                             | 1465                | 155.8                               | 0.88 (0.81–0.95)                 |
| >3–6 years                      | 629               | 80.6                              | 987                 | 110.0                               | 0.87 (0.79–0.96)                 |
| >6–13 years                     | 573               | 61.5                              | 838                 | 78.2                                | 0.87 (0.78–0.97)                 |
| 2-year run-in period            | 1377              | 241.4                             | 2245                | 345.8                               | 0.85 (0.80–0.91)                 |
| Trimmed PS                      | 885               | 133.8                             | 1666                | 225.9                               | 0.88 (0.81–0.95)                 |
| Generalized OA                  | 62                | 249.9                             | 112                 | 349.9                               | 0.76 (0.56–1.03)                 |

CI: confidence interval; HR: hazard ratio; NA: not applicable; OA: osteoarthritis; obs.-time: observation-time; PS: propensity score.

<sup>a</sup> Observation-time in 1000 person-years.

<sup>b</sup> Adjusted for/PS estimation with covariates, see Supplementary File 5.

<sup>c</sup> Results shown stratified by tertiles of follow-up because proportional hazard assumption violated in entire follow-up.

<sup>d</sup> Follow-up started after a 1-year run-in period only.

<sup>e</sup> Follow-up started at day 1 (no run-in period), patients were followed up until the end of the first tertile.

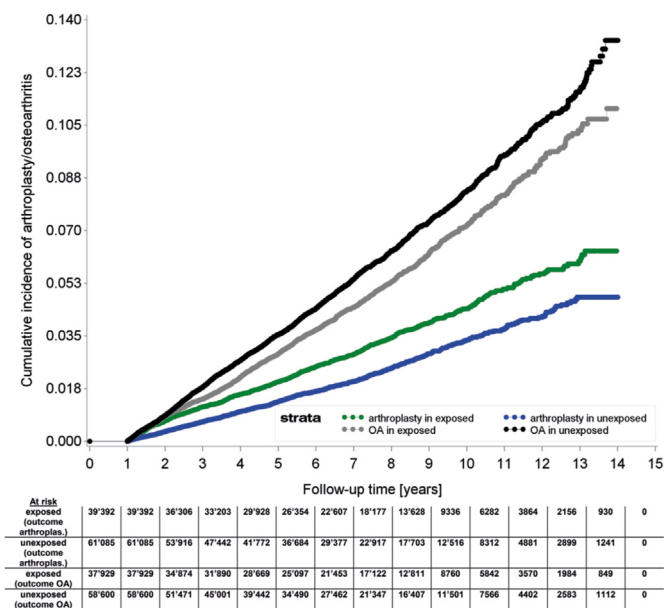


Fig. 4. Cumulative incidences of hip and knee arthroplasty and hip and knee osteoarthritis in bariatric surgery episodes and unexposed episodes.

likely to be selected for hip and knee arthroplasty than patients who did undergo bariatric surgery. This observation further strengthens the argument of increased operability of post-bariatric surgery patients. Some orthopedic clinics in Sweden only perform surgery on patients with a BMI below 35 kg/m<sup>2</sup>, which may have further contributed to the increased risk of arthroplasty post-bariatric surgery that we observed. The same is seen in the UK which also has a tax-paid health care system where several Clinical Commissioning Groups (CCGs) have BMI thresholds in place for hip and knee arthroplasty [41]. As an example, reduced risks of arthroplasty were observed in patients with diabetes in the UK although the opposite was expected [42]. However, to prevent patients from having arthroplasty based on comorbidities is controversially discussed among orthopedic surgeons because there is evidence that also morbid obese patients benefit greatly from joint replacement [43]. Thus, our results on arthroplasty following bariatric surgery may only be generalizable to countries with similar guidelines on provision of arthroplasty as has Sweden.

Most studies performed to date which assessed the association between bariatric surgery or weight loss and hip/knee pain or function as proxies for OA yielded decreased pain and increased functionality of the joint [8,22–27]. In the current study, we did not have any information on joint pain or functionality at hand to compare our results in this respect. Furthermore, outcome recording through ICD codes does not specify whether structural damage or joint pain was the main reason for an OA record. Yet, our results of a decreased risk of hip or knee OA following bariatric surgery as well as continuously decreasing risks of arthroplasty following bariatric surgery over time contribute to existing literature that patients subject to substantial weight loss seem less likely to reach severe OA (i.e. have secondary care OA recorded by an orthopedist). On the other hand, better health status after bariatric surgery may lead to enhanced physical activity and yet increased pressure on joints, as suggested by a small case-control analysis among 15 patients [44]. Yet, the barriers to engage in physical activity post-bariatric surgery in patients who were not used to be physically active prior to surgery persist according to a qualitative study (n = 14) [45]. Thus, the impact of physical activity on osteoarthritis and arthroplasty post-bariatric surgery remains unknown. However, we observed that the risk of knee arthroplasty was increased throughout the entire follow-up of 14 years, whereas, the excess risk for hip arthroplasty following bariatric surgery attenuated after three years of follow-up. This observation was visualized

continuously over time when assessing cumulative incidences of both hip and knee arthroplasty in bariatric surgery patients and unexposed patients. Since it is unlikely that any potential enabling properties of bariatric surgery go by for one arthroplasty but not for another, it seems that this difference is due to the joint location. It is known that the knee is more susceptible to excess body weight than the hip [46]. Thus, our findings may potentially suggest that increased physical activity among bariatric surgery patients which later requires arthroplasty in a damaged knee joint due to previous morbid obesity which seemed not to be the case for the hip joint.

Strengths of this study include the use of nationwide registries. Thus, we have a long follow-up of patients and the large sample size allowed high precision of effect estimates. Moreover, to identify unexposed episodes through a random entry date prior to knowing their eligible periods avoids immortal time bias because we treat unexposed and exposed episodes the same way (exposed episodes are only eligible for matching if their bariatric surgery occurs within their eligible periods). Furthermore, we allocated exposed and unexposed episodes in risk-set sampling and controlled for an extensive set of covariates through PS-matching. This approach yielded highly comparable groups of bariatric surgery episodes and unexposed episodes. Finally, sensitivity analyses yielded similar results to our primary analyses, which suggests that our results are robust across various approaches and cohorts.

However, despite the rigorous methodology of this study, our results must be interpreted in the context of one major limitation. BMI measurements were only available for patients in SOReg, thus, unavailable in unexposed patients. However, unexposed patients had higher prevalence of diseases associated with obesity such as type2 diabetes, hypertension, or cardiovascular disease prior to PS-matching. Thus, unexposed patients are likely more obese than those who underwent bariatric surgery which would have biased our results towards the null given the hypothesis that more obese patients are less likely to be operated. However, after PS-matching, all factors associated with obesity were balanced, and we therefore assume that BMI was also sufficiently balanced. However, residual confounding may remain. Finally, since we did not have data on BMI available, we were not able to stratify our analyses by obesity class which may have been an effect modifier in the association between bariatric surgery and arthroplasty or OA.

Despite these limitations, this is the first study to assess the risk of hip or knee arthroplasty and severe hip or knee OA following bariatric surgery in a large population-based registry.

## 5. Conclusion

Our findings suggest that bariatric surgery was associated with highest risks of hip or knee arthroplasty in early follow-up. Further analyses by joint location suggested that increased risks of hip arthroplasty attenuated after three years of follow-up whereas those of knee arthroplasty remained elevated throughout follow-up. Furthermore, results from a secondary cohort which was free of secondary care OA at follow-up start suggest a decreased risk of incident secondary care OA throughout follow-up without differences between hip and knee OA. This contradiction between observed associations of bariatric surgery with hip or knee arthroplasty and hip or knee OA supports the hypothesis that bariatric surgery may have acted as an enabler for hip or knee arthroplasty due to increased operability but also due to persistent pain in advanced OA and increased mobility after weight loss— especially in the case of knee arthroplasty.

## Declarations

### Ethical approval

The Regional Ethical Review Board in Stockholm, Sweden, approved the study (registration number 2020–04112).

### Sources of funding and support

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### Explanation of the role of funder(s)/sponsor(s)

The funders were not involved in the conduct of the study.

### Conflict of interest

None.

### Responsibility for the integrity of the work as a whole, from inception to finished article

Dr. Burkard had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

### Author contributions

Theresa Burkard: conception and design of the study, analysis and interpretation of data, drafting the article, final approval of the version to be submitted. Dag Holmberg: design of the study, acquisition of data, interpretation of data, revising it critically for important intellectual content, final approval of the version to be submitted. Per Wretenberg: interpretation of data, revising it critically for important intellectual content, final approval of the version to be submitted. Anders Thorell: interpretation of data, revising it critically for important intellectual content, final approval of the version to be submitted. Thomas Hügle: conception of the study, interpretation of data, revising it critically for important intellectual content, final approval of the version to be submitted. Andrea M. Burden: design of the study, Investigation, Methodology, Project administration, Resources, Software, Supervision, revising it critically for important intellectual content, final approval of the version to be submitted.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ocarto.2022.100249>.

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