# Risk of revision and other complications following knee arthroplasty in patients previously exposed to bariatric surgeries: Statistical Analysis Plan for a nationwide, register-based study

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## Objectives

Based on the Danish national registers and databases. The objective of this study is to analyse the association between exposure to Bariatric Surgery (BAS) prior to knee arthroplasty (KA) and the following outcomes: 1) the risk of revision, 2) use of antibiotics and 3) mortality. Furthermore, we want to test whether the association is effect modified by BMI status at the time KA surgery (i.e., non-obese, obese and morbidly obese patients).

## Exposure

We will identify our cohort as patients, who had a BAS before the date of index arthroplasty based on the NOMESCO (Nordic Medico-Statistical Committee) Classification of Surgical Procedures from the DNPR (KJDF10 & KJDF11 [gastric bypass]; KJDF20 & KJDF21 [gastric banding]; KJDF40, KJDF41, KJDF96 & KJDF97 [gastric sleeve]). The comparator (unexposed) group will be patients without BAS before KA.

**Outcomes**

1. Revision due to any cause at two different observation periods within 1) 90 days and b) 2 years following KA. Revision surgery with debridement and/or exchange of at least one component will be based on a composite endpoint
2. Revision due to infection within 1) 90 days and b) 2 years following KA: our definition of infection is adapted from the European Bone and Joint Infection Society (EBJIS) criteria as at least one of the following:
    A. Danish knee register-registered revision surgery due to infection.
    B. At least 2 deep-tissue samples of phenotypically indistinguishable bacteria isolated from at least 3 deep-tissue samples
    C. One or more positive intraoperative samples from a closed fluid aspirate AND a biopsy (fluid AND tissue) of phenotypically indistinguishable bacteria isolated.
3. Antibiotic use within 30- and 90-days following KA as measure of knee related infection will be defined as the use of one of the following oral antibiotics: dicloxacillin, flucloxacillin, phenoxymethylpenicillin, or amoxicillin as suggested by (Milandt et al. Clin Orthop Relat Res 477, 1372-1381 (2019)) Other antibiotics recommended by the international consensus for treating joint infections will also be considered knee-related: oral ciprofloxacin, roxithromycin, linezolid, cefuroxime and cefalexin.
4. Antibiotic use within 30- and 90-days following KA due to other causes: any oral antibiotic other than the forementioned ones.
5. Mortality registered in the Danish Civil Registration System by date up to 2 years following KA surgery.

**Statistical Methods**

We will use descriptive statistics for the baseline characteristics of the two groups stratified for BMI and the type of KA. To address possible survival bias, number of deaths in the exposed and non-exposed groups will be reported.

First, we will run a non-adjusted (crude) analysis comparing outcomes between patients exposed and unexposed to BAS. Then we will perform a propensity score matched analysis, where we do exact matching based on BMI (non-obese: BMI < 30 kg/$m^2$, obese: BMI 30-39 kg/$m^2$, morbidly obese: BMI ≥ 40 kg/$m^2$) and the type of KA (i.e., Total knee arthroplasty (TKA) or Unicondylar Knee arthroplasty (UKA)). Propensity scores will be estimated using a logistic regression model and will be based the forementioned covariates. We will use greedy match algorithm in a ratio of up to 1:5 of patients exposed to bariatric surgery and those who are not, in order to minimize the mean squared error of the estimated treatment effect in several scenarios, difference of maximum of 0.2 logit will be used in propensity score matching. Following that, we will do a propensity score matched analysis with interaction term for BMI.

For dichotomous outcomes, a cox regression will be performed to report Hazards Ratio (HR) with the corresponding two-sided 95% confidence intervals (CIs) and a p-value of <0.05 will be considered as statistically significant. The predetermined equivalence margin of increased risk is set to ±1% point for 95% confidence interval around the absolute risk.

To validate the propensity score matching, we will report the standardized differences of the means (or medians) of continuous variables or the prevalence of dichotomous baseline covariates between each set of groups by using the standardised differences. We will apply a standardized difference of ≥0.25 to indicate that there might be a meaningful imbalance in the baseline covariate.

Figure 1 will present the flowchart for the population.

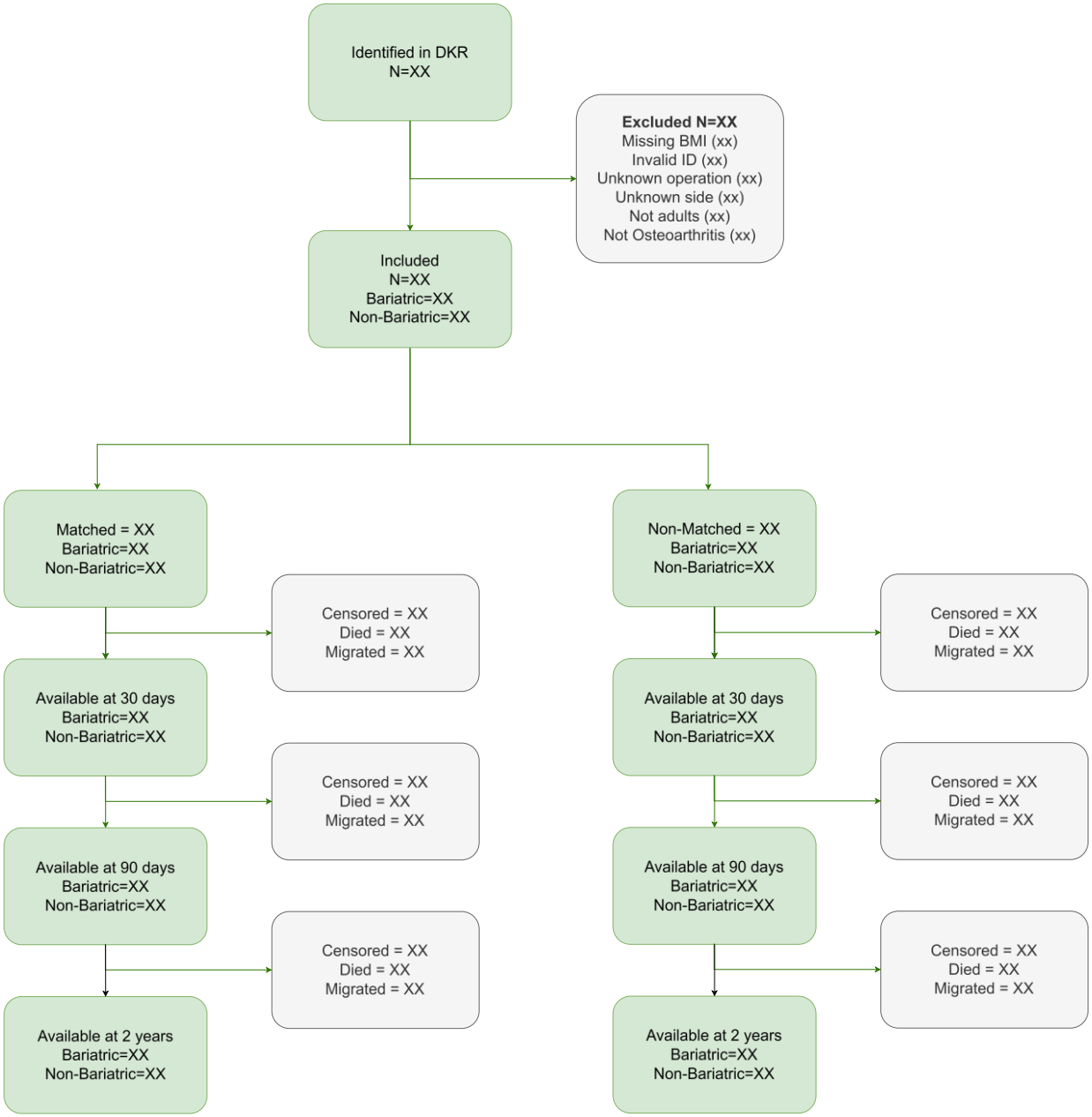


**Table 1** Baseline characteristics at time of knee arthroplasty

| | Unmatched | | | Matched | | |
|---|---|---|---|---|---|---|
| | **Non-Bariatric** | **Bariatric** | **Std. Diff** | **Non-Bariatric** | **Bariatric** | **Std. Diff** |
| N | | | | | | |
| Age, years | | | | | | |
| Female Sex, no. (%) | | | | | | |
| BMI, kg/m2 | | | | | | |
| Obesity Group | | | | | | |
| Non-Obese, no. (%) | | | | | | |
| Obese, no. (%) | | | | | | |
| Morbid Obese, no. (%) | | | | | | |
| Type of operation | | | | | | |
| Total knee arthroplasty | | | | | | |
| Unicondylar Knee arthroplasty | | | | | | |
| Highest completed Education | | | | | | |
| <11 years, no. (%) | | | | | | |
| 11 to 15 years, no. (%) | | | | | | |
| ≥15 years, no. (%) | | | | | | |
| Household income | | | | | | |
| Lowest, no. (%) | | | | | | |
| Low, no. (%) | | | | | | |
| Medium, no. (%) | | | | | | |
| High, no. (%) | | | | | | |
| Comedications | | | | | | |
| Antithrombotics, no. (%) | | | | | | |
| Antibiotics, no. (%) | | | | | | |
| Glucose-Lowering, no. (%) | | | | | | |
| NSAIDs, no. (%) | | | | | | |
| Antiresorptives, no. (%) | | | | | | |
| ECM | | | | | | |
| 0, no. (%) | | | | | | |
| 1 to 2, no. (%) | | | | | | |
| ≥ 3, no. (%) | | | | | | |

Abbreviations: BMI: body mass index; NSAIDs: Non-Steroidal anti-inflammatory drugs; ECM: Elixhauser Comorbidity measure; Std. Diff: Standardized Difference.

**Table 2** Hazards ratios (HR) with 95% confidence interval (CI) for all outcomes performed comparing individuals with bariatric surgery with individuals without using crude and a propensity score matched analysis

| | **Bariatric** | **Non-Bariatric** | **Contrast between bariatric and non-bariatric** | |
|---|---|---|---|---|
| | n/N total | n/N total | HR (95% CI) | P value |
| **Risk of revision ≤ 90 days** | | | | |
| Crude Analysis | xx/XX | xx/XX | xx (xx to xx) | xx |
| Propensity score matched analysis | xx/XX | xx/XX | xx (xx to xx) | xx |
| **Risk of revision ≤ 2 years** | | | | |
| Crude Analysis | xx/XX | xx/XX | xx (xx to xx) | xx |
| Propensity score matched analysis | xx/XX | xx/XX | xx (xx to xx) | xx |
| **Risk of revision due to infection ≤ 90 days** | | | | |
| Crude Analysis | xx/XX | xx/XX | xx (xx to xx) | xx |
| Propensity score matched analysis | xx/XX | xx/XX | xx (xx to xx) | xx |
| **Risk of revision due to infection ≤ 2 years** | | | | |
| Crude Analysis | xx/XX | xx/XX | xx (xx to xx) | xx |
| Propensity score matched analysis | xx/XX | xx/XX | xx (xx to xx) | xx |
| **Risk of receiving knee-related antibiotics ≤ 30 days** | | | | |
| Crude Analysis | xx/XX | xx/XX | xx (xx to xx) | xx |
| Propensity score matched analysis | xx/XX | xx/XX | xx (xx to xx) | xx |
| **Risk of receiving knee-related antibiotics ≤ 90 days** | | | | |
| Crude Analysis | xx/XX | xx/XX | xx (xx to xx) | xx |
| Propensity score matched analysis | xx/XX | xx/XX | xx (xx to xx) | xx |
| **Risk of having non-knee-related antibiotics ≤ 30 days** | | | | |
| Crude Analysis | xx/XX | xx/XX | xx (xx to xx) | xx |
| Propensity score matched analysis | xx/XX | xx/XX | xx (xx to xx) | xx |
| **Risk of having non-knee-related antibiotics ≤ 90 days** | | | | |
| Crude Analysis | xx/XX | xx/XX | xx (xx to xx) | xx |
| Propensity score matched analysis | xx/XX | xx/XX | xx (xx to xx) | xx |
| **Risk of dying ≤ 2 years** | | | | xx |
| Crude Analysis | xx/XX | xx/XX | xx (xx to xx) | xx |
| Propensity score matched analysis | xx/XX | xx/XX | xx (xx to xx) | xx |

**Table 3 Stratified analyses:** Hazards ratios (HR) with 95% confidence interval (CI) for all outcomes in different obesity groups performed using a propensity score matched analysis with an interaction term for obesity group and the type of arthroplasty.

| | **Contrast between bariatric and non-bariatric** | |
|---|---|---|
| | HR (95% CI) | P value |
| **In non-obese** | | |
| Risk of revision ≤ 90 days | xx (xx to xx) | xx |
| Risk of revision ≤ 2 years | xx (xx to xx) | xx |
| Risk of revision due to infection ≤ 90 days | xx (xx to xx) | xx |
| Risk of revision due to infection ≤ 2 years | xx (xx to xx) | xx |
| Risk of receiving knee-related antibiotics ≤ 30 days | xx (xx to xx) | xx |
| Risk of receiving knee-related antibiotics ≤ 90 days | xx (xx to xx) | xx |
| Risk of having non-knee-related antibiotics ≤ 30 days | xx (xx to xx) | xx |
| Risk of having non-knee-related antibiotics ≤ 90 days | xx (xx to xx) | xx |
| Risk of dying ≤ 2 years | | |
| **In obese** | xx (xx to xx) | xx |
| Risk of revision ≤ 90 days | xx (xx to xx) | xx |
| Risk of revision ≤ 2 years | xx (xx to xx) | xx |
| Risk of revision due to infection ≤ 90 days | xx (xx to xx) | xx |
| Risk of revision due to infection ≤ 2 years | xx (xx to xx) | xx |
| Risk of receiving knee-related antibiotics ≤ 30 days | xx (xx to xx) | xx |
| Risk of receiving knee-related antibiotics ≤ 90 days | xx (xx to xx) | xx |
| Risk of having non-knee-related antibiotics ≤ 30 days | xx (xx to xx) | xx |
| Risk of having non-knee-related antibiotics ≤ 90 days | xx (xx to xx) | xx |
| Risk of dying ≤ 2 years | xx (xx to xx) | xx |
| **In morbidly obese** | | |
| Risk of revision ≤ 90 days | xx (xx to xx) | xx |
| Risk of revision ≤ 2 years | xx (xx to xx) | xx |
| Risk of revision due to infection ≤ 90 days | xx (xx to xx) | xx |
| Risk of revision due to infection ≤ 2 years | xx (xx to xx) | xx |
| Risk of receiving knee-related antibiotics ≤ 30 days | xx (xx to xx) | xx |
| Risk of receiving knee-related antibiotics ≤ 90 days | xx (xx to xx) | xx |
| Risk of having non-knee-related antibiotics ≤ 30 days | xx (xx to xx) | xx |
| Risk of having non-knee-related antibiotics ≤ 90 days | xx (xx to xx) | xx |
| Risk of dying ≤ 2 years | xx (xx to xx) | xx |

We will do sensitivity analyses to test whether the type of the surgery (TKA or UKA) will influence the outcomes, we will also test whether the gap between BAS and KA would influence the obtained result by limiting the gap ≤12 months, 13-24 months and >24 months. To investigate whether the type of Bariatric Surgery (BAS), such as gastric banding or gastric bypass, has an impact on the outcomes, we plan to conduct a sensitivity analysis. This will involve narrowing our focus to each specific type of BAS. This particular approach has not been previously applied, and the findings could prove to be significant.

**Sensitivity analysis Table 1:** Hazards ratios (HR) with 95% confidence interval (CI) for all outcomes in total or unicondylar knee arthroplasty performed using a propensity score matched analysis with an interaction term for obesity group and the type of arthroplasty.

| | **Contrast between bariatric and non-bariatric** | |
|---|---|---|
| | HR (95% CI) | P value |
| **In total knee arthroplasty** | | |
| Risk of revision ≤ 90 days | xx (xx-xx) | xx |
| Risk of revision ≤ 2 years | xx (xx-xx) | xx |
| Risk of revision due to infection ≤ 90 days | xx (xx-xx) | xx |
| Risk of revision due to infection ≤ 2 years | xx (xx-xx) | xx |
| Risk of receiving knee-related antibiotics ≤ 30 days | xx (xx-xx) | xx |
| Risk of receiving knee-related antibiotics ≤ 90 days | xx (xx-xx) | xx |
| Risk of having non-knee-related antibiotics ≤ 30 days | xx (xx-xx) | xx |
| Risk of having non-knee-related antibiotics ≤ 90 days | xx (xx-xx) | xx |
| Risk of dying ≤ 2 years | | |
| **In unicondylar knee arthroplasty** | xx (xx-xx) | xx |
| Risk of revision ≤ 90 days | xx (xx-xx) | xx |
| Risk of revision ≤ 2 years | xx (xx-xx) | xx |
| Risk of revision due to infection ≤ 90 days | xx (xx-xx) | xx |
| Risk of revision due to infection ≤ 2 years | xx (xx-xx) | xx |
| Risk of receiving knee-related antibiotics ≤ 30 days | xx (xx-xx) | xx |
| Risk of receiving knee-related antibiotics ≤ 90 days | xx (xx-xx) | xx |
| Risk of having non-knee-related antibiotics ≤ 30 days | xx (xx-xx) | xx |
| Risk of having non-knee-related antibiotics ≤ 90 days | xx (xx-xx) | xx |
| Risk of dying ≤ 2 years | xx (xx-xx) | xx |

**Table 5** Sensitivity analyses showing Hazards ratios (HR) with 95% confidence interval (CI) for the risk of revision due to all causes within 2 years stratified for the gap between bariatric surgery and knee arthroplasty and the type of bariatric surgery

| | **Contrast between bariatric and non-bariatric** | |
|---|---|---|
| | HR (95% CI) | P value |
| **Gap between Bariatric surgery and knee arthroplasty** | | |
| <12 months | xx (xx to xx) | xx |
| 13-24 months | xx (xx to xx) | xx |
| >24 months | xx (xx to xx) | xx |
| **Type of bariatric surgery** | xx (xx to xx) | xx |
| Bypass operations | xx (xx to xx) | xx |
| bariatric surgeries without bypass | xx (xx to xx) | xx |

**Figure 2** will present a love plot to demonstrate the balance through all the included covariates using standardized differences of the mean both before and after propensity score matching.

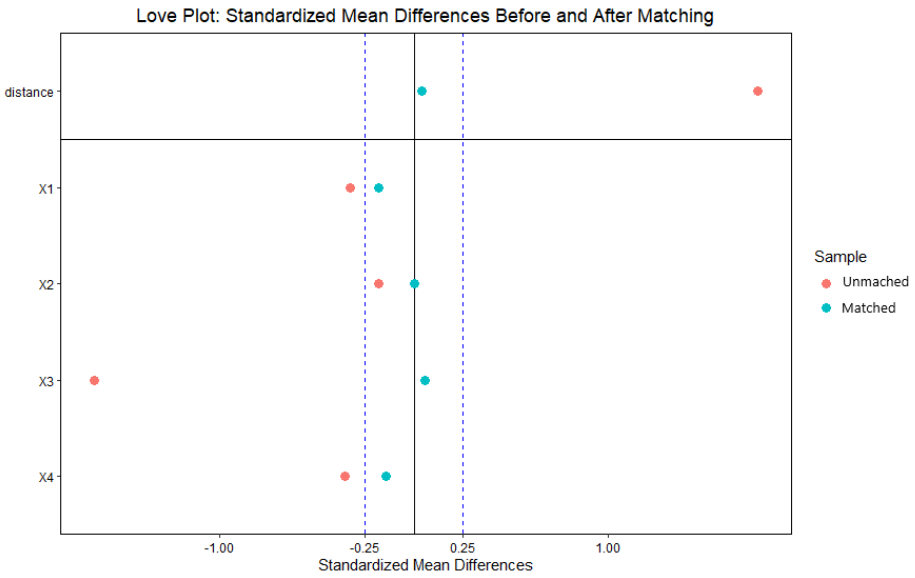
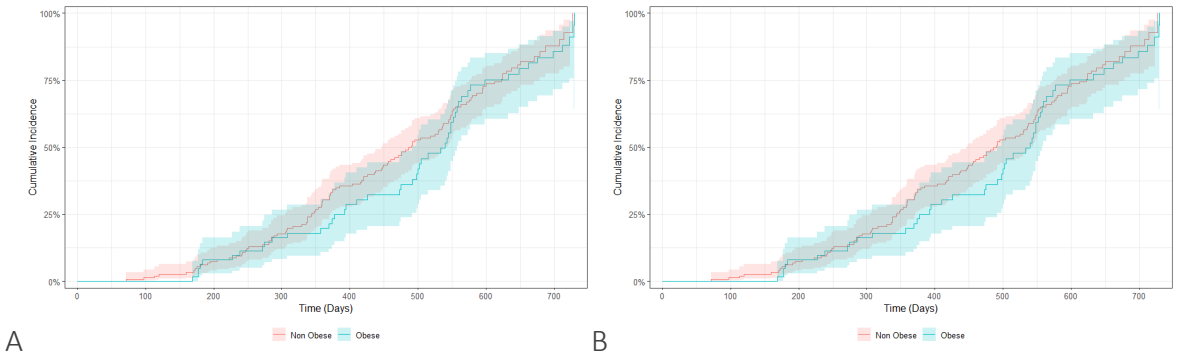


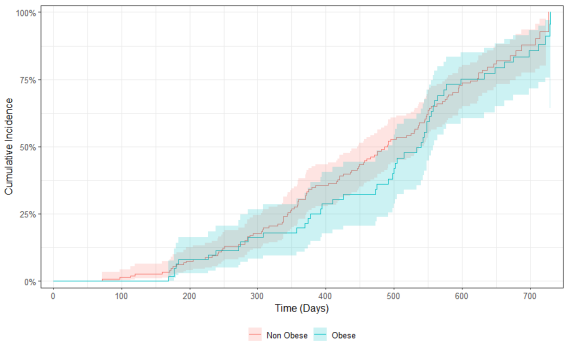

**Figure 3** will present cumulative incidence of having A) revision due to all causes; B) revision due to infection; C) death in patients with previous bariatric surgery vs. those without. All figures come from the propensity score matched population.




A




B




C