Incidence and Microbial Profiles of Periprosthetic Joint Infection After Total Knee Arthroplasty in Obese vs Non-Obese Patients: Protocol and Statistical Analysis Plan for a Nationwide Register-Based Study

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SUMMARY

Importance: After a primary total knee arthroplasty (TKA), we anticipate that obese individuals are more likely to experience a of periprosthetic joint infection (PJI). Knowing the microbial profile in obese patients can potentially help in choosing the proper prophylactic measures for this group as well as tailoring the empirical antibiotics in relation to PJI in obese patients.

Objective: To compare incidence of PJI revisions within 2 years after TKA in obese vs non-obese OA patients. Secondarily: To compare microbial profiles of infections in these groups in two time windows: early (≤90 days) vs late (91–730 days) and incidence of revisions due to all causes within 2 years.**Design and Setting:** We will include patients having primary knee arthroplasty using Danish national registers. Patients will be stratified into anthropometric groups, referred to as exposed and unexposed to obesity, based on their baseline Body Mass Index (BMI). Participants included in the analysis population will be followed up for 2 years, until first revision, death or migration whichever comes first.

Participants: We will include adult patients with available weight and height data with primary/idiopathic or secondary (due to meniscus or cruciate ligament lesion) OA who received primary TKA in the period from 2011-01-01 and 2021-02-28. Patients will be identified from the Danish knee arthroplasty register.

Exposure and Comparator: The cohort will be divided into obese (exposed), defined as body mass index (BMI) ≥ 30 kg/m^2; and non-obese (unexposed), defined as BMI < 30 kg/m^2.

Main Outcomes and Measures: The primary outcome will be revision due to prosthetic joint infection (PJI) within 730 days following TKA. Secondary endpoints will then be to examine revision due to all causes within 730 days following TKA and type of microbial infection between obese and non-obese in the first 90 days and the period from 91 days to 730 days following TKA.

Planned Statistical Analyses: We will use descriptive statistics to summarize the baseline characteristics of the two groups. Hazard ratios with corresponding two-sided 95% confidence intervals (95%CIs) for experiencing the outcome will be estimated using a Cox proportional hazards regression model. We will fit both unadjusted (crude) model and a propensity score adjusted model calculated based on age, sex, highest completed education, household income, comedications, and Elixhauser Comorbidity Measure (ECM), all collected up to the day of surgery. Stratified analyses will categorize PJI cases by bacterial infection and compare crude proportions between groups based on the absolute risk difference with 95% confidence intervals.

Ethical Considerations and Registration: The study and its statistical analysis plan will be registered in clinicaltrials.org prior to conducting the study.

INTRODUCTION

Knee arthroplasty are effective treatments of end-stage joint disease not responding to other treatment measures.[1] Periprosthetic Joint infection (PJI) is an unusual but devastating complication of joint arthroplasty.[2–4] It carries significant burden on patients' morbidity in terms of severe pain, deceased physical activity and quality of life and may lead to death.[5–7] The microbial profile of PJI significantly influences treatment outcomes, with Gram-negative bacteria (GNB), including multidrug-resistant (MDR) pathogens having highest rate of failures,[8] coagulase negative staphylococcus was also found to experience a high risk of re-revision.[9] Studies have linked increasing body mass index (BMI), smoking, male gender, diabetes, rheumatoid arthritis, depression, history of steroid use and previous joint surgery with an increased risk of PJI after Total Knee Arthroplasty (TKA); from these, increasing BMI is found to be the most consistent risk factor for developing PJI.[10–13]

Theories to understand and by that prevent PJI in overweight and obese patients have been proposed; under-dosed prophylactic antibiotics, increased surface tension, increased blood glucose and increased bacterial colonization of the skin in the groin are possible explanations of the association between PJI and overweight. A previous study showed that obese patients have higher rates of polymicrobial and Gram-negative early periprosthetic joint infections of the hip than non-obese patients.[14] This study looked however only in early infections treated with debridement, antibiotics and implant retention (DAIR). A single previous cohort study from England and Wales found that the mean BMI was higher in Mixed genus PJI.[15] We anticipate that knowing the microbial profile in obese patients can help in choosing the proper prophylactic measures for this group as well as tailoring the empirical antibiotics in relation to PJI in obese patients.

Objectives

The primary objective is to compare the incidence of periprosthetic joint infection (PJI) within 2 years of surgery between obese and non-obese patients undergoing primary total knee arthroplasty (TKA) for knee osteoarthritis. Subsequently examine the microbial profiles associated with PJI in these groups withing the first 90 days and in the period from 91 days to 2 years following surgery. Finally we will compare the incidence of revision due to all causes within 2 years of surgery between obese and non-obese patients undergoing primary total knee arthroplasty.

Study design

The study is designed as a nationwide, register-based study investigating the influence of obesity on the microbial profile of PJI after TKA. The study will follow the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) guidelines.[16] We will be comparing the microbial profile of obese patients with BMI of 30 kg/m^2 (exposed) with non-obese (unexposed) patients, defined as BMI < 30 kg/m^2.[17]

Setting

All Danish residents have a personal identification number consistent throughout all registers making register-linkage possible. We will include patients with PJI diagnosis after their primary hip or knee

arthroplasty using Danish national registers. Patients will be followed up for 2 years, until first revision, death or migration whichever comes first.

Data sources

The Danish Civil Registration System (DCRS) contains information on the CPR number, vital and migrant status, cohabiting status, and municipality of residence.[18] The Danish Knee Arthroplasty Register (DKR) is nation-wide register that contains information on all primary knee arthroplasty procedures and revisions performed in Denmark, e.g., baseline characteristics as age, sex, BMI, at the time of TKA operation. The registry started in 1997 and the reporting to the registry became mandatory since 2006. DKR is known for high degree of coverage and completeness.[19,20] The Danish Microbiology Database (MiBa) is a national database containing data from all samples received by the Danish clinical microbiology departments from both hospitals and general practices with complete coverage since 2010.[21]

The Danish National Patient Register (DNPR) is a valuable tool for epidemiological research, providing longitudinal registration of diagnoses, treatments, and examinations derived from every hospital contact in Denmark with complete nationwide coverage since 1978.[22] The Danish National Prescription Registry has kept information on all prescriptions for drugs dispensed by community pharmacies in Denmark since 1994 according to Anatomical Therapeutic Chemical (ATC) classification system (ATC codes). Data from the Danish National Prescription Registry does not include hospital dispensaries.[23]

The Danish Registers on Personal Income and Transfer Payments contains more than 160 variables including salaries, entrepreneurial income, taxes, public transfer payments, capital income, private pension contributions, and pay-outs. In addition, Statistics Denmark provide more detailed registers on specific income transfers, including sickness benefit, old age pension, disability pension, and cash and unemployment benefits.[24] The Danish Population Education Register provides information on education status on Danish population, and it carries high degree of validity and coverage.[25]

Study population

In order to be eligible, we will include adult patients with primary or secondary osteoarthritis (due to meniscus or cruciate ligament lesion) who underwent primary TKA between January 1, 2011, and February 28, 2021, and for whom weight and height data are available. Patients will be identified from the DKR. Patients are followed for 2 years, until first revision, death or migration, whichever comes first.

Variables

Outcomes and endpoints

1. The primary outcome is revision due to prosthetic joint infection (PJI) within 2 years following TKA
2. The first secondary outcome is types of microbial profiles detected in the PJIs, short term (≤90 days) and long-term (91 days to 2 years)
3. Another secondary outcome is revision due to all causes within 2 years following TKA.

For the revision due to PJI, we will stratify the outcome looking into the proportions of the following groups of bacteria within the first 90 days and between 91 and 730 days following TKA:

A. PJI due to Staphylococcus aureus.
B. PJI due to Coagulase-negative staphylococci.
C. PJI due to other gram-positive bacteria.
D. PJI due to gram-negative bacteria.
E. PJI due to anaerobic bacteria.
F. PJI due to mycoplasmic infection.
G. PJI due to polymicrobial infection.
H. PJI with negative culture.

Definitions

PJI: our definition of PJI is adapted from The European Bone and Joint Infection Society (EBJIS) criteria[26] as at least one of the following:

A. DKR-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.

Covariates

The cohort will be divided into two groups at baseline: obese, defined as BMI ≥30 kg/m², and non-obese, defined as BMI <30 kg/m².For descriptive purposes and adjusting, we will be using the following pre-TKA exposure covariates: age (years) at the time of TKA, sex (coded as female=1; male = 0), household income (at the year before KA, categorized into quartiles), highest completed education (at the year of KA, categorized into 3 categories: <11, 11 to 15, and >15 years). Comedication (at least one redeemed prescription 365 days earlier to index KA - 60 days for antibiotics): 1) Glucose-lowering due to the association between DM and surgical complications.[27,28] 2) Antithrombotic medications and 3) NSAIDs because of the possible postoperative bleeding-related complications[29] and 4) Antiresorptives due to the possible increased risk of revision.[30] The last covariate to be included in matching and adjustment is Elixhauser Comorbidity Measure (ECM) (at the year of KA, categorized into 3: 0, 1-2 and ≥ 3), ECM is validated comorbidity scoring measure that has shown highest discriminative ability for the occurrence of all categories of postoperative adverse outcomes following orthopedic surgeries.[31–33]

Statistical Methods

We will use descriptive statistics to summarize baseline characteristics of the two groups and will compare them using standardized differences. . The 2-year (730 days) cumulative incidence of PJI will be reported for both groups. Hazard ratios with corresponding two-sided 95% confidence intervals (CIs) will be estimated using a Cox proportional hazards regression model. We will fit both unadjusted (crude) models and propensity adjusted models using inverse probability of treatment weighting (IPTW).[34] For the adjusted model, propensity scores will be calculated based on age in years, female sex, completed education, household income, comedications, and ECM (all collected prior to surgery). Subsequent stratified analyses will categorize the observed PJI cases by bacterial infection type (within the first 90 days postoperatively or between 91 days and 2 years) and compare crude proportions between groups based on the absolute risk difference with 95% confidence intervals.

We present several analyses corresponding to the main results with 95% confidence intervals rather than P values, and comply with 2 Acta Orthopaedica principles for concluding whether scientifically important differences exist [35]:

- A statistically non-significant test is not sufficient to claim "no difference." To show "no difference," a smallest clinically relevant size of the difference (it might be 0) must be defined. If all clinically relevant differences are excluded from the difference's confidence interval, a "no difference" or similarity/comparability conclusion is reasonable.
- A statistically significant test does not necessarily imply a clinically important difference. The importance of the tested null hypothesis depends on the smallest clinically relevant difference that should be defined a priori. If the difference's confidence interval excludes all clinically irrelevant differences, a conclusion concerning the existence of a clinically important difference is reasonable.

To evaluate imprecision in the estimated treatment effect, a clinically important difference must first be defined. Based on an expected 2-year incidence of PJI of about 1%,[36] a 50% increase in risk would be considered clinically relevant. In a time-to-event analysis, this corresponds to a hazard ratio of 1.5. Accordingly, non-inferiority—or absence of a clinically meaningful increase in risk—will be established if the upper bound of the 95% confidence interval for the hazard ratio remains below 1.5. We will visualize the 2-year cumulative incidence of all outcomes for both groups using the cumulative incidence functions (CIFs).

Handling of missing data and sensitivity analyses: Missing data is unavoidable in epidemiological and clinical research and must be explained otherwise it could undermine the credibility and validity of the research results. Missing values, for either predictors or outcomes, occur in all types of medical research. Unless prompted to do otherwise, most statistical packages explicitly exclude individuals with any missing value on any of the data analyzed. The resulting so-called "available case" or "complete case" analysis is the most common "default approach" to handle missing data, although it is rarely justified. [35] Subjects with missing weight or height will be excluded from the analysis. Missingness of data on some of the covariates used for adjusting will be ignored but the subjects will not be excluded. Patients who will be lost during the follow up period (e.g., due to death or migration) are expected to be extremely few and no systematic difference is expected to be seen.

Therefore, this missingness of outcome data will be assumed "Missing completely at random" (MCAR), as there is no evidence to suggest systematic differences between the missing values and the observed values and will be ignored. For the purpose of sensitivity, we will potentially re-do the main analysis where missing outcome data is replaced twice, using best-case imputation (y=0; no PJI) and worst-case imputation (y=1, PJI yes).

Figure 1 (Mockup): study flow chart

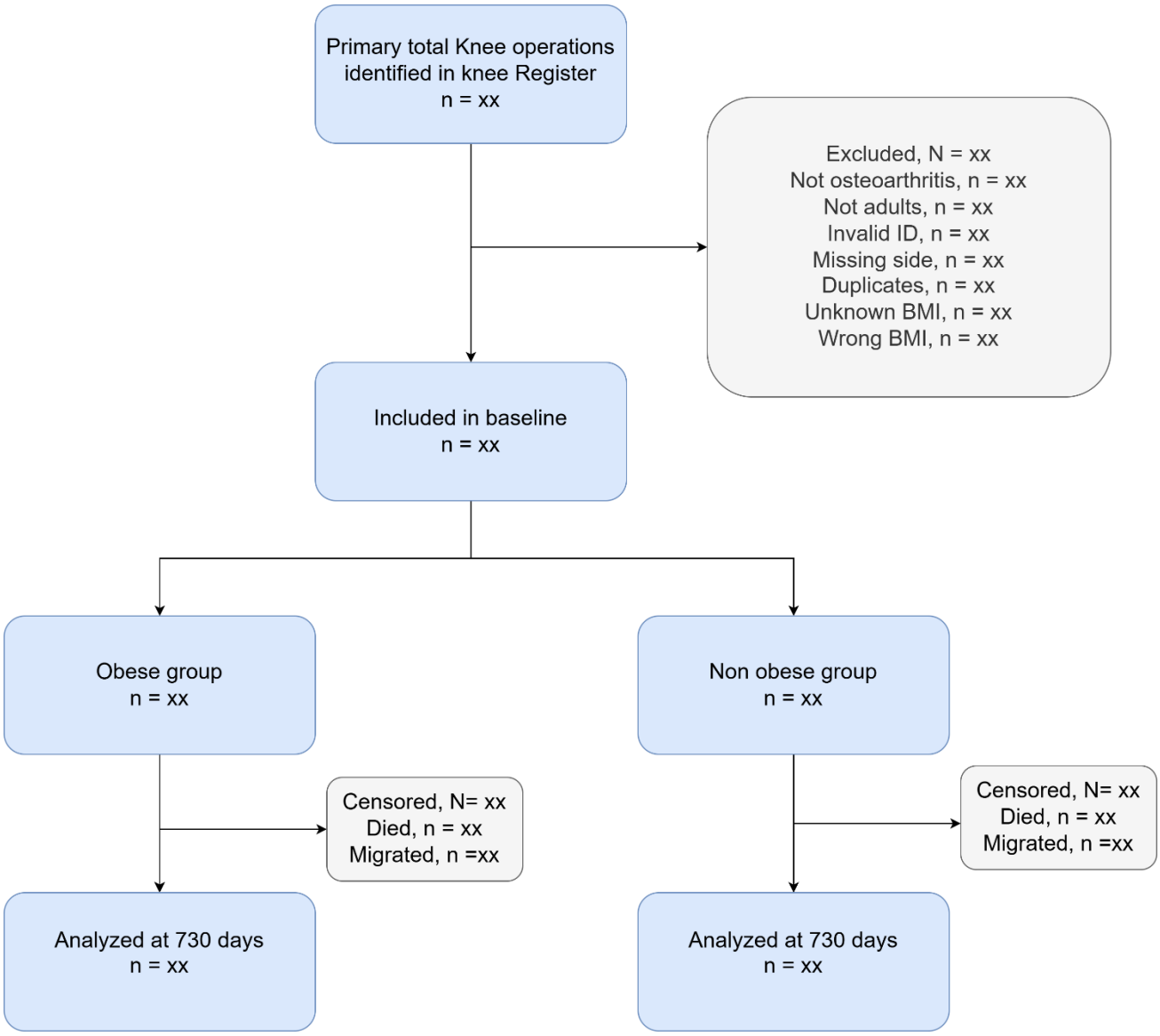
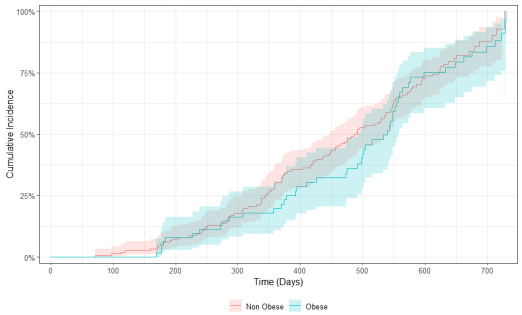


Table 1 (Mockup). Baseline characteristics at time of total knee arthroplasty

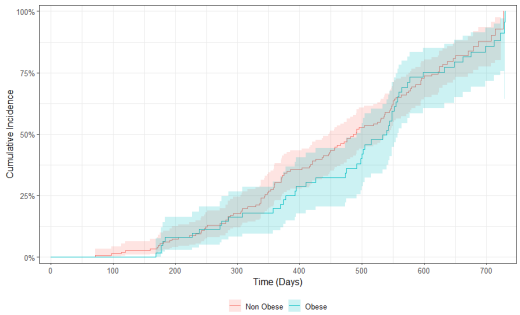
	Obese	Non-Obese	Std. Diff
Age, years			
Female Sex, no. (%)			
BMI, kg/m²			
Highest completed Education:			
<11 years, no. (%)			
11 to 15 years, no. (%)			
>15 years, no. (%)			
Household income:			
Lowest (1st quantile), no. (%)			
Low (2nd qunatile), no. (%)			
Medium (3rd quantile), no. (%)			
High (4th quantile), 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.

Figure 2 (Mockup): Simulated data illustrating the cumulative incidence of A) Prosthetic joint infection (PJI); B) all-cause revision.



A



B

Table 2 (Mockup): Incidence for Periprosthetic joint infection (PJI) and all cause revision at 2 years in obese and non-obese patients with an unadjusted and adjusted analyses of the Hazard Ratios (HR) between the 2 groups over the full 2-year period

	Obese	**Non-Obese**	**HR [95% CI*]**
Crude analyses:			
N	xx	xx	
PJI, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
All cause revision, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Adjusted analyses:			
N	xx	xx	
PJI, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
All cause revision, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]

*CI: Confidence Interval

Table 3 (Mockup): Microbial profiles in revisions for prosthetic joint infection (PJI) within the first 90 days and between 90 days and 2 years postoperatively.

	Obese	**Non-Obese**	**Absolute Risk Difference [95% CI*]**
N	xx	xx	
PJI, 90 days, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Staphylococcus aureus, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Coagulase-negative staphylococci, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Other gram-positive, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Gram-negative, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Anaerobes, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Fungal, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Mycoplasma, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
polymicrobial, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Culture-negative, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
PJ, 91 days - 2 years, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Staphylococcus aureus, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Coagulase-negative staphylococci, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Other gram-positive, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Gram-negative, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Anaerobes, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Fungal, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Mycoplasma, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
polymicrobial, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Culture-negative, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]

*The 95% confidence intervals (CI) will not be adjusted for multiplicity and should not be used in place of hypothesis testing.

Sensitivity analyses

A sensitivity analysis will also be done to report PJI-likely revisions and the microbial profiles in these patients. PJI-likely revisions will be defined as revisions surgeries with at least one of the following: A) One single intraoperatively obtained positive culture obtained from the revision surgery (aspiration fluid OR tissue biopsy) regardless of the microorganism. B) One single positive culture obtained from aspiration of synovial fluid regardless of microorganism. If we do not find a difference between obese and non-obese, we will run a sensitivity analysis where we compare morbidly obese patients (BMI ≥ 40 kg/m²) with other patients (BMI<40 kg/m²). If the primary analysis showed a difference between obese and non-obese, a sensitivity analysis comparing morbidly obese (BMI≥40 kg/m²) with non-morbidly obese (BMI 30-40 kg/m²) will be done.

Sensitivity analysis table 1: Incidence for Periprosthetic joint infection-likely (PJI) revision at 2 years in obese and non-obese patients with the relative risk (RR) and an unadjusted and adjusted analyses of the Hazard Ratios (HR) between the 2 groups

	Obese	**Non-Obese**	**HR [95% CI*]**
Crude analyses:			
N	xx	xx	
PJI-likely, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Adjusted analyses:			
N	xx	xx	
PJI-likely, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]

*CI: Confidence Interval

Sensitivity analysis table 2: Prosthetic joint infection-likely (PJI-likely) within the first 90 days and in 91 days-2 years postoperatively stratified by the type of infection

	Obese	**Non-Obese**	**Absolute Risk difference [95% CI*]**
N	xx	xx	
PJI-likely, 90 days, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Staphylococcus aureus, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Coagulase-negative staphylococci, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Other gram-positive, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Gram-negative, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Anaerobes, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Fungal, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Mycoplasma, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Multibacterial, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
PJI-likely, 91 days - 2 years, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Staphylococcus aureus, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Coagulase-negative staphylococci, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Other gram-positive, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Gram-negative, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Anaerobes, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Fungal, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Mycoplasma, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Multibacterial, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]

*The 95% confidence intervals (CI) will not be adjusted for multiplicity and should not be used in place of hypothesis testing.

Sensitivity analysis table 3: Incidence for Periprosthetic joint infection (PJI) and all cause revision at 2 years in morbidly obese and non-morbid patients with an unadjusted and adjusted analyses of the Hazard Ratios (HR) between the 2 groups

	Morbidly-Obese	**Non-morbid**	**HR [95% CI*]**
Crude analyses:			
N	xx	xx	
PJI, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Revision due to all causes, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Adjusted analyses:			
N	xx	xx	
PJI, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Revision due to all causes, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]

*CI: Confidence Interval

Sensitivity analysis table 4: Prosthetic joint infection in morbidly-obese within the first 90 days and in 91 days-2 years postoperatively stratified by the type of infection

	Morbidly-obese	**Non-morbid**	**Absolute Risk difference [95% CI*]**
N	xx	xx	
PJI, 90 days, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Staphylococcus aureus, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Coagulase-negative staphylococci, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Other gram-positive, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Gram-negative, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Anaerobes, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Fungal, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Mycoplasma, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Multibacterial, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
PJI, 91 days - 2 years, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Staphylococcus aureus, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Coagulase-negative staphylococci, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Other gram-positive, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Gram-negative, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Anaerobes, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Fungal, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Mycoplasma, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]
Multibacterial, no. (%)	xx (xx)	xx (xx)	xx [xx to xx]

*The 95% confidence intervals (CI) will not be adjusted for multiplicity and should not be used in place of hypothesis testing.

HEALTH RESEARCH ETHICS AND GENERAL CONSIDERATIONS

Funding

Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital is supported by a core grant from the Oak Foundation (OCAY-18-774-OFIL). Saber M. Saber is supported by a grant from Karen Elise Jensens Fond. The supporting institutions had no role in study design or writing of this protocol.

Conflict of interest

All will be disclosed.

Disclaimers

The views expressed in the submitted protocol are the authors' own and not an official position of the institution or funder.

Ethics

In Denmark, the Act on Processing of Personal Data does not require ethical permission or obtained consent for anonymised retrospective register studies. The Danish Data Protection Agency has approved the study with nr p-2023-14433.

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