The impact of socioeconomic status on total hip arthroplasty

Utilization and postoperative complications

PhD dissertation

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"If we knew what it was we were doing, it would not be called research, would it", Albert Einstein

"The more difficult the victory, the greater the happiness in winning", Pelé

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List of papers

The thesis is based on the following four original studies, which will be referred to in the following text by their roman numerals (I-IV).

I. **The impact of socioeconomic status on the utilization of total hip arthroplasty during 1995-2017: 104,055 THA cases and 520,275 population controls from national databases in Denmark.**
Edwards NM, Varnum C, Overgaard S, Pedersen AB. *Acta Orthopaedica.* 2021; 92 (1): 28–34. DOI: 10.1080/17453674.2020.1840111. Epub 2020 Oct 27

II. **Impact of socioeconomic status on the 90- and 365-day rate of revision and mortality after primary total hip arthroplasty: A cohort study based on 103,901 patients with osteoarthritis from national databases in Denmark.**
Edwards NM, Varnum C, Overgaard S, Pedersen AB. *Acta Orthopaedica.* 2021 DOI:10.1080/17453674.2021.1935487. Epub 2021 Jun 04

III. **The Association between Socioeconomic Status and the 30- and 90-day risk of Infections after Primary Total Hip Arthroplasty: A Registry-Based Cohort Study on 103,901 Patients with Osteoarthritis**
Edwards NM, Varnum C, Nelissen RGHH, Overgaard S, Pedersen AB.
Resubmitted to The Bone & Joint Journal

IV. **The association between socioeconomic status and the 90-day risk of cardiovascular events after total hip arthroplasty - A registry-based study of 103,286 patients.**
Edwards NM, Kristiansen EB, Varnum C, Nelissen RGHH, Overgaard S, Pedersen AB.
Submitted to JAMA

Abbreviations

aHR	Adjusted hazard ratio
aOR	Adjusted odds ratio
aRR	Adjusted relative risk
ATC	Anatomical Therapeutic Chemical Classification
BMI	Body Mass Index
CCI	Charlson Comorbidity Index
CI	Confidence interval
CVD	Cardiovascular disease
DAGs	Directed acyclic graphs
DCRS	Danish Civil Registration System
DHR	Danish Hip Arthroplasty Registry
DNPR	The Danish National Patient Registry
DVT	Deep vein thrombosis
HR	Hazard ratio
ICD	International Classification of Diseases
MI	Myocardial infarction
OA	Osteoarthritis
OR	Odds ratio
PJI	Prosthetic joint infection
PE	Pulmonary embolism
SES	Socioeconomic status
THA	Total hip arthroplasty
UTI	Urinary tract infection
VTE	Venous thromboembolism
WHO	World Health Organization

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1. Introduction

1

In 2005, The Commission on Social Determinants of Health was set up to marshal the evidence of actions to promote health equity.[1] Based on this, the World Health Organization (WHO) encouraged all countries to evaluate social inequality in health and to set the goal of reducing the inequality, aiming to close the health gap in a generation's time. The nature and the scope of inequality in health were explored in Denmark. This led to a report from the Danish government in 2020 stating that social inequality in health is a growing problem despite universal tax-supported healthcare.[2,3]

Almost every chronic disease, from arthritis to cardiovascular disease (CVD), shows a pattern of higher prevalence with lower income.[4] Therefore, a successful orthopedic surgical procedure, such as total hip arthroplasty (THA), may also be influenced by socioeconomic status (SES). This would lead to differences in utilization and outcome of the surgical procedure in regard to socioeconomic stratification.[5] With this thesis, we provide new knowledge on the impact of SES on THA and cover statistical associations between SES and the utilization of THA, postoperative complications, and mortality after THA.

The thesis contains an introduction to THA and SES with a reflection on the different SES markers followed by a description of the methodological choices made when designing the studies. The main results are presented and discussed in comparison to the existing literature and the general population. Figure 1 shows the number of THAs and the number of adverse events registered during 1995-2017, which the thesis is based on.

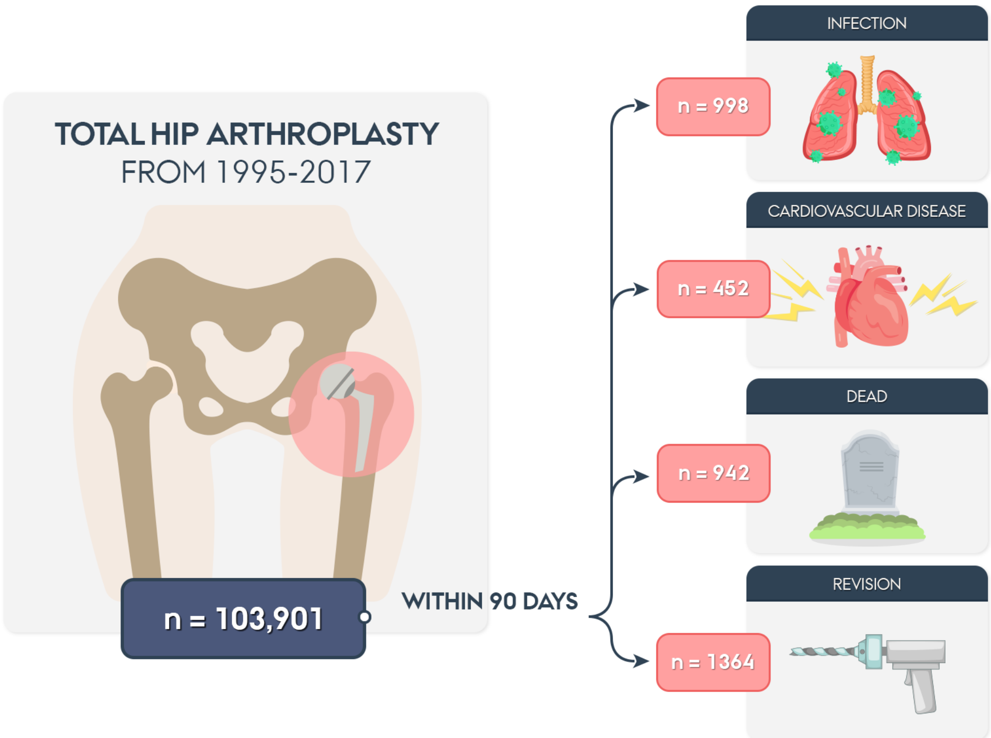


Figure 1: Flowchart of adverse events after total hip arthroplasty studied in this thesis.

2. Background

2.1. The hip joint

The hip joint is the largest joint of the human body and is designed as a ball-and-socket joint involving the head of femur and the acetabulum of the pelvis securing a large degree of freedom movement including flexion/extension, adduction/abduction, and rotation. The primary function of the joint is stabilizing the weight of the body, while facilitating force to the lower extremities.

Osteoarthritis (OA) is a degenerative disease affecting the articular hyaline cartilage in the load-bearing joints, such as the hip (Figure 2). OA is a multifactorial disease affecting the entire joint, including the joint capsule synovium and subchondral bone. As the disease progresses, the cartilage degenerates, the joint space narrows, the subchondral bone thickens, and osteophytes form. This all leads to inflammation of the joint in addition to swelling and pain.[6] In Denmark, OA of the hip affects 5-6% of individuals older than 60 years, in whom it causes impaired daily function and loss of quality of life.[7] Risk factors are multiple and include systemic factors such as obesity, female gender, and age, and localized factors such as congenital structural abnormalities in the joint and acute joint trauma.[6,8] Occupational workload; such as standing, running, squatting, and heavy lifting, is also evidently a risk factor for OA.[8] Multiple treatment modalities are recommended with a combination of rehabilitation and pharmacological interventions as first-line treatment and surgical treatment as a last resort.

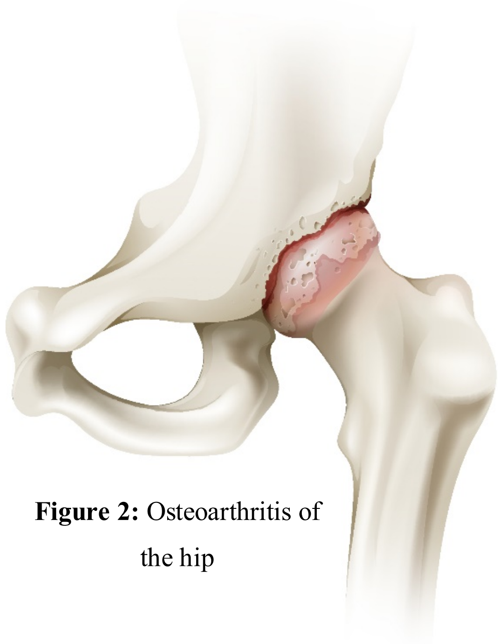


Figure 2: Osteoarthritis of the hip

2.2. Total hip arthroplasty

Total hip arthroplasty (THA) has been called "the operation of the century"[9] and has undergone extensive technological development over the past century. In 1938, a vitallium mold was produced and is regarded the first THA.[10] The idea progressed in the 1950s and 1960s to the modern concept of a low torque friction arthroplasty with the use of acrylic cement to fix components and high-density polyethylene as a bearing material.[9]

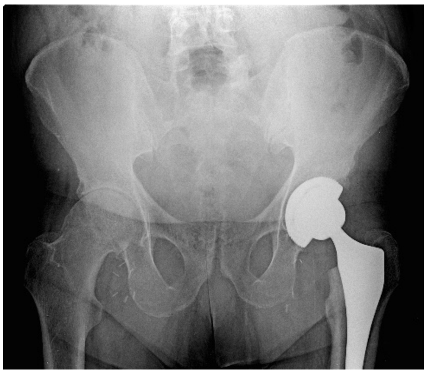


Figure 3: Total hip arthroplasty

The prosthesis consists of two components: a femoral stem with a head and an acetabular cup (Figure 3). Different designs exist with different fixation techniques and several types of bearings.

The incidence of THA in 2020 was 185 per 100,000 persons in Denmark. The THA population is characterized by a higher proportion of female than male patients (60%) and a mean age of 70 years for female patients and 67 years for male patients.[11] The primary diagnosis leading to THA was OA in 79% of all THA in the period 1995-2017, and the utilization of THA with the primary diagnosis OA steadily increased in the same period of time (Figure 4).[12] The increase in utilization of THA is induced by the recognition of the benefits of the procedure, by the increasing age of the population, by the improvements in surgical technique, and by the advances in the design of the prosthesis.[13]

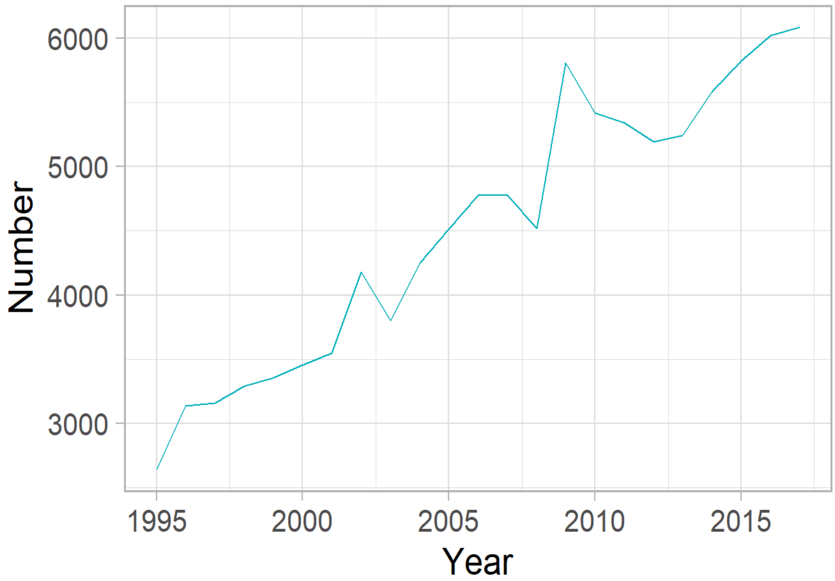


Figure 4: Number of total hip arthroplasty from 1995-2017 in patients over the age of 45 with osteoarthritis as the primary diagnosis.

2.3. Outcome after THA

THA is an effective procedure for reducing pain and improving quality of life for patients suffering from OA in the hip joint. However, the procedure entails an increased risk of adverse events, which seriously affect in-hospital patient safety and quality of care. Adverse events are defined as any medical or surgical event that requires additional monitoring, treatment, and hospitalization, or that results in death.[14] Some adverse events after THA are serious complications potentially leading to increased morbidity and mortality. Individual patient factors can affect the risk of adverse events, why much research is done to identify these risk factors after THA, facilitating a reduction of the operative risk and improving patient outcome. In general, older age and obesity are regarded risk factors for adverse events.[15] However, specific risk factors have been identified for specific adverse events.

2.3.1 Revision

Revision is defined as any later surgical procedure involving the primary THA, including change or removal of any component or debridement without removal of any part of the prosthesis.[16] In Denmark, the 5-year survival of a THA with the primary diagnosis OA is 94.8% (94.2-95.3%), and revision surgery was performed 1,441 times in 2017.[17] In 1995-2017, the primary indications for early revisions within two years were dislocation in 16% of all cases, prosthetic joint infection (PJI) in 11% of all cases, and fracture in 8% of all cases.[12] Revision due to aseptic loosening typically occurs several years after surgery, and was the primary indication for revision in 49% of all cases in 1995-2017. [12] Risk factors associated with revision include, but are not restricted to, male gender, younger age, hypertension, smoking, fixation technique, comorbidity, and bearing size and design.[12,18-20]

2.3.2 Infection

During surgery, the natural skin barrier is broken, enabling pathogens to enter the body, potentially leading to surgical site infections. Surgical site infections are defined as a postoperative infection occurring within one year of a permanent implant and can be classified by the depth and by the tissue space involved.[21,22] However, this is not the only kind of infection that THA patients are in an increased risk of. Patients risk prolonged immobilization after surgery. This affects almost every organ system and increases the risk of pneumonia and urinary tract infection (UTI).[23] These infections are serious complications and are independent risk factors for PJI.[24] These different infections have different etiologies. However, the infections have similar patient-related risk factors, such as male gender, advanced age, body mass index (BMI), and comorbidity including depression, smoking, diabetes, congestive heart failure, and hypertension.[19,25,26]

2.3.3 Cardiovascular disease

Thromboembolic complications are well known to occur after any major surgery including THA. Patients therefore receive thromboprophylaxis as standard treatment in relation to THA.[27] However, within 90 days after THA, the risk of venous thromboembolism (VTE) has been reported to be as high as 1.3%.[28] In addition, THA patients are at increased risk of sustaining other cardiovascular diseases (CVDs) in relation to THA. The risk of myocardial infarction (MI) and stroke is reported to be 0.5% within 90 days.[28] Risk factors for CVD are male gender, advanced age, comorbidity, previous history of thromboembolic event, and known cardiac disease.[28,29]

2.3.4 Mortality

THA causes a short-term increase in the risk of mortality due to MI and VTE,[30] and the estimated 90-day mortality after THA is 0.65% (0.50-0.81%).[31] CVD is repeatedly reported as the leading cause of death following THA, while male gender, advanced age, blood transfusion, diabetes, rheumatological disease, and prior CVD all are risk factors for mortality after THA.[19,31]

2.4. Socioeconomic status

Socioeconomic status (SES) is a concept describing societal stratification, which in health research often is operationalized according to economy, education, and occupation.[32] Socioeconomic inequality in health is increasingly recognized as an important public health issue, since studies repeatedly have found socioeconomic inequalities, where people of low SES have poorer health and have lower life expectancy than those with more favorable SES (Figure 5).[2,33-35]

Socioeconomic inequality in health is the product of the interplay between two life-long processes:

- The development and changes in an individual's SES[34]
- The development and changes in an individual's health[34]

These in turn affect each other, as the relationship between SES and health is reciprocal; SES influences health (social causation) and health influences SES (health selection).[34] These two causal models will be further discussed in the Discussion section 6.2.1.

Figure 5: Illustration of high and low socioeconomic status (SES)

2.4.1. Socioeconomic status markers

The most commonly used SES markers, when evaluating health inequalities, are cohabitation, education, income, and occupation. Inequality in many life circumstances can be identified along gradients of these markers, particularly in health. Here the inequality is important not only by those who are most deprived measured with an absolute poverty scale, but also as a gradient creating a relative inequality in health as inequality exists in all societies. They all have overlapping properties representing different aspects of SES, but they also have independent associations with health linked by different mechanisms and should therefore not be used interchangeably.[33,34]

Cohabitation and marital status

Social support enables an individual to deal with life's physical and psychological stresses and is usually performed by an individual's significant others.[36] There is substantial evidence showing that social support is positively associated with health and with increased life expectancy.[36,37] However, the effect of social support on health is a complex phenomenon and varies with specific dimensions of support.[38] A crude measurement of social support can be obtained by dichotomizing patients according to cohabitation status or marital status.[38] Furthermore, as economic inequality escalates, SES is increasingly associated with marital status and cohabitation status.[37]

Education

Education is a widely used international marker of SES. An individual's highest attained level of education is generally achieved in early adulthood and is therefore relatively constant throughout life. This makes it a simple, comparable, and available marker.[33,34,39] Education as a marker captures the long-term influence of early life circumstances on adult health since education is achieved early in life. Even more, it captures the influence of resources on health because of the impact on health by the achieved education.[39] There is substantial evidence that higher education is positively associated with health and with higher life expectancy.[37] This association is suggested to be driven by the cognitive ability to process complex information regarding healthy behavior, psychosocial resources, lifestyle, and health literacy.[33,34,40] Hereby reducing stress and providing a more effective coping and flexible problem-solving behavior with a sense of control. All in all these mechanisms shape healthy lifestyle by creating incentives for investments in health.[34]

Income and liquid assets

Income is often considered a straightforward marker of material resources. However, income varies widely between those still in the labor market and those who have retired,[33] since retirement is often accompanied by a decline in income.[41] Using income as an marker of SES in the elderly may therefore mask the level of economic status, and income has therefore been criticized as a marker of SES in old age.[41] Adding liquid assets to the equation leaves the possibility of assessing the cumulative effects of a lifetime of deprivation or privilege, and is therefore seen as a better predictor of health in the elderly.[41] Internationally, income and liquid assets have been shown to be strongly associated with health and mortality through the affordability of healthcare, healthy diet, good housing quality, safe environment, and the psychological burden of being poor. The psychological burden of being poor is explained by the biology of chronic stress in the sense that income inequality acts as a social stressor by lower levels of social cohesion and generalized trust.[42] Being poor is not only an issue when based on the absolute poverty score but is also an issue when based on the relative score when comparing poverty in a community.

Occupation

Occupation influences health through the general position and prestige in a society that a job can provide and also through physical and mental health risks at the workplace.[34] The practical implementation of occupation as an SES marker is limited, however, by the fact that a high proportion of the elderly are retired and no longer are exposed to current work conditions. Further, it cannot be distinguished if they never were employed or held various employments over their lifetimes.[34,41] Another limitation is that occupation is influenced by education and influences income and may therefore not have much additional effect besides education and income.[34]

2.5. Literature review

A review of selected relevant background literature for this thesis was performed. I identified literature which had studied the association between SES and THA utilization (Study I) and the association between SES and the risk of revision, mortality, infection, and CVD after THA (Studies II, III, and IV). I used MEDLINE (PubMed) for my primary search, using the major Medical Subject Heading (MeSH) search terms: "socioeconomic status" and "total hip arthroplasty". In addition, I searched PubMed and EMBASE for studies using the MeSH and non-MeSH terms: "socioeconomic status", "total hip arthroplasty", "utilization", "revision", "prosthetic joint infection", "cardiovascular disease", "mortality", and "infections". The last search was performed on the 19th of April 2021. I assessed the titles and abstracts for papers listed in the search results as an initial screening for relevance. I retrieved full-text papers where abstracts suggested applicability. I supplemented the searches by reviewing the reference lists of retrieved relevant full-text papers.

The primary search in PubMed yielded 48 papers. Table 1 summarizes the results of the literature search.

Table 1: Overview of the different searches using MeSH terms and non-MeSH terms i**n PubMed, and using EMBASE, yielding a**n amount **of relevant literature**.

	MeSH	**Non-MeSH**	**EMBASE**	**Relevant**
Study I[43]	38	29	18	7
Study II (revision)[44]	8	13	6	8
Study II (mortality)[44]	1	7	16	8
Study III	5	9	11	6
Study IV	1	3	2	5*

*** all five papers are previously described**

Table 2 summarizes the results of the literature review.

Table 2: Summary of the literature

Study I – The impact of socioeconomic status on the utilization of total hip arthroplasty during 1995-2017			
Author, journal, year	**Design, setting, period**	**Population, exposure, controls (if applicable), outcome**	**Results, limitations**
Ackerman et al.[45] - 2012 - Best Practice & Research: Clinical Rheumatology	- Review	- OA, RA - Joint replacement - Education, income, occupation, deprivation, and insurance.	- Disparities in surgical treatment.
Agabiti et al.[35] - 2007 - International Journal for Quality in Health Care	- Population-based retrospective study - 1997-2000 - Italy	- Age > 65 - 6140 patients - Income index (**area),** collected in 1998 -> family income - Hospital discharge abstracts: patient characteristics, diagnosis, and surgical procedure codes (ICD-9) - Population data = register - Mean age 72 - Outcomes within **90 days**: acute adverse medical events (PE, hemorrhagic anemia, and cardiac complication), orthopedic complications (hematoma, dislocation, and joint infections), general infections, and decubitus (ICD-9) **Rates** of revision and death - Follow-up: 2004 - Poisson regression for the incidence of THA (rate ratios), adjusted for age, gender, city of residence - Cox (HR) of revision and mortality by income. Covariates were age, gender, city of residence, and coexisting conditions.	- Patients in low income area were 13% less likely to have had THA - Likelihood was lowest for those aged >75 living in the lowest income area.
Wetterholm et al.[46] - 2016 - Acta Orthopaedica	- Prospective cohort study - 2004-2013 - Sweden	- 50,498 knee OA and 20,882 hip OA - Income, education, and occupation **(individual-level)** - First total or partial replacement of the knee or hip - Index date: first OA diagnosis - Calculate incidence rates and HRs.	- THA was most common in the highest income group, most educated group, legislators, senior officials, managers, and professionals - Age- and sex-adjusted rates were highest in the high income group, and highly educated group.
Cooksen et al.[47] - 2005 - European Journal of Public Health	- Cross-country comparison, case-control - 2002-2009 - Denmark, England, Portugal, and Spain	- All over the age of 35 - THA - Income index (area) - Rates with area-level Poisson regression CI.	- No inequality in THA rates in Denmark.
Brennan et al.[48] - 2012 - BMC Musculoskeletal Disorders	- Retrospective - 2006-2007 - Australia	- 642 THA from the AOANJRR - Index of Relative Socioeconomic Disadvantage - Calculated rates, Poisson regression to calculate RR.	- Higher rates for both the most disadvantaged and least disadvantaged groups.
Mahomed et al.[49] - 2003 - TJB & J Surgery	- Prospective cohort study - 1995-1996 - USA	- All THA and revision 1995-1996 = 61,568 patients - Medicare - Low income was defined as those receiving Medicaid supplement - THA and revision incidence rates - 90 days - (**Individual)** Income based on receiving Medicaid supplement - Rate ratios with Poisson regression - Adjusted for the numbers of THA performed annually at the hospital and by the surgeon.	- Those receiving Medicaid supplements had lower rates of primary THA - Low income was associated with an increased risk of adverse outcome (death, wound infection) - Only risk within 90 days - No definition of wound infection, hip dislocation (defined through an algorithm).
Makela et al.[50] - 2010 - Archives of Orthopaedic Trauma Surgery	- Retrospective cohort study - 1998-2005 - Finland	- Average income in a region - 34,675 THA with OA.	- No correlation between income and THA incidence - Considerable geographical variations in THA incidence rates.

Study II – Impact of socioeconomic status on the 90- and 365-day rate of revision and mortality after primary total hip arthroplasty

Author, journal, year	Design, setting, period	Population, exposure, controls (if applicable), outcome	Results, limitations
Agabiti et al.[35] - 2007 - International Journal for Quality in Health Care	- Population-based retrospective study - 1997-2000 - Italy	- Age > 65 - 6140 patients - Income index (**area),** collected in 1998 -> family income - Hospital discharge abstracts: patient characteristics, diagnosis, and surgical procedure codes (ICD-9) - Population data = register - Mean age 72 - Outcomes within **90 days**: acute adverse medical events (PE, hemorrhagic anemia, and cardiac complication), orthopedic complications (hematoma, dislocation, and joint infections), general infections, and decubitus (ICD-9) **Rates** of revision and death - Follow-up: 2004 - Poisson regression for the incidence of THA (rate ratios), adjusted for age, gender, and city of residence - Cox (HR) of revision and mortality by income. Covariates were age, gender, city of residence, and coexisting conditions.	- Patients in low income area were 13% less likely to have had THA - Likelihood was lowest for those aged >75 living in the lowest income area.
Jenkins et al.[51] - 2009 - Surgeon	- Prospective cohort study - 1998-2005 - Scotland	- All THA, 1725 patients (all cemented) - OA - (**Area**) The Scottish Index of Multiple Deprivation - HHS pre-operatively, 6 months and 18 months - SF-36 pre-operatively, 6 months and 18 months - Outcome: HHS, SF-36, complications (PE, DVT, transfusion, infection, and dislocation), and mortality (total, 90 days).	- HHS was lower in more deprived groups pre-operatively, 6 months and at 18 months - SF-36 physical score was lower - SF-36 mental score was lower - No differences detected on 90-day mortality, TE, dislocation, or infection - Adjusted for age and sex - No definition of complications and mortality - Only results are N and %, and only few counts.
Mahomed et al.[49] - 2003 - The journal of Bone & Joint Surgery	- Prospective cohort study - 1995-1996 - USA	- All THA and revision = 61,568 patients - Medicare - Low income was defined as those receiving Medicaid supplement - THA and revision incidence rates - 90 days - (**Individual)** Income based on receiving Medicaid supplement. - Rate ratios with Poisson regression - Adjusted for the numbers of THA performed annually at the hospital and by the surgeon.	- Those receiving Medicaid supplements had lower rates of primary THA - Low income was associated with an increased risk of adverse outcome (death, wound infection) - Only risk within 90 days - No definition of wound infection, hip dislocation (defined through an algorithm).
Kremers et al.[52] - 2015 - Journal of Arthroplasty	- Prospective cohort study - 2002-2009 - USA	- All THA, 9688 patients - USA - Single institution - (**Individual/patient-reported**) Institutional joint registry = demographics, surgical characteristics (surgery type, indications), prior surgery (ASA, BMI, DM), outcomes (dates and types of complications < one year, reoperations, revision, death) - Info on marital status, education, smoking, and alcohol = patient-provided forms - Marital status, education, smoking, and alcohol - Outcome: Surgical site infections, overall complications (implant loosening, instability, dislocation, fractures, vascular, neurological, soft tissue, alignment, wound problems, TV events, osteolysis) and death - Follow-up 12 months	- No association between marital status, educational attainment, and the risk of surgical site infection complications, reoperation, or revisions - Marital status and educational attainment were predictors of death, similar to those observed in the general population - Smoking was associated with higher risk of surgical site infections (HR 1.7) - Alcohol was associated with lower risk of reoperation and revision (HR 0.7) - Revision performed for infected joint arthroplasties were excluded - 30% missing on risk factors - No definition of revision and reoperation.

		- Multivariable Cox, adjusted for age, gender, BMI, calendar year, surgery type, number of prior surgeries on the same joint, DM, ASA, procedure duration.	
Peltola et al.[53] - 2014 - Archives of Orthopaedic Trauma Surgery	- Retrospective cohort study - 1998-2010 - Finland	- 33,249 THA - Finnish Arthroplasty Register - **Individual** - Cox regression - Data on revision (reoperation and removals of prostheses) were verified from two registries - Outcome: risk of revision, timespan from primary to revision - Short- (<3 years) and long-term revision risk - Annual household income = Income distribution statistics (adjusted for family size, deflated to the 2009 level). One income year, one year prior to surgery - Adjusted for age, sex, CHD, AF, HF, psychotic disorders, cancer, and depression.	- No association between income and revision (small insignificant difference, low income – smallest risk of revision) - 1-year income - Median age 67.7 (pension).
Weiss et al.[54] - 2019 - Acta Orthopaedica	- Prospective cohort study - 1992-2012 - Sweden	- **Individual** - Swedish Hip Arthroplasty Register - All THA, 166,076 patients - Income, education, cohabiting status, hospital type, immigration, and CCI - Outcome: 30- and 90-day mortality, readmission due to cardiovascular reasons or for any reason	- High income was associated with lower 30-day mortality (HR 0.5), lower 90-day mortality (HR 0.7), and readmission for cardiovascular reasons (HR 0.7). - High education was associated with lower risk of readmission for cardiovascular reasons (HR 0.7) - Adjusted for age, sex, comorbidity, income, and education. - No info on when SES data were obtained, no mean of income. Median age at index = 70 (pension).

Study III – The impact of socioeconomic status on the 30- and 90-day risk of severe infection after primary total hip arthroplasty

Author, journal, year	**Design, setting, period**	**Population, exposure, controls (if applicable), outcome**	**Results, limitations**
Agabiti et al.[35] - 2007 - International Journal for Quality in Health Care	- Population-based retrospective study - 1997-2000 - Italy	- Age > 65 - 6140 patients - Income index (**area),** collected in 1998 -> family income - Hospital discharge abstracts: patient characteristics, diagnosis, and surgical procedure codes (ICD-9) - Population data = register - Mean age 72 - Outcomes within **90 days**: acute adverse medical events (PE, hemorrhagic anemia, and cardiac complication), orthopedic complications (hematoma, dislocation, and joint infections), general infections, and decubitus (ICD-9) **Rates** of revision and death - Follow-up: 2004 - Poisson regression for the incidence of THA (rate ratios), adjusted for age, gender, and city of residence - Cox (HR) of revision and mortality by income. Covariates were age, gender, city of residence, and coexisting conditions.	- Patients in low income area were 13% less likely to have had THA - Likelihood was lowest for those aged >75 living in the lowest income area.
Clement et al.[55] - 2011 - The Journal of Bone & Joint Surgery	- Prospective study - 2006-2008 - Scotland	- All THA with OA, 1312 patients - Mean age: 68.1 - Deprivation score - PROM: Oxford score - Patients reviewed at 6 weeks, 6 months, and 12 months - Outcome: Postoperative complications: pneumonia, need of transfusion, MI, DVT, PE, deep infection, and early dislocation (before one year) were obtained from hospital electronic database and patient notes	- Deprivation score was an independent predictor of mean improvement at 12 months: most affluent patients had a greater improvement than the most deprived patients - The most deprived groups were more likely to dislocate than all other categories - Increased mortality risk at 90 days for the most deprived - No association between deprivation, deep infection, and pneumonia.

		- 90-day mortality - Logistic regression (OR).	
Weiss et al.[54] - 2019 - Acta Orthopaedica	- Prospective cohort study - 1992-2012 - Sweden	- **Individual** - Swedish Hip Arthroplasty Register - All THA, 166,076 patients - Income, education, cohabiting status, hospital type, immigration, and CCI - Outcome: 30- and 90-day mortality, readmission due to cardiovascular reasons or readmission due to any reason.	- High income was associated with lower 30-day mortality (HR 0.5), lower 90-day mortality (HR 0.7), and readmission for cardiovascular reasons (HR 0.7) - High education was associated with lower risk of readmission for cardiovascular reasons (HR 0.7) - Patients living alone had an increased risk of readmission due to cardiovascular reasons - Patients with low income and patients living alone had increased risk of readmission due to any reason - Adjusted for age, sex, comorbidity, income, and education. - No info on when SES data were obtained, no mean of income. Median age at index = 70 (pension).
Jenkins et al.[51] - 2009 - Surgeon	- Prospective cohort study - 1998-2005 - Scotland	- All THA, 1725 patients (all cemented) - OA - (**Area**) The Scottish Index of Multiple Deprivation - HHS pre-operatively, 6 months and 18 months - SF-36 pre-operatively, 6 months and 18 months - Outcome: HHS, SF-36, complications (PE, DVT, transfusion, infection, and dislocation), and mortality (total, 90 days).	- HHS was lower in more deprived groups pre-operatively, 6 months and at 18 months - SF-36 physical score was lower - SF-36 mental score was lower - No differences detected on 90-day mortality, TE, dislocation, or infection - Adjusted for age and sex - No definition of complications and mortality - Only results are N and %, and only few counts.
Keeney et al.[56] - 2015 - The Journal of Arthroplasty	- Retrospective cohort study - 2006-2013 - USA	- All THA and TKA from hospital admission database, 3825 THA patients - Low SES = Medicaid or Medicare + <65 - Hospital database and electronic medical records were reviewed: patient demographics (age, gender, BMI, and comorbidity) and info about primary THA - Outcome: readmission, all	- Highest risk of readmission if low SES - No distinction and information about readmission causes.
DeKeyser et al.[32] - 2020 - The Journal of Arthroplasty	- Retrospective cohort study - 1996-2013 - USA	- All primary joint arthroplasty - Cases (PJI) = 2282 - Controls (THA+TKA) = 73,196 - 2-year follow-up - Area household income, education from APCD - Cox, RR (HR).	- Patients with Medicaid had greater risk of PJI (RR 1.4(1.08-1.82)) than private insurance - No difference in risk associated with education or income.
Baker et al.[57] - 2012 - The Lancet	- Retrospective cohort study - 1989-2008 - New Zealand	- National (New Zealand) with all hospital admissions - Hospital admission events - SES by use of New Zealand deprivation index (**Area**) - Adjusted rates, rate ratios.	- Most socioeconomically deprived had higher risk of admission for infectious diseases

Study IV – Impact of socioeconomic status on the 90-day risk of cardiovascular disease after primary total hip arthroplasty

Author, journal, year	Design, setting, period	Population, exposure, controls (if applicable), outcome	Results, limitations
Weiss et al.[54] - 2019 - Acta Orthopaedica	- Prospective cohort study - 1992-2012 - Sweden	- **Individual** - All THA, 166,076 patients - Swedish Hip Arthroplasty Register - Income, education, cohabiting status, hospital type, immigration, and CCI - Outcome: 30- and 90-day mortality, readmission due to cardiovascular reasons or readmission due to any reason.	- High income was associated with lower 30-day mortality (HR 0.5), lower 90-day mortality (HR 0.7), and readmission for cardiovascular reasons (HR 0.7) - High education was associated with lower risk of readmission for cardiovascular reasons (HR 0.7) - Adjusted for age, sex, comorbidity, income, and education. - No info on when SES data was obtained, no mean of income.

			Median age at index = 70 (pension).
Agabiti et al.[35] - 2007 - International Journal for Quality in Health Care	- Population-based retrospective study - 1997-2000 - Italy	- Age > 65 - 6140 patients - Income index (**area),** collected in 1998 -> family income - Hospital discharge abstracts: patient characteristics, diagnosis, and surgical procedure codes (ICD-9) - Population data = register - Mean age 72 - Outcomes within **90 days**: acute adverse medical events (PE, hemorrhagic anemia, and cardiac complication), orthopedic complications (hematoma, dislocation, and joint infections), general infections, and decubitus (ICD-9) **Rates** of revision and death - Follow-up: 2004 - Poisson regression for the incidence of THA (rate ratios), adjusted for age, gender, and city of residence - Cox (HR) of revision and mortality by income. Covariates were age, gender, city of residence, and coexisting conditions.	- Patients in low income area were 13% less likely to have had THA - Likelihood was lowest for those aged >75 living in the lowest income area.
Mahomed et al.[49] - 2003 - The journal of Bone & Joint Surgery	- Prospective cohort study - 1995-1996 - USA	- All THA and revision = 61,568 patients - Medicare - Low income was defined as those receiving Medicaid supplement - THA and revision incidence rates - 90 days - (**Individual)** Income based on receiving Medicaid supplement. - Rate ratios with Poisson regression - Adjusted for the numbers of THA performed annually at the hospital and by the surgeon.	- Those receiving Medicaid supplements had lower rates of primary THA - Low income was associated with an increased risk of adverse outcome (death, wound infection) - Only risk within 90 days - No definition of wound infection, hip dislocation (defined through an algorithm) - No association between THA and PE.
Jenkins et al.[51] - 2009 - Surgeon	- Prospective cohort study - 1998-2005 - Scotland	- All THA, 1725 patients (all cemented) - OA - (**Area**) The Scottish Index of Multiple Deprivation - HHS pre-operatively, 6 months and 18 months - SF-36 pre-operatively, 6 months and 18 months - Outcome: HHS, SF-36, complications (PE, DVT, transfusion, infection, and dislocation), and mortality (total, 90 days).	- HHS was lower in more deprived groups pre-operatively, 6 months and at 18 months - SF-36 physical score was lower - SF-36 mental score was lower - No differences detected on 90-day mortality, TE, dislocation, or infection - Adjusted for age and sex - No definition of complications and mortality - Only results are N and %, and only few counts.
Clement et al.[55] **-** 2011 - The Journal of Bone & Joint Surgery	- Prospective study - 2006-2008 - Scotland	- All THA with OA, 1312 patients - Mean age: 68.1 - Deprivation score - PROM: Oxford score - Patients reviewed at 6 weeks, 6 months, and 12 months - Outcome: Postoperative complications: pneumonia, need of transfusion, MI, DVT, PE, deep infection, and early dislocation (before one year) were obtained from hospital electronic database and patient notes - 90-day mortality - Logistic regression (OR).	- Deprivation score was an independent predictor of mean improvement at 12 months: most affluent patients had a greater improvement than the most deprived patients - The most deprived groups were more likely to dislocate than all other categories - Increased mortality risk at 90 days for the most deprived - No association between deprivation, deep infection, and pneumonia - No association between deprivation, MI, DVT, and PE.

Abbreviations: All Payers Claims Database (APCD), Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR), American Society of Anesthesiologists score (ASA), Body Mass Index (BMI), Charlson Comorbidity Index (CCI), coronary heart disease (CHD), deep vein thrombosis (DVT), diabetes mellitus (DM), hazard ratio (HR), International Classification of Diseases (ICD), myocardial infarction (MI), odds ratio (OR), osteoarthritis (OA), patient reported outcome measure (PROM), pulmonary embolism (PE), socioeconomic status (SES), thromboembolism (TE), total hip arthroplasty (THA).

2.6. THA utilization (Study I)

The association between SES and utilization of THA has been studied in several papers, but the results are ambiguous. Mahomed *et al.*[49] were pioneers when they in 2003 published a prospective cohort study evaluating rates of THA. Using Medicaid as a surrogate for low income, they showed that low income was associated with lower rates of THA.[49] Cooksen *et al.*[47] performed a cross-country comparison of healthcare inequality in 2005. They relied on area-based data and found no inequality in the rates of THA in Denmark. They did, however, find inequality in England and Spain.[47] This incentive was further explored by Agabiti *et al.,*[35] whose paper is widely cited and is considered the first to examine the effect of SES on the rates of THA and outcome in depth. They also relied on area-based assessment of income and found a 13% less likelihood of receiving a THA in the low income areas.[35] A smaller retrospective study from Australia found a U-shaped association with greater rates of THA for both the most and least disadvantaged groups measured using an index for assessing the relative socioeconomic disadvantage.[48] In 2010 Makela *et al.*[50] found no association between area-based income and the incidence of THA in Finland.[50] Finally, SES was assessed using individual-based data without surrogates and with multiple SES markers in a study from Wetterholm *et al.*[46]. They found THA to be most common in the highest income group and in the most educated group.[46]

Overall, the literature review shows that the previous studies have contradicting results regarding the associations between SES and THA rates. This could be due to the different methodologies and definitions of SES, where individual-based register data with several SES markers are superior to area-based measurements and evaluating SES with only one marker.[54] The inconsistencies could also be due to different healthcare settings, from financing healthcare through the tax system to financing through insurance or private funding. The underlying mechanisms will therefore vary between inequality concerning access to healthcare and more complex etiologies relating to the need of THA. Individuals with a lower SES have higher incidence of OA and refrain to a greater extent from seeking medical care.[46,58] Therefore, an increased need of THA among low SES is plausible.

2.7. Revision and mortality after THA (Study II)

The results of previous studies on the association between SES and the risk of revision and mortality are all contradictory. Mahomed *et al.* and Agabiti *et al.* also investigated the outcome after THA. Mahomed *et al.* found that low income was associated with an increased mortality. In contrast, Agabiti *et al.* found no association between income, revision, and mortality,[35,49] and furthermore Peltola *et al.*[53] also found no association between income and revision.[53] In 2015, Maradit Kremers *et al.*[52] conducted a prospective cohort study using individual-based data on marital status and education from a single institution using patient-reported data. They found no association between SES and the risk of revision.[52] In 2019, a prospective study was performed by Weiss et *al.*[54] They used individual-based register data with multiple SES markers and found that low income was associated with higher mortality.[54] However, this study has no information on when they obtained information regarding socioeconomic factors, and neither to what extent they took annual variation and inflation into account. In addition, the mean age of the population was above the age of retirement, leaving a population with an income with less fluctuation and perhaps skewed values.

Previous literature is therefore limited by insufficient definitions and measurements of SES, reliance on patient-reported data collection, and missing data. The impact of SES on mortality in different populations will be further discussed in the Discussion section 6.1.2 of this thesis.

2.8. Severe infection after THA (Study III)

Quite a few studies have investigated the association between SES and the risk of infections. The same study from 2007 by Agabiti *et al.* also looked at the risk of infections. They found that low income was associated with a higher risk of general infections (sepsis, UTI, and pneumonia).[35] In 2010, Clement *et al.*[55] preformed a single center study with prospectively collected data using a score system to measure the level of deprivation. They found no association between deprivation groups, deep wound infection, and pneumonia, and a similar study by Jenkins *et al.* found the same absence of an association.[51,55] Weiss *et al.* found that patients with low income and patients who were living alone had an increased risk of readmission due to any reason.[54] However, there is no provision of readmission causes other than a differentiation between readmission due to cardiovascular reasons and due to any reasons. A retrospective cohort study from 2015 using insurance payer type and age as surrogates for SES, found an association between socioeconomic disadvantaged patients and higher readmission rates due to any reason. The newest study by DeKeyser *et al.*[32] from 2020 evaluated the influence of both insurance payer type, household income, and educational level on rates of PJI. They found that patients with Medicaid had greater risk of PJI than private insurance patients had, and that there was no difference in the risk associated with education or income. However, income level was area-based thereby introducing misclassification and the study was missing a substantial amount of data on the level of education.[32,59]

Overall, there are disparities in the previous studies related to the risk of infection after THA with a lack of distinguishing between different infection causes thereby disregarding their different etiology, different risk factors, and different treatment modalities. The social inequality may therefore differ between causes. Thus, the literature is limited by these factors, by using area-based measurements, and by using statistical methodology inferior when managing competing risk issues and interdependency on hospital level which all are relevant when studying infections. The impact of SES on the risk of infections in different populations will be further discussed in the Discussion section 6.1.3 of this thesis.

2.9. Cardiovascular events after THA (Study IV)

To our knowledge, no other study has investigated the association between SES and CVD in THA patients, with CVD as the main outcome, and differentiating between CVD causes. Agabiti *et al.*[35] found that low income was associated with higher risk of acute adverse medical events (pulmonary embolism [PE], haemorrhagic anaemia, and cardiac complication) and Weiss *et al.*[54] found the same association. In confliction, Mahomed *et al.*,[49] Jenkins *et al.*,[51] and Clement *et al.*[55] found no association. All used pooled CVD outcomes, area-based measurements, or used statistical methodology inferior when managing competing risk issues and interdependency on hospital level which all are relevant when studying the risk of CVD. It is well known that SES has a measurable and significant effect on the risk of CVD.[60] This is thought to be due to biological, behavioral, and psychosocial risk factors prevalent in disadvantaged individuals, which emphasizes the link between SES and CVD.[60] Therefore, further investigation may enlighten the potentially reinforced association between SES and THA in regards to CVD.

The impact of SES on the risk of CVD in different populations will be further discussed in the Discussion section 6.1.4 of this thesis.

2.10. Knowledge gaps

Study I The association between SES and THA utilization has been studied before. However, no other study has examined the association using individual-level register-based data in Denmark, while evaluating if the potential inequalities are age- or time-dependent.

Study II The majority of register studies have been performed using Cox regression to estimate time to revision or death with contradicting results. However, no previous study has assessed the association using a multilevel model hereby accounting for the within-cluster homogeneity. No other study has assessed the association while differentiating between revision causes and clinical relevant timespans.

Study III Cox regression only considers the risk of an event among those still at risk. However, the interpretation of the hazard ratio (HR) is not uncomplicated and is challenged by the presence of competing risk. Therefore, the previously published studies are with contradicting results. No other study has evaluated the association between SES and different infection types while using the pseudo-observation method, which enables the calculation of relative and absolute risk estimates.

Study IV There are discrepancies in the previous published literature. No other study has investigated the association between SES and CVD in THA patients, where CVD has been the main outcome, and when differentiating between CVD causes using the pseudo-observation method.

3

3. Hypotheses and aims

Our overall aim of this thesis was to examine the associations between SES and THA risk and prognosis with focus on the utilization of THA and the postoperative complications after THA. The hypothesis and specific aims are listed below:

Study I

Hypothesis: There is socioeconomic inequality in THA utilization in Denmark, where low SES is associated with lower rates of THA.

Aim: To examine the association between SES and the utilization of THA across different age groups and over time.

Study II

Hypothesis: There is socioeconomic disparity in regard to the risk of revision and mortality, where low SES is associated with higher rates of revision and mortality.

Aim: To examine the association between multiple SES markers and the rates of any revision as well as revisions due to infection, fracture, and dislocation, and mortality within 90 and 365 days after THA.

Study III

Hypothesis: There is socioeconomic disparity in regard to the risk of severe infection, where low SES is associated with higher risk of infection.

Aim: To examine the association between multiple SES markers and the risk of severe infection, while distinguishing between any infection, pneumonia, UTI, and PJI within 30 and 90 days after THA.

Study IV

Hypothesis: There is socioeconomic inequality in the risk of CVD after THA, where low SES is associated with higher risk of CVD.

Aim: To examine the association between multiple SES markers and the risk of CVD, while disguising between MI, VTE, and stroke within 30 and 90 days after THA.

4. Methods

4

This section describes the methods used in the different studies. An overview is provided in Table 3.

4.1. Setting

Denmark has national tax-supported healthcare for the entire Danish population, guaranteeing free access to general practitioners and hospitals.[61] All Danish residents have the right to be listed with a general practitioner, whose function is to act as gatekeeper to specialized care including inpatient hospital care.[62] general practitioners also refer patients to municipal services for rehabilitation and home care.[62]

4.2. Data sources

All four studies used prospectively collected data recorded in medical and administrative databases. The Danish Civil Registration System (DCRS) assigns all Danish residents and immigrants a unique and permanent civil registration number. This number is included in all Danish registries allowing for unambiguous record linkage on an individual level between multiple registries and nearly complete long-term follow-up.[61]

4.2.1. Administrative and medical databases

The Danish Civil Registration System (DCRS) was initiated in 1968. The DCRS contains information on vital status with the exact date of birth and death, emigration status, immigration status, civil status, and municipality of residence.[61] We collected information on age and sex.

The Danish Hip Arthroplasty Registry (DHR) was established in 1995 and is a part of the Danish National Clinical Quality Database with the aim of registering and improving the results after THA in Denmark.[63] All Danish hospitals and some private clinics report to the DHR.[63] The registry contains preoperative data, peroperative data, and postoperative data and includes data on primary THA and revision surgeries. The DHR has high completeness, 91%-98% for primary THA and 75%-92% for revision surgeries from 1995 to 2017.[16,17,64] We collected information regarding the type of surgery (primary or revision), operated side, primary diagnosis, fixation technique, implant size, date of surgery and revision, revision cause, duration of surgery, and hospital code.

The Danish National Patient Registry (DNPR) is an administrative registry established in 1977 covering all hospitalizations since 1977 and outpatient clinic and emergency room contacts since 1995. The registry is updated continuously, and hospitals are required by law to submit data at least once a month. The registry includes administrative data, both primary (primary reason for contact) and secondary diagnoses (additional conditions), treatments, and examinations.[65] The diagnosis codes are coded according to the International Classification of Diseases (ICD) Eighth Revision (ICD-8; from 1977 to 1993) or Tenth Revision (ICD-10; starting in 1993).[65] The positive predictive value for pneumonia is 90-93%,[66] 77% for UTI,[67] and 77% for PJI.[68]

The Danish National Health Service Prescription Database has kept information on all prescriptions for reimbursed drugs dispensed by community pharmacies in Denmark since 2004. The registry contains information on drug name and type according to the Anatomical Therapeutic Chemical classification system (ATC codes).[69]

Statistics Denmark contains detailed individual-level information on socioeconomic characteristics on all Danish citizens. The Income Statistics Registry includes information about family annual household income and liquid assets, and the data are primarily supplied by the tax authorities. The Population Education Registry obtains information about the highest completed level of education from data generated from administrative records of educational institutions and from surveys. The Registry-based Labour Force Statistics (RAS) contains a description of the affiliation with the labor market. The registries are administered by the Danish government and are updated yearly.[70,71] We retrieved information on SES using the following markers: cohabitating status, marital status, highest obtained education, family income, family liquid assets, and occupation.

4.3. Study designs and study populations

The timeline for all four studies is shown in Figure 6.

In Study I, we wanted to estimate the utilization of THA in different SES stratifications. We therefore chose to use a population-based case-control study.[43] The DHR was used to identify all patients undergoing primary THA in Denmark from the 1st of January 1995 to the 31st of December 2017 with the primary diagnosis OA (cases). Only the first THA during 1995-2017 was included in the study cohort, and if the patient received bilateral THA on the same date, only the right THA was included in the study. The date of THA surgery was considered as the index date and the same date was used to identify the population controls by matching on sex and region of residence on the index date. We used the DCRS to randomly select five population controls for each THA case.[43] A selected control could be included as a case if eligible later on. Studies II and III are cohort studies and the study population was defined equivalent to the cases in Study I. Study IV was likewise a cohort study defined equivalently and in addition excluding outliers to avoid distortion of our statistical analyses.[72] Outliers were defined by age as those older than the 75% percentile plus 1.5 standard deviation leading to an age of 90.09 years. For an overview, see flow charts in Appendices I, II, and IV. In Study IV, we stratified the population according to previous CVD occurrence. This was done to enable the risk calculation in different subpopulations in relation to previous CVD. The study designs will be further discussed in section 6.2.3 on methodological considerations.

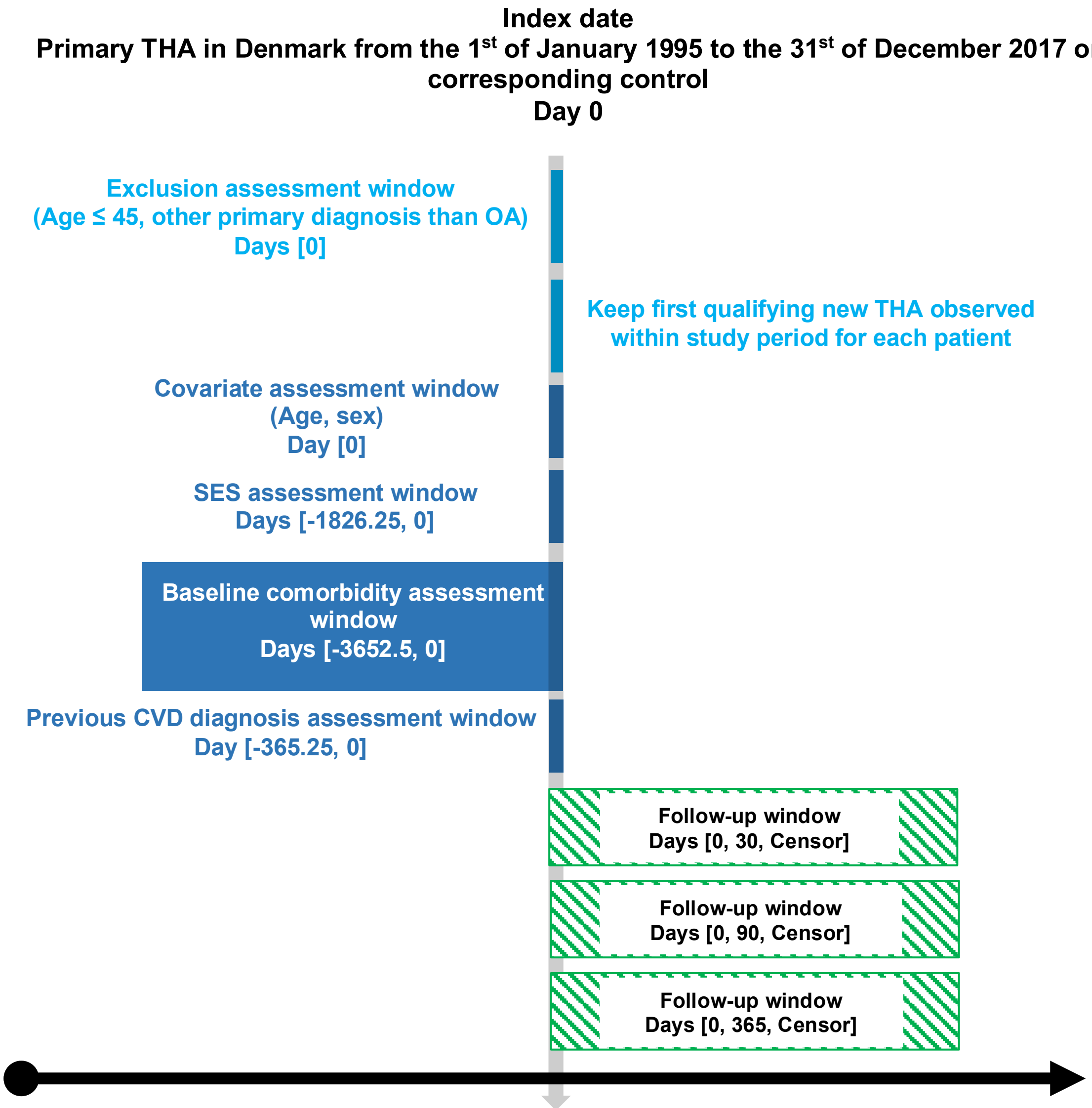


Figure 6: Time line for Studies I-IV.
OA: Idiopathic osteoarthritis.
THA: Total hip arthroplasty.
SES: Socioeconomic status: Cohabitating status, marital status, highest obtained education, family mean income, mean family liquid assets, and occupation. Income and liquid assets were obtained for the five years prior to surgery.
Baseline assessment: We summarized the ten-year pre-surgery hospital comorbidity history for each patient, and measured the comorbidity status by Charlson Comorbidity Index (CCI) score.
CVD: cardiovascular disease
Censor: Earliest of outcome of interest, death, disenrollment, end of follow-up, or end of the study period.

Table 3: Summary of materials and methods.

	Study I	Study II	Study III	Study IV
Objectives	To examine the association between SES and the utilization of THA across different age groups and over time.	To examine the association between multiple SES markers and the rates of any revision as well as revisions due to infection, fracture, and dislocation, and mortality within 90 and 365 days after THA.	To examine the association between multiple SES markers and the risk of severe infection, while distinguishing between any infection, pneumonia, UTI, and PJI within 30 and 90 days after THA.	To examine the association between multiple SES markers and the risk of CVD, while disguising between MI, VTE, and stroke within 90 days after THA.
Setting	Denmark, 1995-2017.	Denmark, 1995-2017.	Denmark, 1995-2017.	Denmark, 1995-2017.
Design	Case-control.	Prospective cohort study.	Prospective cohort study.	Prospective cohort study.
Data sources	DCRS, DHR, DNPR, DST.	DCRS, DHR, DNPR, DST.	DCRS, DHR, DNPR, DST.	DCRS, DHR, DNPR, DST, DNHSP.
Study population	All primary THA, when only including the first THA. If the patient received bilateral THA on the same date, only the right THA was included in the study. The date of THA surgery was considered as the index date and the same date was used to identify the population controls by matching on sex and region of residence on the index date. We used the DCRS to randomly select five population controls for each THA case.	All primary THA, when only including the first THA. If the patient received bilateral THA on the same date, only the right THA was included in the study. The date of THA surgery was considered as the index date.	All primary THA, when only including the first THA. If the patient received bilateral THA on the same date, only the right THA was included in the study. The date of THA surgery was considered as the index date.	All primary THA, when only including the first THA. If the patient received bilateral THA on the same date, only the right THA was included in the study. The date of THA surgery was considered as the index date. Stratified into subgroups according to previous CVD history.
Exposures	Cohabitation status, marital status, education, income, liquid assets, and occupation.	Cohabitation status, education, income, and liquid assets.	Cohabitation status, education, income, and liquid assets.	Cohabitation status, education, income, and liquid assets.
Outcomes	THA.	Any revision and revisions due to fracture, infection, and disclocation, and mortality.	Any severe infection, and severe infections due to pneumonia, UVI, and PJI.	Any CVD, stroke, MI, VTE, PE, and DVT.
Covariates	Age, sex, CCI, calendar year, and SES.	Age, sex, CCI, calendar year, hospital, and cohabitation.	Age, sex, CCI, hospital, and cohabitation.	Age, sex, CCI, CVD medication, hospital, and cohabitation.
Statistical analysis	Calculation of proportions of cases and controls with each specific marker. Calculation of OR using logistic regression.	Calculated the cumulative incidence of revision and mortality, treating death as a competing risk, using the *cmprsk* package in R. Calculation of HRs using a multilevel model with inclusion of random effects into the Cox proportional hazards model when clustering for hospitals using the *coxme* package in R.	Calculated the cumulative incidence of any infection, treating death as a competing risk, and the cumulative incidence of mortality using the *cmprsk* package in R. Calculating RR and RD based on the pseudo-observation method using the *stset* and *stpci* command in STATA and using generalized linear regression with the stats package in R.	Calculated the cumulative incidence of CVD, treating death as a competing risk, using the *cmprsk* package in R. Calculating RR and RD based on the pseudo-observation method using the *stset* and *stpci* command in STATA and using generalized linear regression with the stats package in R.
Sensitivity analyses	Stratifying for age and calendar year.	Stratifying for calendar year and age (<65/≥65) for income and liquid assets.	Cumulative incidence at five years. Stratifying by calendar year and by gender (data not shown).	Cumulative incidence at five years. Stratifying by CVD history.

Abbreviations:
Charlson Comorbidity Score Index (CCI), Cardiovascular disease (CVD), The Danish Civil Registration System (DCRS), The Danish Hip Arthroplasty Registry (DHR), The Danish National Patient Registry (DNPR), The Danish National Health Service Prescription Database (DNHSP), Statistic Denmark (DST), deep vein thrombosis (DVT), hazard ratio (HR), myocardial infarction (MI), prosthetic joint infection (PJI), pulmonary embolism (PE), relative risk (RR), risk difference (RD), socioeconomic status (SES), urinary tract infection (UTI), vein thromboembolism (VTE)

4.4. Exposures

Exposure refers to any factor that may be associated with an outcome of interest.[73]

4.4.1. Utilization of THA (Study I)

In study I,[43] we included several exposures to estimate SES. For each THA case and population control we obtained information on marital status, cohabitation, highest obtained education, family income, family liquid assets, and occupation. Marital status was categorized as never married, married, divorced, or widow/widower. Cohabitation was divided into living alone or cohabiting. Highest obtained education was classified into three categories: low, defined as none or elementary school; medium, defined as more than elementary school, but less than university completed; and high, defined as university degree completed. Since a large proportion of the THA patients are senior citizens (≥65 years of age) with a state pension, family liquid assets was used to describe SES in patients >65 years of age, whereas family income was used to assess SES in patients <65 years of age.[41] We retrieved information on family income and liquid assets for the five years prior to surgery. We calculated the average yearly total income and liquid assets in the five years prior to surgery for the patient and cohabiting partner to account for yearly variations in income and liquid assets. The family mean income and liquid assets were categorized into tertiles of increasing amount: low, medium, and high. Occupation was divided into the following categories: on benefits, early retirement/pension, unemployed, unskilled worker, skilled worker, employer/self-employed, director/chief executive, and others. Because of low numbers, we regrouped occupation in the age groups 76-85 and >86 to only include retirement, working and others. An overview of the grouping is provided in Appendix I.[43]

4.4.2. Revision and mortality (Study II)

In Study II, we retrieved information on cohabitation, highest obtained education, family income, and family liquid assets.[44] Marital status was evaluated in Study I[43] as being nearly the same estimates as cohabiting, therefore we only included cohabitation status in the following studies. Occupation was likewise evaluated and the relevance of this marker decreased in the following studies and was therefore not included in Studies II-IV.

4.4.3. Hospital-treated complications (Studies III and IV)

In Studies III and IV, we retrieved information on cohabitation, highest obtained education, family income, and family liquid assets. The age stratification was not possible due to too few events in the younger age groups, forcing us to use both income and liquid assets throughout all ages. In addition, to account for yearly inflation during the long study period, we grouped all mean income and mean liquid assets by year and finally categorized them into three groups of increasing amount according to tertiles: low, medium, and high.

4.5. Outcomes

4.5.1. THA (Study I)

The outcome in Study I was the utilization of THA calculated according to each SES marker.[43] We also evaluated the age- and time-trends when stratifying for age and calendar year. For more information see Appendix I.[43]

4.5.2. Revision and mortality (Study II)

The primary outcomes in Study II were time to revision divided into time to any revision or time to revision due to infection, fracture, or dislocation.[44] Revisions were identified in the DHR and defined as any later surgical procedure involving the primary THA, including change or removal of any component or debridement without removal of any part of the prosthesis.[16] In addition, we studied time to mortality, defined by date of death due to any cause identified from the DCRS. All outcomes were evaluated within 90 or 365 days after the date of the primary THA procedure (Figure 6). We also evaluated the outcome in regard to calendar year and age, see Appendix II.[44]

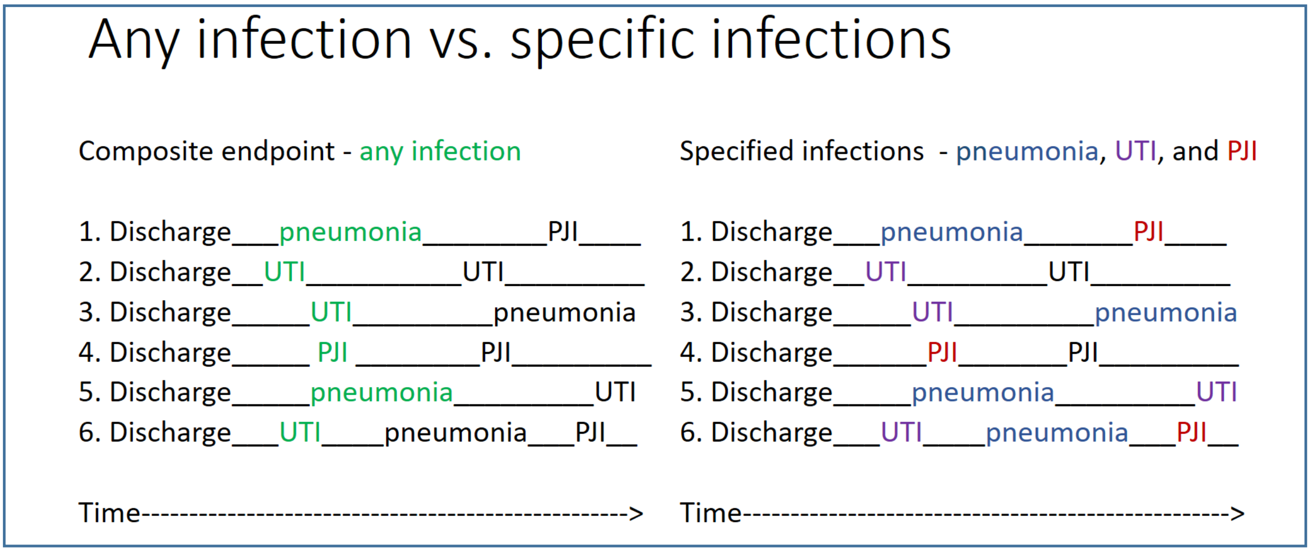


Figure 7: Example of discharge data for six random patients.
Data setup for the composite infection outcome, where only the first event for every patient is included vs. the individual infection subgroup, where the same patient can contribute with several events, if the events are in different subgroups. Only the first colored (green, blue, lilac, and red) outcomes are included.

4.5.3. Infections (Study III)

The outcome in Study III was a composite endpoint of any severe infection and specified endpoints due to pneumonia, UTI, and PJI. The composite endpoint was defined as first-time readmission due to hospital-treated infections including all possible infection types (see Appendix III), while specific endpoints were defined as first-time readmission due to hospital-treated pneumonia, UTI, and PJI. More than one outcome was possible for each patient. The data structure and setup are shown in Figure 7. The figure illustrates six patients with any infection, but when evaluating the specific endpoints, four out of six patients have pneumonia, four out of six patients have UTI, and three out of six patients have PJI. Readmissions were identified in the DNPR and evaluated within 30 and 90 days after the date of the primary THA procedure (Figure 6).

4.5.4. CVD (Study IV)

The outcome in Study IV was a composite endpoint of cardiovascular events and individual subgroups comprised of CVD, VTE, deep vein thrombosis (DVT), stroke, PE, and MI. The composite endpoint was defined as first-time readmission due to hospital-treated CVD including all possible CVD types (see Appendix IV), while specific endpoints were defined as first-time readmission due to hospital-treated VTE, DVT, stroke, PE, and MI. Readmissions were identified in the DNPR and evaluated within 90 days after the date of the primary THA procedure (Figure 6). More than one outcome was possible for each patient. The data structure and setup were equivalent to Study III and Figure 7.

4.6. Covariates

Information on covariates was retrieved on the index date to characterize study population (Studies I, II, and IV). We also included covariates based on the confounding criteria. This was done to be able to adjust for confounding, which occurs when there is a presence of a common cause of exposure and outcome, leading to a distortion of the association.[73] Age and sex were considered confounders in all studies, and information on this was collected from the DCRS.[19,20,48]

Information on comorbidities was obtained from the DNPR. The 10-year pre-index-date hospital comorbidity history for each case and population control was summarized. We measured the comorbidity status by Charlson Comorbidity Index (CCI) score based on the 19 disease categories and defined three levels of the CCI: a score of low was given to patients with no known comorbidities included in the CCI; a score of medium was given to patients with one or two known comorbidities included in the CCI; and a score of high was given to patients with three or more known comorbidities included in the CCI.[74] A more detailed overview of the chronic diseases included in the CCI and the distribution between cases and controls is provided in Appendix I[43], and the distribution in the cohort in Appendices II[44] and IV. The CCI was considered a confounder in all studies.[19,20,48]

The 1-year pre-surgery history of CVD medications was added as a covariate to the model in Study IV and obtained from The Danish National Health Service Prescription Database.[28,75]

4.7. Statistical analyses

In Studies I, II, and IV, we provided patient demographics of the study populations included in each study; in Study I according to the SES markers for both cases and controls (see Appendix I),[43] and in Study II and IV according to the SES markers shown in a demographic figure (see Appendix II and IV).[44] The statistical analyses used for Studies I-IV are summarized in Table 3.

4.7.1. Logistic regression (Study I)

Study I was a case-control study, why logistic regression was used to model the probability of our binary outcome, THA yes/no.[43,76] Odds ratios with 95% confidence interval (CI) for THA according to each marker of SES were calculated. We calculated crude odds ratios and odds ratios adjusted for age, SES markers independently (cohabitation, marital status, education, income, liquid assets, and occupation), calendar year, and CCI score. Sensitivity analyses were done when stratifying for age and calendar year.

4.7.2. Cumulative incidence (Study II, III, and IV)

In Studies II-IV, we calculated the cumulative incidence of revision, hospital-treated infection, and CVD, treating death as a competing risk, and the cumulative incidence of mortality using the *cuminc* function in the *cmprsk* package in R according to the different SES markers.[44] The cumulative incidence function allows for estimating the incidence of the occurrences of an event while taking competing risk into account. In the competing risk setting, only one event type can occur, precluding other subsequent occurrence of events. The function denotes the probability of experiencing the event before the occurrence of a different type of event.[77]

4.7.3. Cox proportional hazard regression models (Study II)

In Study II, our outcome was time to revision and mortality.[44] This was examined using the Cox proportional hazard regression function to calculate HRs and adjusted HR (aHR), a frequently used survival analysis using the *coxme* package in R according to the different SES markers. Covariates were included based on the confounding criteria illustrated in the directed acyclic graph (DAG) in Figure 8.[73] The arrows represent associations between the covariates, and confounding arises when backdoor paths open between exposure and outcome.[78] Of the possible SES markers, only cohabiting status was evaluated as a confounder, when evaluating income and liquid assets. Although education is considered a confounder in this DAG, we did not adjust for it due to other statistical considerations, otherwise discussed in section 6.2.1. The Cox regression is commonly used in medical reports because of its convenience in allowing investigation of the event rate when adding multiple prognostic covariates.[79] A multilevel model with inclusion of random effects was incorporated. This enhances the model by accounting for within-cluster homogeneity in the outcomes and allows the intercept to vary randomly across clusters.[80] A within-cluster homogeneity may be induced by unmeasured hospital characteristics that affect the outcome, since subjects who are nested within the same higher-level unit are likely to have outcomes that are correlated with one another.[80] The HR should be described as a relative rate and not as a relative risk as it is a function of the instantaneous rate of an event occurring at a specific time point.[79] The interpretation of the HR is therefore not straightforward and is even more challenged in the presence of competing risk. In this cohort, death is a competing risk as individuals may die before the need of a revision. The consequence is that in the presence of competing risk, there is no longer a one-to-one correspondence between the hazard rate and the risk of revision.[81] The assumption of proportionality of hazards was investigated by calculating scaled Schoenfeld residuals and by graphical

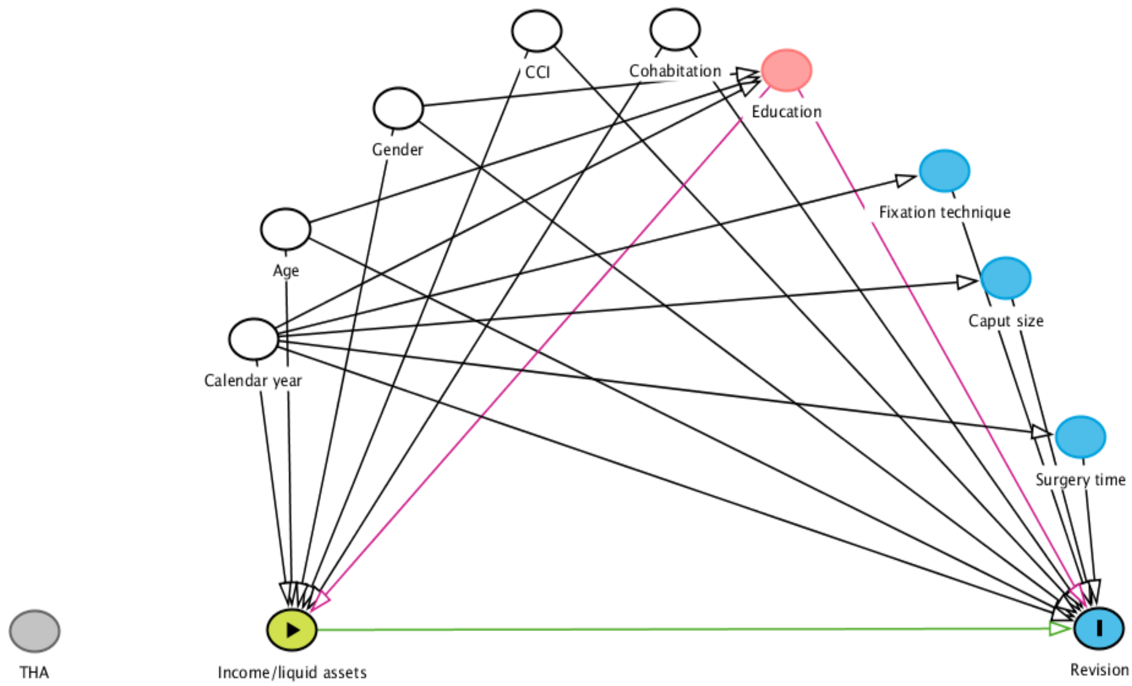


Figure 8: DAG illustrating potential confounders in Study II.[44]
CCI: Charlson Comorbidity Index
DAG: directed acyclic graph
THA: Total hip arthroplasty

assessment by plotting the residuals against time. The assumptions were fulfilled. A sensitivity analysis was preformed to account for yearly variations, dividing the period into two: 1995-2005 and 2006-2017.

4.7.4. Pseudo values (Studies III and IV)

Taught by former experience, we wanted to model the cumulative incidence of the SES stratified revision risk and compare the entire cumulative incidence curves between the groups in a setting where data are censored independently and when adjusting for covariates.[82] This is possible when modelling the cumulative incidence function for each individual and time point on a prespecified grid and hereby computing pseudo values. Estimates and standard errors are obtained by using generalized linear regression and using pseudo values as the dependent variables,[82] thereby calculating relative risks and risk differences and adjusted RR (aRR) and adjusted risk differences based on the pseudo-observation method using the *stset* and *stpci* command in STATA and using generalized linear regression with the stats package in R.[83] The within-cluster homogeneity was accounted for when using the generalized linear regression, however, this was not done by multilevel modelling. When all hospitals are accounted for, the within-cluster homogeneity can be resolved by adding the intended level, i.e. the hospitals, as a covariate to the regression model thereby using a fixed-effect model instead. As hospital volume has an impact on the risk of adverse effect,[84] the hospital covariate was constructed accordingly. In Study III, the hospital covariate was constructed consistent to the number of THA procedures performed throughout the study period, where hospitals were grouped when the number of procedures were fewer than 200 and when the number was between 201-2000. If hospitals had performed ≥2001, the hospital was included as an individual factor. In Study IV, hospitals were categorized and grouped if they were in the lowest 40th percentile by annual volume. Hospitals were grouped if they were between the 41th and 80th percentile, and grouped if they were in the highest 21th percentile.[85] In Study IV, covariates were included based on the DAG in Figure 9, enabling the calculation of the aRR. In Studies III and IV, calendar year was not included as a covariate even though it is a confounder. This will be further discussed in the methodological considerations in section 6.2.4. In Study III, sensitivity analyses were done when stratifying by gender and calendar year, and calculating the cumulative incidence at five years. In Study IV, sensitivity analyses were done by calculating the cumulative incidence at five years and by stratifying for previous CVDs.

In all studies, the data management was performed in STATA version 15 (STATACorp, TX, USA) and the statistical analyses in R version 3.6.1 (R Foundation for Statistical Computing).

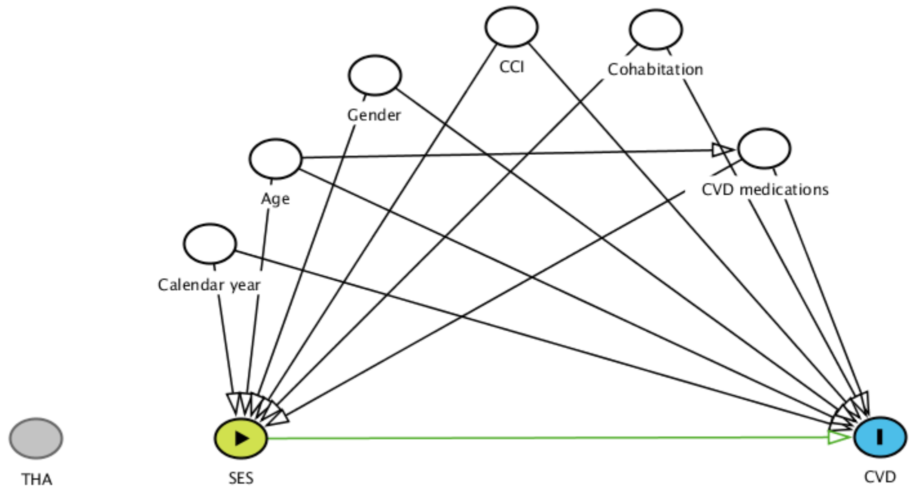


Figure 9: DAG illustrating potential confounders in Study IV.
CCI: Charlson Comorbidity Index
DAG: directed acyclic graph
THA: Total hip arthroplasty

4.8. Ethical considerations

The studies were reported to the Danish Data Protection Agency through registration at Aarhus University (record number: AU-2016-051-000001, sequential number 880).

5. Results

The main findings from Studies I-IV are presented below. For a more detailed description see the full manuscripts in Appendices I-IV.

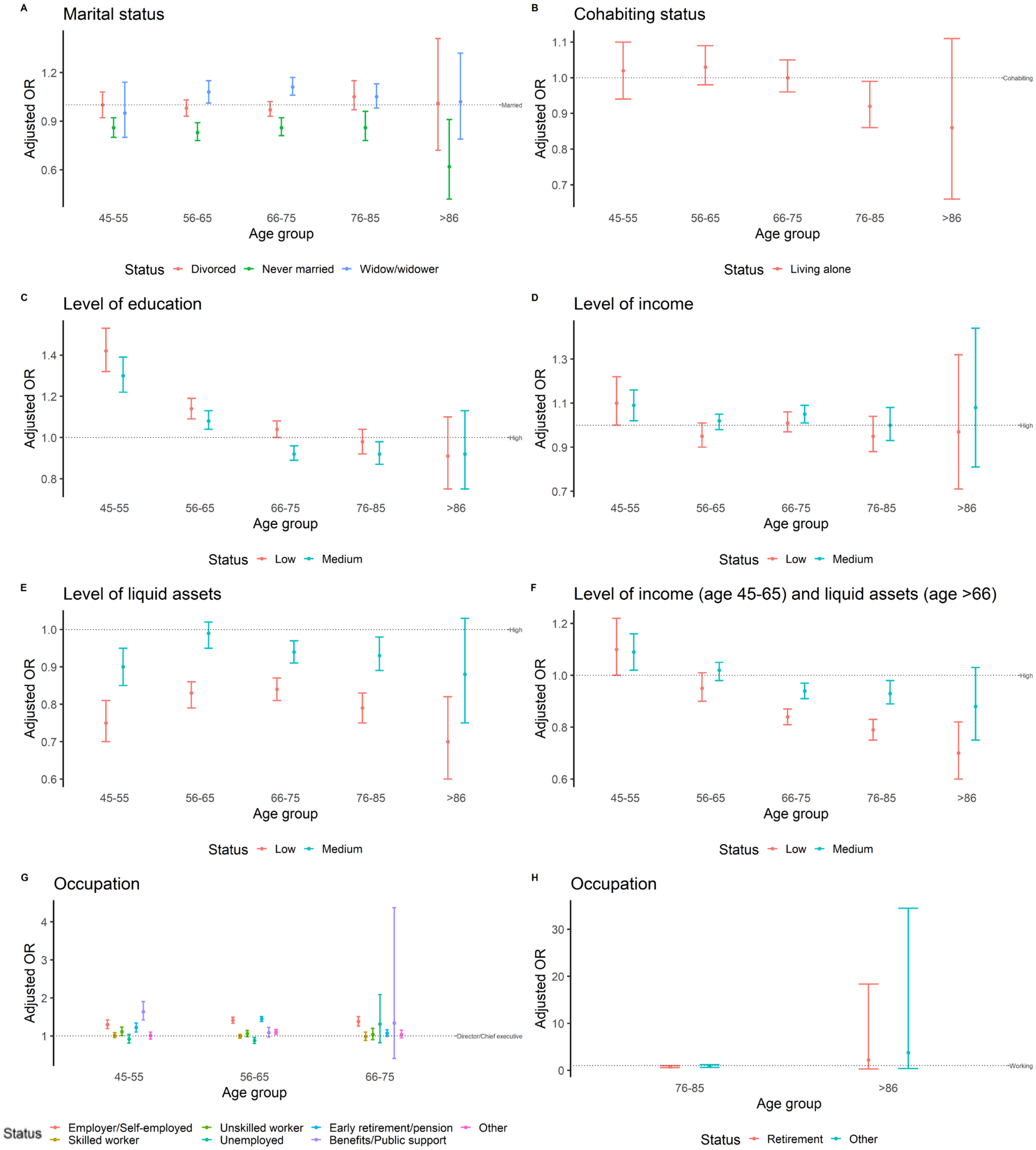
5.1. Utilization of THA (Study I)

A detailed description and flowchart of the final study population are provided in Appendix I with 104,055 identified cases and 520,275 corresponding controls.[43]

The overall associations are shown in Appendix I.[43] We found a lower risk of receiving a THA among patients who never married (adjusted odds ratio [aOR] 0.8 [CI 0.7–0.8]) or were widow/widower (aOR 0.9 [CI 0.9–0.9]) than married patients. Patients living alone also had a lower risk (aOR 0.9 [CI 0.9–1.0]) than the cohabiting. We found a higher risk among patients with the lowest level of education (aOR 1.1 [CI 1.1–1.1]) than patients with the highest level of education, and patients with the lowest level of income also had a higher risk (aOR 1.2 [CI 1.2–1.2]) than patients with the highest level of income. Similarly, patients with the lowest level of liquid assets had a lower risk (aOR 0.7 [CI 0.7–0.7]) of receiving a THA than patients with the highest level of liquid assets. We also found differences in the risk of THA in regards to occupation as being employer/self-employed, skilled worker, unskilled worker, on early retirement/pension, and receiving benefits/public support constituted a higher risk than being a director or chief executive.[43]

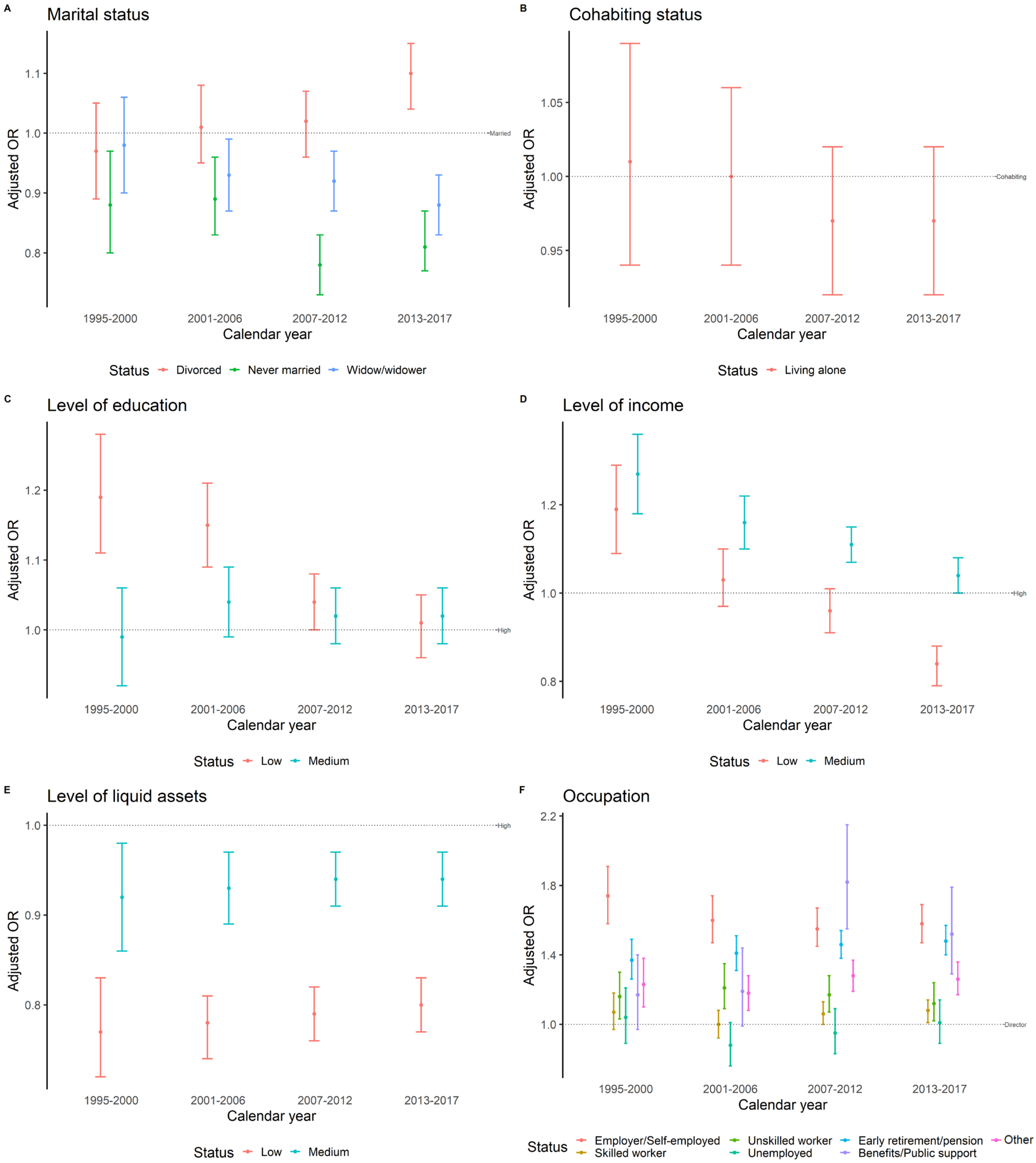
Figure 10 shows the aOR with CI stratified for age. We found that the age trend for cohabitation was a shift from a higher risk of THA in the youngest age groups when living alone towards a lower risk of THA in the oldest age groups when living alone (Figure 10B). The same trend was seen for education and for the combined exposure of income and liquid assets (Figure 10F). Early retirement/pension was associated with a higher risk of THA in all under the age of 75 (Figure 10G). Figure 11 shows the aOR with CI stratified for calendar year. In regards to the time trends, we found that for marital status there was an increase in the inequality in the later years (Figure 11A) and for income we found a shift in the inequality over time periods (Figure 11D). For education, we found a time trend towards a decrease in the inequality in the later years (Figure 11C).[43]

Figure 10: Dot plot for the adjusted odds ratios (aORs) with 95% confidence intervals, stratified for age and adjusted for socioeconomic status markers independently, calendar year, and Charlson Comorbidity Index score. Each separate dot plot is for an individual SES marker: A: marital status; B: cohabiting status; C: level of education; D: level of income; E: level of liquid assets; F: combined dot plot with the level of income in the age group 45-65 and liquid assets in the age groups over 65; G: occupation under the age of 75; and H: occupation over the age of 76. Striped line are the references i.e. married, cohabiting, high level, director/chief executive, and working



Modified figure from Edwards NM, Varnum C, Overgaard S, Pedersen AB. The impact of socioeconomic status on the utilization of total hip arthroplasty during 1995-2017: 104,055 THA cases and 520,275 population controls from national databases in Denmark. Acta Orthop 2020:1-5. DOI: 10.1080/17453674.2020.1840111. [43] Appendix I.

Figure 11: Dot plot for the adjusted odds ratios (aORs) with 95% confidence intervals, stratified for calendar year and adjusted for age, socioeconomic status (SES) markers independently, and Charlson Comorbidity Index score. Each separate dot plot is for an individual SES marker: A: marital status; B: cohabiting status; C: level of education; D: level of income; E: level of liquid assets; and F: occupation. Striped line are the references i.e. married, cohabiting, high level, director/chief executive, and working



Modified figure from Edwards NM, Varnum C, Overgaard S, Pedersen AB. The impact of socioeconomic status on the utilization of total hip arthroplasty during 1995-2017: 104,055 THA cases and 520,275 population controls from national databases in Denmark. Acta Orthop 2020:1-5. DOI: 10.1080/17453674.2020.1840111.[43] Appendix I.

5.2. Revision and mortality (Study II)

The final study population is described in detail in Appendix II showing 103,901 THA patients.[44]

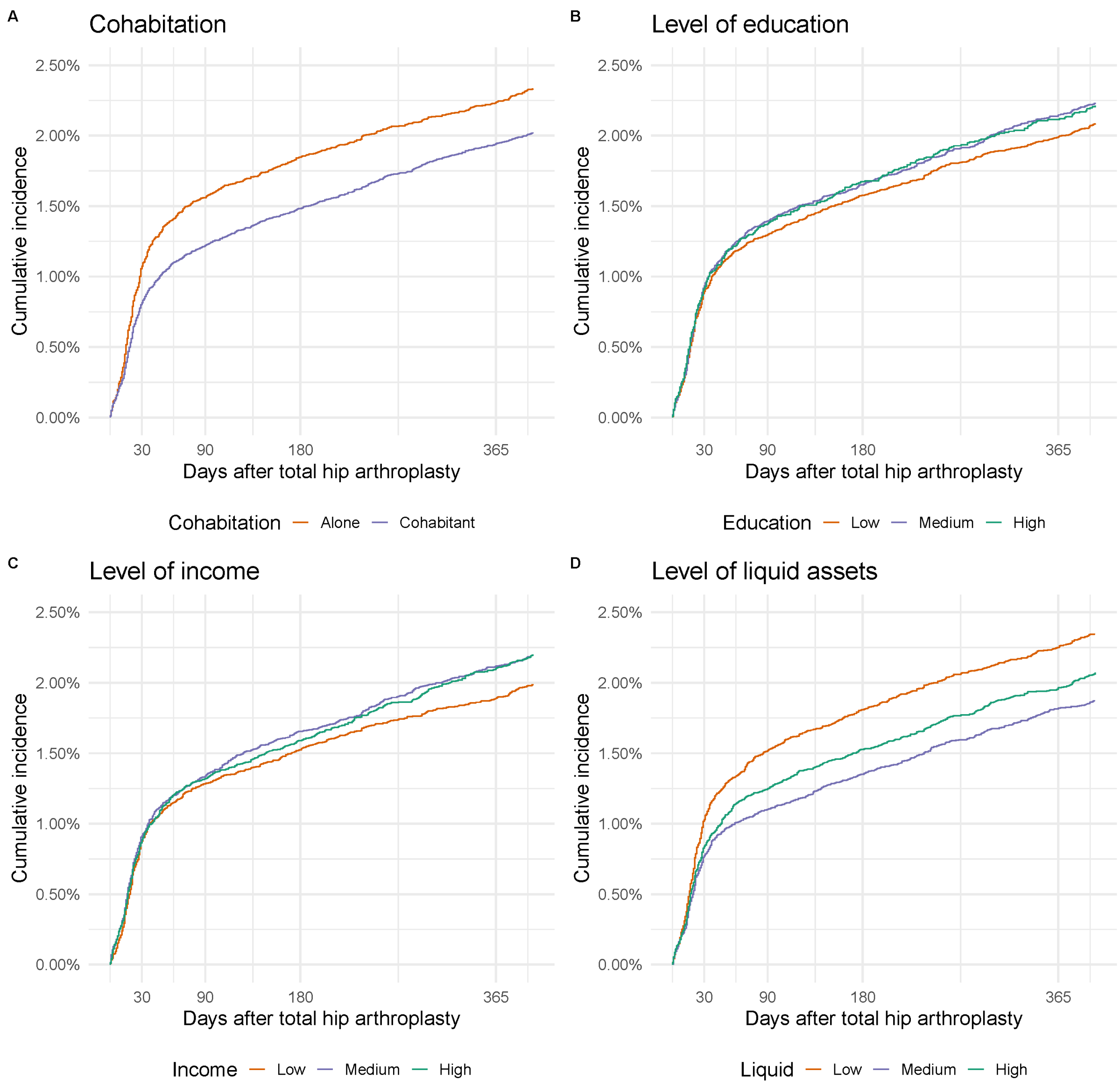
Within the first 365 days after primary surgery, 2.0% of the study population received revision surgery. The cumulative incidence of any revision is shown in Appendix II.[44] The cumulative incidence was highest among patients who lived alone (2.2% [CI 2.1-2.4]), had the highest level of education (2.1% [CI 1.9-2.9]), had the highest income (2.1% [CI 2.0-2.3]), and had the lowest liquid assets (2.3% [CI 2.1-2.4]) (Figure 12).[44]

We found that within the first 90 days, living alone was associated with a higher aHR for any revision (1.3 [CI 1.1-1.4]) than cohabiting (Figure 13A). Education was not associated with the 90-day revision rate. For patients with low income, we found a higher aHR for any revision (2.0 [CI 1.4-2.9]) than high-income patients in the age group under 65 years. For patients with low liquid assets, we found a higher aHR (1.3 [CI 1.1-1.5]) than patients with high liquid assets in the age group over 65 years. The results are shown in Appendix II and were similar to the results within the first 365 days after surgery (Figure 13B).[44] Results for the different subgroups are shown in Appendix II.[44]

Within the first 365 days after surgery, 2.2% of the study population died. The cumulative incidence for mortality at 365 days is shown in Appendix II.[44] The cumulative incidence was highest among patients who lived alone (3.0% [CI 2.8-3.2]), had the lowest level of education (2.4% [CI 2.3-2.5]), had the lowest income (3.9% [CI 3.7-4.1]), and had the lowest liquid assets (1.9% [CI 1.8-2.1]).[44]

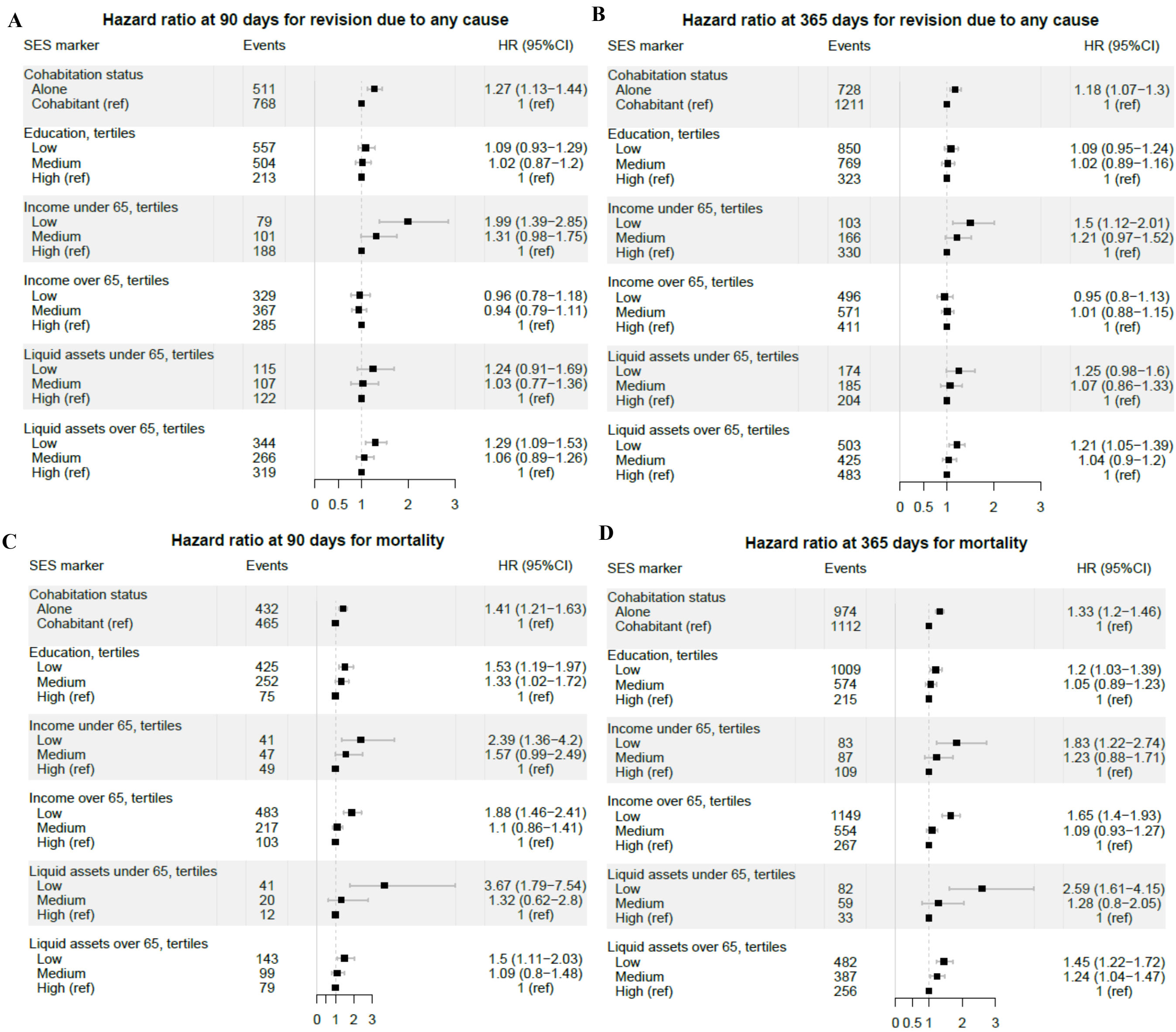
We found that within the first 90 days, living alone was associated with a higher aHR (1.4 [CI 1.1-1.6]) for mortality than cohabiting (Figure 13C). In general, for the 90-day mortality, we found that patients with a low level of education had a higher aHR than patients with a high level of education (1.5 [CI 1.2-2.0]), we found a higher aHR among patients younger than 65 years and with a low income (2.4 [CI 1.4-4.2]) than high income patients, and we found a higher aHR among patients older than 65 years and with low liquid assets (1.5 [CI 1.1-2.0]) than high liquid assets. The results are shown in Appendix II and were similar to the results within the first 365 days after surgery (Figure 13D).[44]

Figure 12: Cumulative incidence for any revision for the four SES markers individually within 365 days.



Modified figure from Edwards NM, Varnum C, Overgaard S, Pedersen AB. Impact of socioeconomic status on the 90- and 365-day rate of revision and mortality after primary total hip arthroplasty: a cohort study based on 103,901 patients with osteoarthritis from national databases in Denmark. Acta Orthopaedica 2021:1-8. DOI: 10.1080/17453674.2021.1935487.[44] Appendix II

Figure 13: Hazard ratios for any revision and mortality for the four SES markers adjusted for age, gender, calendar year, and Charlson Comorbidity Index score. Income and liquid assets were also adjusted for cohabiting status.



Modified figure from Edwards NM, Varnum C, Overgaard S, Pedersen AB. Impact of socioeconomic status on the 90- and 365-day rate of revision and mortality after primary total hip arthroplasty: a cohort study based on 103,901 patients with osteoarthritis from national databases in Denmark. Acta Orthopaedica 2021:1-8. DOI: 10.1080/17453674.2021.1935487.[44] Appendix II

5.3. Hospital-treated infections (Study III)

We found that within 90 days, 998 patients experienced an infection that needed hospital admission, corresponding to 1.0% of the study population. The cumulative incidence for any infection at 90 days is shown in Appendix III. The cumulative incidence was highest among patients who lived alone (1.5% [CI 1.4-1.6]), had the lowest education (1.1% [CI 1.0-1.2]), had the lowest income (1.6% [CI 1.5-1.7]), and had the lowest liquid assets (1.3% [CI 1.2-1.4]) (Figure 14).

We found that after the first 90 days, there was a higher risk of an infection when patients were living alone than when cohabiting (aRR 1.3 [CI 1.2-1.4]) (Figure 15B). The same higher risk was found in patients with a low level of education (aRR 1.2 [CI 1.0-1.3]) than high education, low income (aRR 1.7 [CI 1.4-2.1]) than high income, and low liquid assets (aRR 1.5 [CI 1.4-1.8]) than high liquid assets. All of the point estimates (crude and adjusted) are shown in Appendix III. The results seen after 30 days were similar to the results seen after 90 days (Figure 15A). The RRs for all the individual subgroups are shown in Appendix III.

Figure 14: Cumulative incidence for any infection for the four SES markers individually within 90 days.

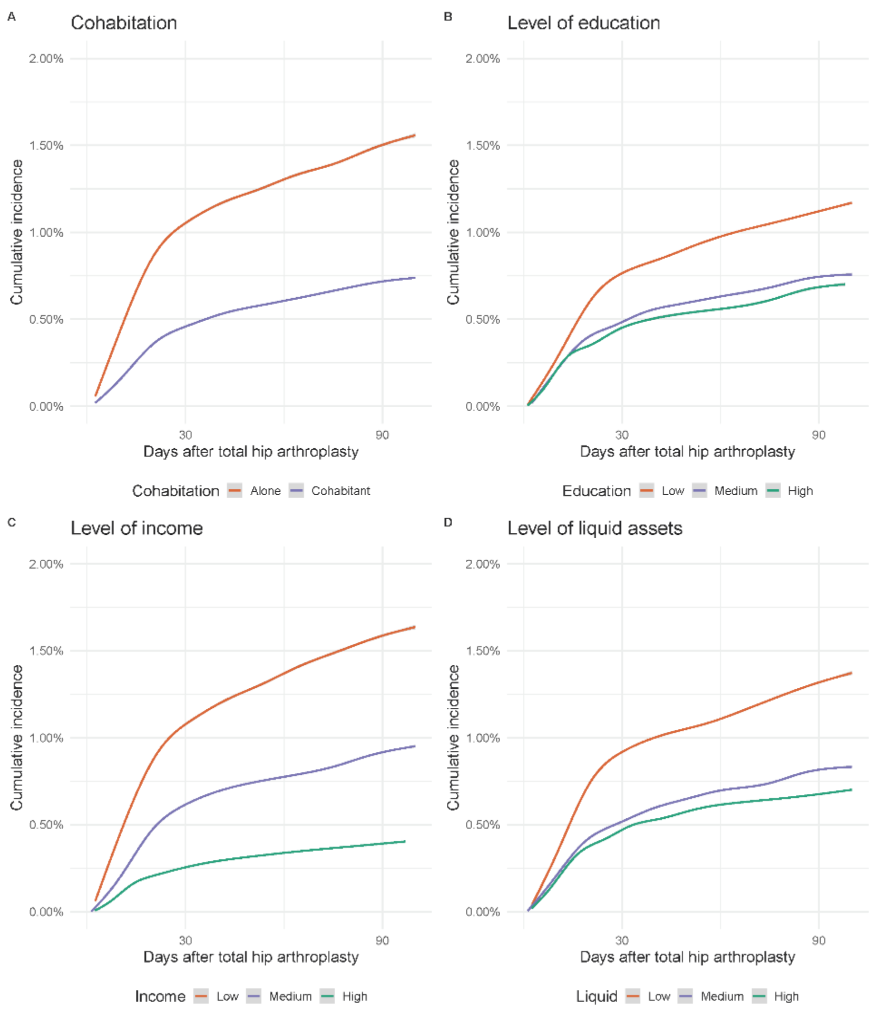
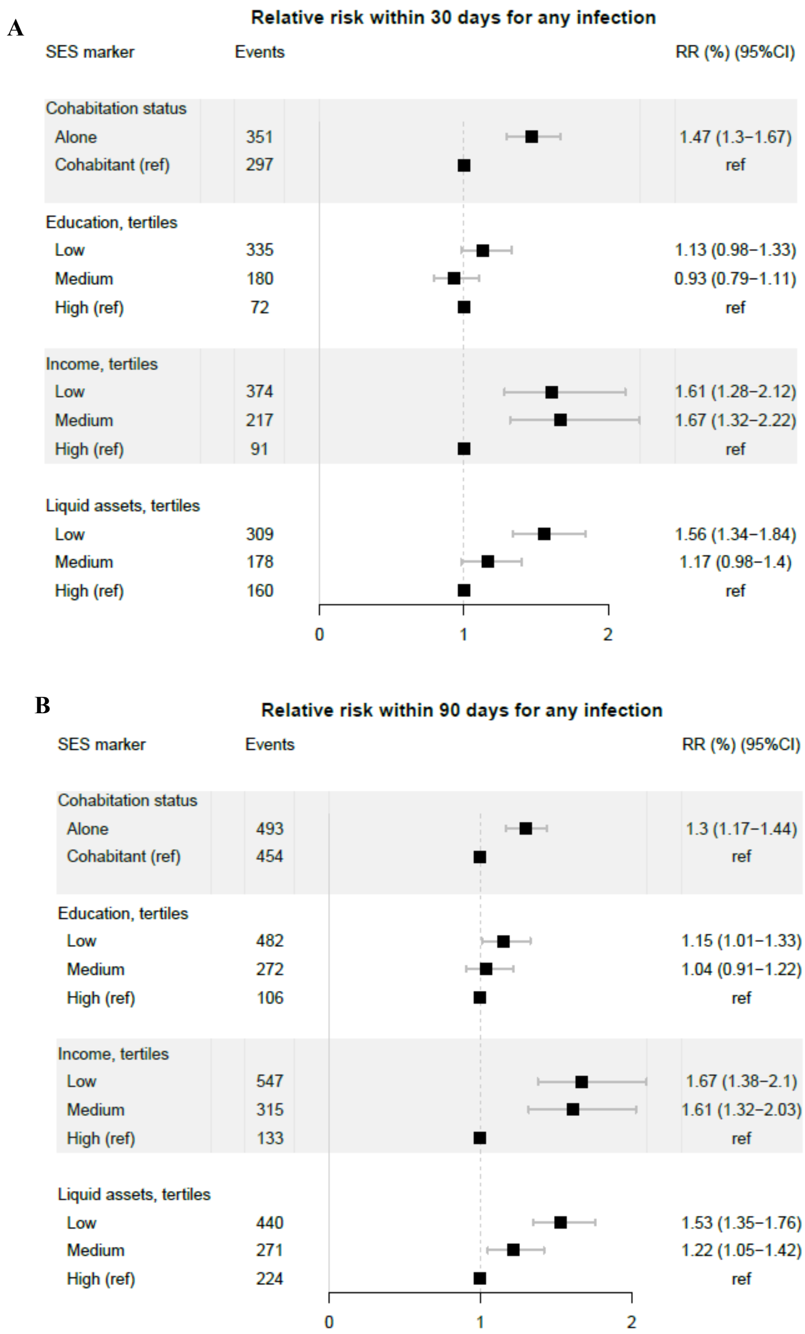


Figure from Edwards NM. *et al.* Appendix III.

Figure 15: Relative risks for any infection for the four SES markers adjusted for age, gender, Charlson Comorbidity Index score, and hospital. Income and liquid assets were also adjusted for cohabiting status.



Modified figure from Edwards NM. *et al.* Appendix III.

5.4. Cardiovascular disease (Study VI)

The final study population is described in detail in Appendix IV showing 103,286 THA patients after excluding outliers. Outliers deviated from the main population in regards to statistical and clinical characteristics. Of the main study population, 452 patients experienced a cardiovascular event, corresponding to 0.4%. The cumulative incidence for any CVD at 90 days is shown in Appendix IV. We found the highest cumulative incidence among patients who lived alone (0.7% [CI 0.6-0.7]), had the lowest education (0.5% [CI 0.5-0.5]), had the lowest income (0.7% [CI 0.6-0.8]), and had the lowest liquid assets (0.6% [CI 0.5-0.7]) (Figure 16).

We found that after the first 90 days, there was a higher risk of any cardiovascular event when patients were living alone than when cohabiting (aRR 1.1 [CI 0.7-1.7]) (Appendix IV). The same higher risk was found in patients with a low level of education (aRR 1.3 [CI 0.7-2.3]) than high education, low income (aRR 1.4 [CI

Figure 16: Cumulative incidence at 90 days for any CVD

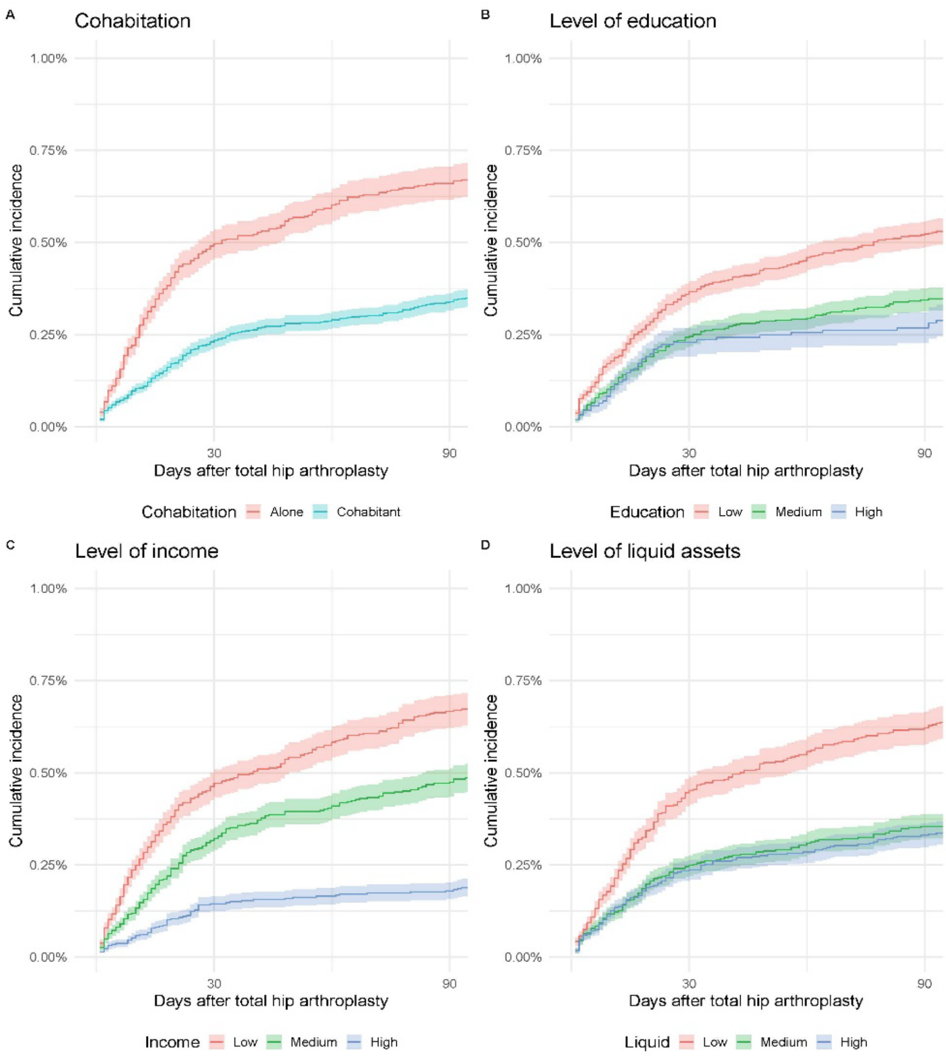


Figure from Edwards NM. *et al.* Appendix IV.

0.8-2.6]) than high income, and low liquid assets (aRR 1.3 [CI 0.8-2.1]) than high liquid assets (Figure 17). Note that all of the CIs are wide, i.e. the point estimates are imprecise. The same trends were seen when evaluating stroke (Appendix IV). The results are shown in Appendix IV, which also contains the RRs for all the sensitivity analyses.

Figure 17: Relative risk at 90 days for: A: cardiovascular disease (CVD); B: acute myocardial infarction (AMI); C: venous thromboembolism (VTE); D: deep vein thrombosis (DVT); E: stroke; and F: pulmonary embolism (PE) adjusted for age, gender, Charlson Comorbidity Index score, and hospital. Income and liquid assets were also adjusted for cohabiting status.

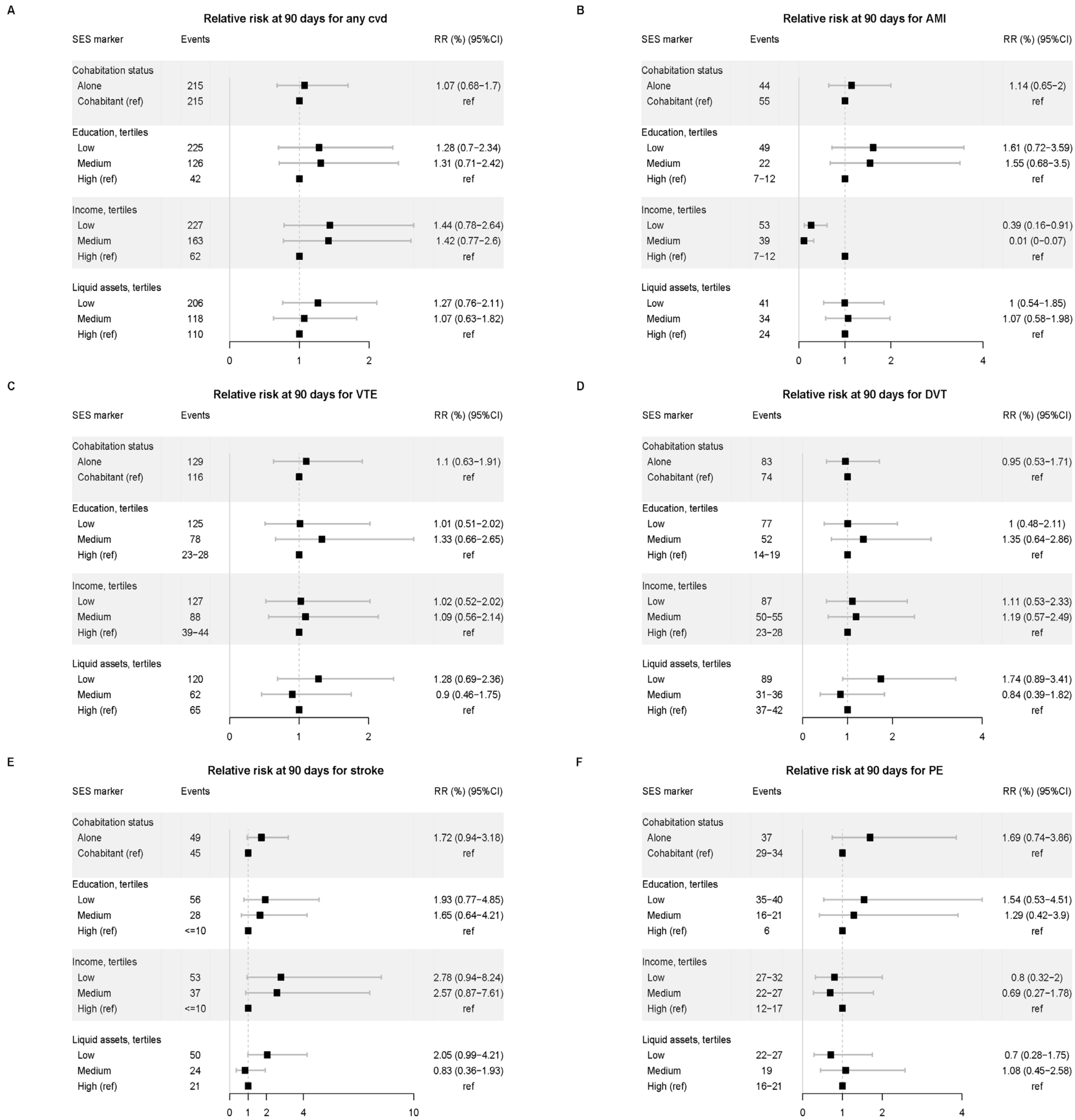


Figure from Edwards NM. *et al.* Appendix IV.

6. Discussion

6

6.1. Comparison to existing literature

The following section will include a comparison of the results to the existing literature (Table 2). Possible explanations will be discussed, and concerning Studies II, III and IV, the discussion will also involve other populations than THA patients.

6.1.1 Utilization of THA (Study I)

Previous research has examined the relationship between SES and THA utilization, originating from Italy (1997-2000),[35] combination of European countries (2002-2009),[47] and Sweden (2004-2013).[46] The study most compatible to ours is the Swedish study[46] as regards to exposure assessment. They found that receiving a THA was most common in the most educated group and in the highest income group. Conversely, in our study, THA was most common in the least educated group and in the lowest and medium income group. Supporting our findings, individuals with low education and low income have an increased risk of OA, giving them a potential higher need of THA.[40] Individuals with higher education may have an improved ability to process information on healthy behavior and may therefore postpone the need of a THA.[40,48] This ability would equalize the risk in the older age groups, which is the trend seen in our study. The Swedish study also evaluated the rate of THA in different occupational groups and found evidence of the lowest-skilled groups all having lower rates of THA.[46] A clear dose-response relationship is evident between occupational workload and increased risk of hip OA, leading to an increased risk of THA.[8,86] This supports our findings, where we found higher risks, when the patient's occupation was unskilled worker as compared to a position as a director with a potentially lower manual workload. Some of the differing results may be explained by methodological differences including different study design. We conducted a case-control study with the purpose of providing an assessment of the distribution of SES (exposure) in the source population, securing comparability to the general population.[73] This is in contrast to the approach used in the Swedish cohort study in which they calculated an HR for receiving a THA, including only patients with an OA diagnosis in the study population. They assessed OA exclusively through the healthcare contact diagnosis which possibly led to missing subjects in the analysis. Based on health-seeking behavior, the missing subjects would be the most deprived leading to selection bias.[46,58,87] This bias would, however, lead to an underestimation of their results. Furthermore, the calculated income quartiles would be skewed and not representative of the general population.

No other study has evaluated the age trends, and only one previous study has evaluated the time trends regarding the risk of THA in Denmark, despite the relevance and importance of this subject.[47] We found differences between the age groups, which reveal that the impact of the different SES markers was age-dependent. We also found time trends regarding SES showing a development over time. Cookson *et al.* found no time trend regarding inequality.[47] However, they used area-based measurements and looked at a time span running annually from 2002-2009, whereas our grouping in the same period was divided differently with a 6-year span (2001-2006 and 2007-2012) making the results difficult to compare. In general, comparison with other studies had been easier if we had assessed SES using area-based measurements. However, using area-based measurements introduces misclassification, which in Denmark would have been profound, as Danish law assures that a least 20% of all housing is social housing.[88]

A factor that may influence our results is that the threshold for receiving a THA has changed over time. The mean age has decreased over time and patient comorbidity has increased over time.[89,90] Possible explanations for this could be changes in the demands from society, where patients have higher physical activity demands; changes in surgeon-related factors; and improvements of surgical procedures with improved polyethylene and shorter hospitalization due to fast-track procedures.

6.1.2. SES, revision, and mortality (Study II)

Few former studies have investigated the impact of SES on the risk of revision and on the risk of mortality. The studies originate from the US (1995-1996[49] and 2002-2009[52]), Finland (1998-2007),[53] and Sweden (1992-2012).[54] The study most compatible to ours is the Swedish study[54] as regards to exposure assessment using several SES markers. They found an increased risk of readmission due to any cause when having low income and when living alone, though only investigated with a combined outcome with no specification of revision. This supports our findings of a higher rate of revision due to fracture, infection, and dislocation when living alone. In our study, the association was most prominent within the first 90 days, where social support is a central element when trying to maintain a household and everyday living arrangements following a THA. This could reduce the risk of falling by preventing a forced and perhaps premature mobilization. One of the studies from the US found no association between marital status and the risk of revision. However, their study was based on patient-provided forms, was only based on 9688 patients, and had a substantial amount of missing data which was treated as a separate category. This could all explain the diverging results. They did, on the other hand, have information regarding lifestyle factors, which we were unable to attain in our study.[52]

A surprising result in our study was the weak association between low education and increased revision rate. A positive correlation between education and health supports the expectation of an association. Furthermore, education affects the relationship between the patient and the physician as well as healthcare utilization. The anticipation of a stronger association was not a consequence of two previous studies on the subject, as no association was found by them.[52,54] An assessment of patient education is critical to ensure patient comprehension regarding risks and benefits of surgical interventions and compliance with postoperative protocols.[5] A possible explanation for the weak association could be that there has been a considerable change in educational opportunity over the recent decades with better opportunities for especially women and the elderly.[39] This leads to an overrepresentation among the less educated of these subgroups. Women and the elderly also have a decreased risk of revision, which all in all could lead to an underestimation of our estimates.[44] The study from Finland found a 21% higher risk for early revision in the highest income group compared to the lowest income group.[53] We found the opposite effect of income, however a closer look at the Finish estimates revealed a U-formed tendency with higher HR in the lower income categories as well as in the higher. The differences seen between the studies could be explained by the missing stratification by age, as most study populations, including the Finish, have a median age above the age of retirement.[52-54] Adding liquid assets as an SES marker and using this when evaluating patients over the age of 65, as we did, may better incorporate the effect of age.

The Swedish study also evaluated the risk of mortality after THA.[54] They found that low income was associated with higher mortality, which is similar to our results showing higher mortality in all low SES strata. The same associations are found in the general population, where health inequalities account for a difference in life expectancy of five to ten years between low and high SES strata.[34] This is also the case when evaluating socioeconomic differences in Denmark, where similar inequalities are found in regard to life expectancy, attained education, and level of income.[2] There has been found to be a larger effect of income than education on mortality, which was also seen in our study when evaluating mortality after 365 days. Education and income are highly correlated, as higher education provides better labor market opportunities. The consequence is that income is partly mediated by education.[34] This will be further discussed in section 6.2.1, where the choice of SES markers in this study are evaluated.

6.1.3. SES and hospital-treated infections (Study III)

Our results show an increased risk of readmission due to an infection of any reason after THA in the most disadvantaged, which corroborates with findings from other studies.[32,35,54,56] However, the studies differ from ours in either exposure assessment by using area-based measurements, or by pooling the outcome with no definition of the cause of readmission. The most comparable studies are the studies originating from Italy (1997-2000),[35] Sweden (1992-2012),[54] and the US (1996-2013[32] and 2006-2013[56]).

We found a higher risk of any infection in patients living alone. The same association was found in our study when evaluating pneumonia, UTI, and PJI, although the point estimates were imprecise with wide CIs. Cohabitation is a marker of social support, where social support is characterized by the amount of resources within a social network. The application of these resources can be an essential factor in obtaining positive outcomes and has in addition a protective effect on general health.[91,92] Cohabitation may therefore apply a diminishing effect on the risk of infection.

The study from the US from 1996-2013 found a higher risk of PJI in patients with Medicaid as primary payer than patients with private insurance.[32] This is in accordance with our results, showing a higher risk of any infection and PJI in patients with low income and low liquid assets. The US study did, however, not find a difference in the risk, when using the average household income and not Medicaid as a surrogate for lower SES.[32] This exposure would have been more compatible with ours if they had not based income on a neighborhood median calculated by patient address, as this may have led to a misclassification bias. In addition, poverty rates are high in the US compared to Denmark.[93] This increased inequality would, however, lead to a reinforced association and not a lack of relationship.[42]

We investigated the risk of hospital readmission in a population of THA patients. The same association is found in other populations too. A study from New Zealand investigated risk factors for hospital admissions for infectious diseases in the general population. The risk seemed to be associated with SES, where the most economically deprived had higher risks.[57] This underlines our assumption regarding the cumulative incidence of infections after five years. It showed an enhancement of the inequality trend, suggesting that the inequality is associated with SES, and not a reflection of an effect of SES on the THA procedure.

The observed associations cannot be due to the affordability of healthcare, as Denmark has a universal tax-supported healthcare system. Therefore, the results must be driven by other mediating factors such as the CCI. In addition, the CCI is associated with an increased risk of adverse outcome and is related to low income and low liquid assets.[44,49] Furthermore, diabetes and obesity are related to an increased risk of infection and are also associated with low income.[92] Smoking, alcohol consumption, diet, and physical activity are all lifestyle factors related to health behavior and are all socially patterned being more prevalent in the most deprived SES groups due to financial limitations and lack of resources to buy suitable food.[94]

6.1.4. SES and cardiovascular events (Study IV)

Few studies propose a relationship between SES and CVD after THA,[35,54] while others find none.[49,51,55,95] The most compatible study is again the Swedish study by Weiss et al., using individual data on cohabitation, education, and income.[54] They found an increased adjusted risk of readmission for any cardiovascular reasons in the most disadvantaged patients for all three SES markers. We found similar results, yet our point estimates were imprecise. Some of the studies showed no relationship, however, they used deprivation scores as surrogates for low SES.[51,55,95]

Similar associations are found when evaluating the association in the general population. A combined study from Belgium and France using questionnaires showed that individuals with no regular social support had an increased risk of CVD.[75] Further, the studies revealed that lower level of education and lower income also were associated with an increased risk. Evidence has indicated a strong association between SES and cardiovascular health, where living conditions, level of education, and income play important roles in the development, progression, and outcomes of CVD.[75] Biological, behavioral, and psychosocial risk factors are more prevalent in the most disadvantaged, which accentuates the connection between SES and CVD.[60] This increased burden of low SES may therefore constitute as a risk factor to CVD that is equivalent to traditional risk factors.[60] In particular, cohabitation has been suggested to be an unconventional risk factor, as marriage seems to have a protective role against cardiovascular events.[96] A suggested explanation to this association may be an earlier recognition of changes in health, improved adherence, and encouraged promotion of healthy behaviors by cohabiting partners.[96] The empathic understanding from significant others, who accept and validate concerns, alleviates tension as well as enhances self-esteem. This coping assistance protects physical and psychological well-being and ultimately promotes a sense of control. This promotes further coping efforts that decrease the harmful consequences of stress.[36] In an elderly population as in the study from Belgium and France, the increasing age places the patients more in jeopardy of social isolation through deaths of friends and partners.[75] This was also the case in our study, as living alone was predominant in the population.

Chronic social stress induced by low educational attainment and by low income can enhance the risk of CVD, as chronic stress impairs memory, lowers the immune responses, and elevates blood pressure leading to progression of atherosclerosis.[42,96,97] The increased stress induced by the THA surgery may therefore potential reinforce the association between SES and CVD.

We found a trend showing inequality in regard to CVD. However, this trend was not present in all of our subgroups. When evaluating acute MI, an opposite effect was seen revealing a protective influence of low income. A study performed in the US using survey data investigated the variation and disparity in awareness of acute MI symptoms.[98] They found that individuals with low income were more unaware of acute MI symptoms than individuals with high income. In addition, low income individuals had a more inappropriate response to the acute MI symptoms. Both would result in a lower registration of acute MI in the patients with low income than in the patients with high income. This effect would be further reinforced by the consequence of this inappropriate response, as it would result in premature death. All in all this would lead to an increased mortality in patients with low income, which is in accordance with the results shown in Study II.[44] However, we do not have information regarding cause of death, limiting our ability to determine the proportion of deaths that are in fact caused by acute MI.

6.2. Methodological considerations

Several considerations should be taken into account, when planning a study.

6.2.1. Study design

Depending on the research question, several study designs exist. These designs have potential inherent limitations, which leads to the traditional ranking of validity (Figure 18).[73]

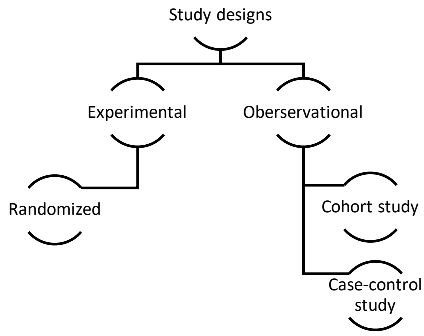


Figure 18: Study designs with a hierarchy of validity

In Study I, we performed a population-based case-control study.[43] It is possible to investigate multiple exposures with this study design. In this design, the cases are a complete count (i.e., all THA patients in Denmark) and the controls are a random sample from the well-defined source population of cases (i.e., Denmark). Every person in the source population has an equal chance of being selected as a control, and every control is eligible to become a case later on. The control selection should ensure that the distribution of exposure among the controls is similar to the distribution of exposure seen in the source population of cases.[73] If this is accomplished, the ratio of the outcome frequency in exposed relative to that in the unexposed can be determined.[73] This distribution can be ensured by matching, where the sampling of controls is independent of the exposure. The validity of a case-control study design is ranked lower than that of a cohort study, because sampling of the controls rather than using the whole source population as in a cohort study has a cost.[73] This cost is a loss of precision of the estimates. However, the loss will be limited if the number of controls matched per case is large. Further, the matching of the controls introduces selection bias, which will be further discussed in section 6.2.3. In Study I, we matched on gender and region of residence, not including age as a factor.[43] If age had been included as a matching factor, it would no longer be possible to estimate the effect of age as matching distorts the relation.[73]

Studies II-IV were cohort studies.[44] A cohort study is defined as an investigation of study cohorts free of the outcome of interest (revision, death, infections, or CVD) that differ according to the extent of an exposure (SES stratifications) to a potential cause of disease.[73] In a cohort study (in particularly in a register-based cohort study), it is possible to obtain a large population size, which enables a potentially greater precision than a randomized controlled trial does. Further, it is possible to investigate rare or multiple outcomes that may be associated with multiple exposures.[73] Registry-based cohort studies are time-efficient and cost-effective, however, as the information in the registries are collected with a different purpose than answering a specific research question, the registries may lack information regarding specific covariates. Information regarding different important confounders may therefore be missing, introducing the possibility of a distortion of the association.[73]

6.2.2. Choice of SES markers

There are mainly two causal models describing the relationship between SES and health, as defined earlier in section 2.4. The social causation hypothesis and the health selection hypothesis. The social causation hypothesis claims that circumstances in SES influence health, by creating a social gradient through factors that are socially stratified such as resources, support, knowledge, or behavior.[34,99] The health selection hypothesis claims that health influences SES.[34] A process by which differences in health lead to differences in SES.[99] Both hypotheses contribute to health inequalities, however, several authors argue that the main pathway is from SES to health, especially in an elderly population such as the THA population.[34,99] The main pathway may also depend on the chosen SES markers, which again may influence the findings. The choice of SES markers is therefore crucial, and the selection of markers consequently evolved throughout our studies to reflect the research question.

In the first study, we chose to include both cohabiting status and marital status as SES markers. Marital status provided the opportunity of a more comprehensive stratification. The stratification on marital status was important in estimating the utilization of THA, since marital status also holds information on previous status with shared household among widow/widower and divorced people. However, the observation that the results between the two markers were similar, led us to the conclusion of using just cohabitation as a marker in the succeeding studies. Further, cohabitation is becoming more institutionalized with more living as a civil union than as married couples with a converging effect of health between cohabiting and married adults. In addition, there is a decline in the overall health among singles including both previously married and never married adults, all supporting our choice of marker.[37]

In addition, we chose to include occupation as an SES marker in Study I.[43] This was to evaluate the effect of occupational habits and workload concerning the utilization of THA. The association of occupation with health and SES is reciprocal. Unhealthy individuals are less capable of investing time and energy in their occupation, and therefore career trajectory and occupational status are affected by health.[34] Health is also affected by occupational status, as there is a clear dose-response relationship between occupational workload and the risk of OA.[8,86] OA takes many years to develop, and the occupational status may therefore reflect both the workload when developing OA but also the need and desire for a THA, as well as the economic leeway resulting from the current occupational status at the time of deciding on the procedure. The difficulty in interpreting the results of occupation and the difficulty in determining a clear causality between occupation and the other outcomes led us to excluding this marker from the following studies.

In the succeeding studies, we decided to include only cohabitation status, educational attainment, income, and liquid assets as SES markers, excluding marital status and occupational status from the analysis. This decision was further supported by occupation having a minor effect on mortality, as the effect of occupation on mortality has been found to be mainly mediated by income and liquid assets.[34]

In studies of health inequalities, SES markers are frequently used interchangeably, despite the wide-ranging discussion regarding what the SES markers actually measure. As described earlier, the different markers relate to different causal processes and they are unlikely related to the same underlying mechanisms. In addition, the correlation between the markers are considerably inconsistent leaving individuals with different statuses depending on the evaluated marker. The markers should therefore not be treated as indicators of the same underlying mechanism, which is the main reason for including several markers when evaluating SES in our studies.[100]

During the studies, we considered the SES markers' interdependency, as SES markers are often associated. There is a constant association between health and a wide range of SES markers, which suggests a correlation between the overlapping concepts of SES and health. Mutually adjusting for each SES marker, as we did in Study I, would lead to the assumption that the common aspects of SES across the markers have no effect, and that all effects are basically a result of the unique aspects of the different SES markers (Figure 19A).[43,101] We wished to evaluate the effect of both the independent and the common aspects of the markers to enable a comparison with other studies. In addition, mutually adjusting the comparison between the different markers becomes difficult, as it is not a like-for-like comparison but a comparison between different assumptions (total effect vs. direct effect) and therefore different interpretations (Figure 19B).[101] Therefore, we analyzed the markers independently in Studies II-IV.[44]

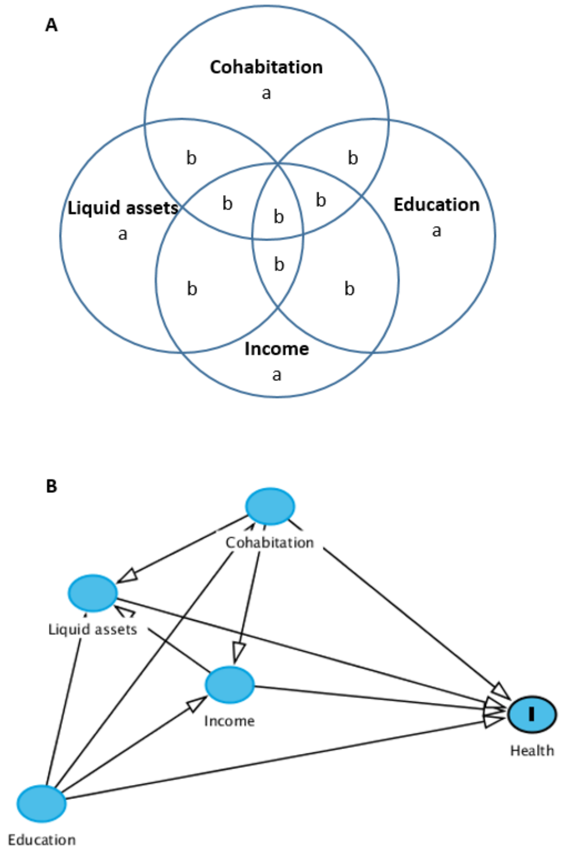


Figure 19: A: Unique (a) and common (b) aspects of SES by cohabitation, education, income, and liquid assets.
B: Directed acyclic graph showing a plausible causal pathway with different assumptions for the different markers. Total effect vs. direct effect and confounding effect vs. mediating effect.

6.2.3. Sources of bias in epidemiological studies

The main goal of an epidemiological study is to achieve valid and precise estimates of the effect an exposure has on an outcome.[73] Errors will, however, occur and threaten the accuracy by systematic errors that affect the internal validity, and by random errors that affect the precision. The main sources of systematic errors are information bias, selection bias, and confounding.

Information bias

The systematic error of misclassifying collected information regarding exposure or outcome is referred to as information bias.[102] Misclassification can either not depend on other variables (non-differential misclassification) or depend on other variables (differential misclassification). Non-differential misclassification bias the effect towards the null if the variable is dichotomous (towards no association), whereas if the variable is polytomous, the effect will be a bias towards one another of the categories (towards a uniform association). Differential misclassification can bias the effect in either direction (exaggerate/underestimate).[102]

Misclassification of exposure: In all of the studies in this thesis, SES categories served as the exposure through different markers. The data on income and liquid assets are obtained from the Tax Administration's registry and is presumed to be identical to the real income. However, these data are based on the reports to the tax authorities and cannot account for undeclared work and defective reports. Despite this, the data are of high quality and validity.[70] We used a classification of income into low, medium, and high, and thus non-differential misclassification of individuals in the different categories would lead to a bias of the risk estimates towards an equalization between the categories. Since a correction corresponding to the yearly variation (due to inflation) in income and liquid assets was done in Studies III and IV, the risk of non-differential misclassification was more predisposed in Studies I and II.[43,44] Data from the education registries and the information regarding cohabitation are of high validity with few missing, leaving a limited risk of misclassification.[71] Yet, the potential misclassification would bias the risk estimates in a similar way as described for income and liquid assets.

We categorized income and liquid assets using percentiles. When categorizing a continuous variable, one assumes that all values of the continuous variable have the same association with the outcome. Further, when using percentiles, the boundaries may not correspond to the quantities at which biologically meaningful changes occur. However, using a continuous variable when interpreting the effect of income on our outcome becomes very difficult, complicating the communication of the results and the comparison of the results across studies. The boundaries could have been explored by using restricted cubic spline, enabling an exploration of the potentially non-linear continuous association.[103] This was however not done, and our choices might have influenced our results by introducing a non-differential misclassification.

Misclassification of outcome: A correct classification of outcome is dependent on several factors, such as healthcare-seeking behavior among patients, quality of clinical diagnoses, and reporting to the registries. There is a variation of the completeness in the different registers. However, despite this variation, the missing registrations in the different registers are most likely due to factors concerning the clinician and not the patient. This would lead to a non-differential misclassification. In Study I, the risk of misclassification of the outcome (THA) is limited due to high completeness (91%-98%) in the DHR.[17,43,64] In Study II, the outcomes were revision and mortality.[44] The registration of revisions in the DHR has a lower completeness (75%-92% from 1995-2017)[17,64] than that of primary THA and an unknown positive predictive value (only the positive predictive value for PJI is known, see later). Any misclassification would likely be non-differential and would therefore bias the association with SES towards the null value and cannot explain our findings. Information on mortality is based on vital status from the Civil Registration System and is very rarely misclassified with nearly no loss to follow-up.[61] Misclassification of mortality is therefore unlikely. In Study III, the outcomes were a composite endpoint of hospital-treated infections and specified subgroups of hospital-treated infections. The positive predictive value for infections in the DNPR has been estimated to be 90-93% for pneumonia,[66] 77% for UTI,[67] and 77% for PJI.[68] The misclassification of these outcomes would most likely be non-differential and bias the risk estimates towards the null, and therefore cannot explain our findings of an association between SES and the risk of infections. In Study IV, the outcomes were a composite endpoint of CVDs. The positive predictive value of CVD in the DNPR is generally high and is 88-97 % for MI and 70-90% for VTE.[104] The validity is lower for stroke, with a positive predictive value of 43-87%.[105] Again, the misclassification of these outcomes would most likely be non-differential and bias the risk estimates towards the null. This bias can perhaps explain the weak association between the risk of CVD and SES.

Surveillance bias: One type of information bias is surveillance bias, also called detection bias. This occurs when the collected information regarding exposure is dependent on surveillance. In Studies III and IV, we

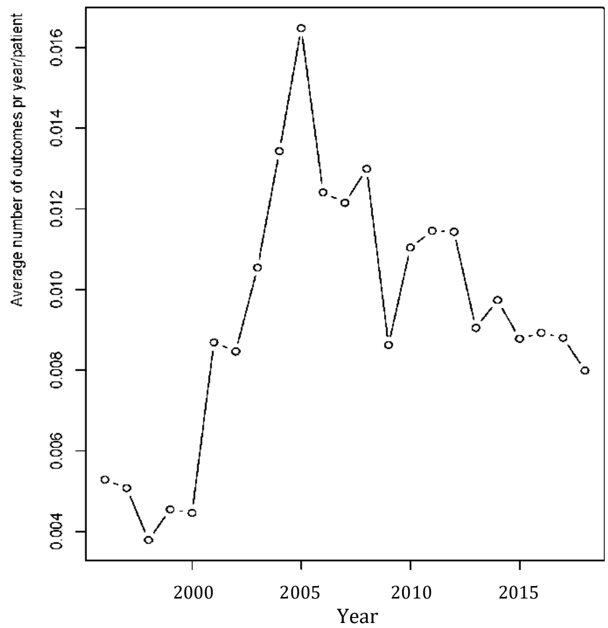


Figure 20: Average number of infection outcomes per year per total hip arthroplasty patient.

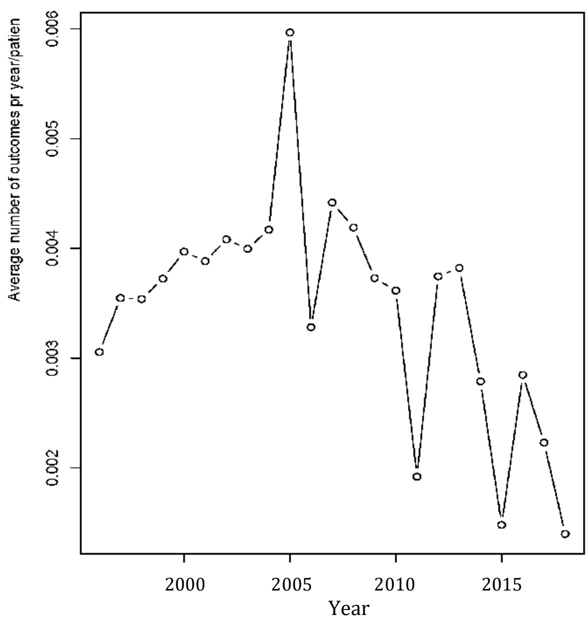


Figure 21: Average number of cardiovascular outcomes per year per total hip arthroplasty patient.

initially wanted to include calendar year as a covariate. However, even though calendar year is a confounder, the variable was deemed invalid. We identified problems with convergence during the analyses, and an absence of a linear tendency between calendar year and our exposure and outcome was explored (Figures 20 and 21). Changes in the Danish law in 1999 coincide with the figuration of abnormal patterns around the years 2004 and 2007. With this law, the government implemented major changes on the administrative level of Danish hospitals regarding activity and tariff management. Up until 2004, 10% of the hospital funding depended on the hospital activity. It then rose to 20% of the funding and in 2007 it rose again, this time to involve 50% of the hospital funding.[106] Therefore, the abnormal patterns in the reported diagnoses crudely seen in 2004 and 2007 are independent of the incidence of infection and CVD but rather a response to hospital management.

Selection bias

When the association between the exposure and outcome differs for those who participate in the study and for those who are eligible, a selection bias occurs. This systematic error can occur if the outcome affects participation or if the outcome is associated with the selection of participants. A selection bias can also occur in a case-control study and is introduced if the controls are selected to match the cases on a factor that is associated with the exposure.[107] In Study I, we matched on gender and region of residence.[43] Suppose region of residence is associated with SES, then the selection of controls would be associated with the exposure. This might be the case, as a larger proportion of residents with a higher level of education has been found in the Capital Region of Denmark, although the overall SES characteristics generally are considered to be representative of the Danish population in all of the five Danish regions.[108] In general, this bias would be in the direction of a null effect by pulling the exposure frequency in the matched controls towards that of the cases to a larger extend than if controls were selected at random. It can be necessary to control for this bias introduced by matching even if the matching factors are not confounders.[107] The possible bias introduced in our Study I is therefore controlled by adjusting for SES individually, however, this adjustment is associated with difficulties in the interpretations, as stated in section 6.2.2.[43]

Cohort studies are prone to loss to follow-up, which is potentially a major source of selection bias. The bias is introduced if both the exposure and factors related to the outcome affect participation.[107] We assessed a low risk of selection bias in our studies. This was based on the fact that the DHR cohort has a virtually complete inclusion and follow-up is complete due to the linkage to the Danish health registries. The low risk was further supported by handling death as a competing risk in our analyses.[61] Further, we included all patients reported to the DHR in which the completeness for registration of primary THA is high (91%-98% from 1995-2017), and the missing registrations are due to factors concerning the surgeon and not the patient.[16,17,64] The missing has therefore no association with the registration in the DHR and the outcomes of interest.

The statistical methods used in this thesis are based on the assumption of independent observations.[72] However, several patients receive THA surgery bilaterally, violating the assumption of independency. During the cohort selection for Studies II, III, and IV, we included the first THA if the patients were operated on both sides consecutively, and we included only the right THA, excluding the contralateral, if the patients were operated bilaterally on the same date.[44] This could introduce a selection bias. During this selection, we removed all information regarding the contralateral THA and the revisions performed on this side, as all revisions are side-specific. However, a study showed that if a patient was revised in the contralateral THA, this would influence the risk of a revision on the included side. In addition, if a patient is bilaterally operated and the time between the two surgeries is more than two years, then the first THA has an increased risk of revision.[109] If this is the case in our study, then the not included THAs differ in concern to the outcome compared to the included THAs.

Confounding

A simple definition of confounding is a confusion of effect and occurs when a common cause of exposure and outcome is present, leading to a distortion of the association.[73] There are three conditions which must be present to fulfil the criteria of a confounder: 1) A factor has to be associated with the outcome; 2) the factor must be unevenly distributed among exposure groups; and 3) the factor cannot be an intermediate step on the causal pathway from exposure to outcome.[73] Confounding concerns all observational studies and can be a threat to the validity if not controlled for by design (randomization, matching, and restriction), or in the statistical analysis (stratification, adjustment, and standardization). Residual and unmeasured confounding may, however, still exist despite attempts to control for it.[73]

In Study I, we addressed confounding by matching, stratification, and adjustment. However, unmeasured confounding is a limitation, since we have no information regarding lifestyle factors such as smoking, alcohol, BMI, and physical activity. These factors are unevenly distributed among the exposure groups and can therefore potentially influence our results.[43,54,110] These limitations are apparent in all four studies. In Study II, we addressed confounding by stratification and adjustment. We only adjusted for calendar year and not for fixation technique, head size of the prosthesis, and surgery time although different distributions were found among the exposure groups. In addition, these factors (fixation technique, head size of the prosthesis, and surgery time) are associated with the outcome.[20,111,112] Nevertheless, all reason must support the assumption that fixation technique and head size did not depend on the surgeon's knowledge concerning patient SES but rather on specific time trends with evolving techniques and on patient risk factor profile. We are therefore confident that adjusting for calendar year is sufficient. In Studies III and IV, we also addressed confounding by stratification and adjustment. A firm causal inference cannot be drawn explaining the effect of SES on health outcomes as the mechanisms are complex and not always clear. Thus, it is unclear whether other factors not accounted for may influence SES and independently influence the risk of infections or

CVD. It is also unclear if some of these factors may be an effect of the life course of the ever-presence socioeconomic circumstances, and thus be an intermediate factor on the pathway from SES to infection or CVD.[113]

Some of the exposures included in this thesis are time-dependent such as cohabitation, marital status, income, liquid assets, and occupation. These exposures are challenged by reverse causation and residual confounding.[114] We asses that most of the time-dependent variables are fairly constant over recent time in this elderly population, diminishing the challenges with reverse causation and having little impact on our results.[114]

Random error

Random error, often equivalent to chance, is associated with statistical precision. The amount of random error determines the width of the CI, and therefore the width is a rough estimate of the uncertainty of the results due to random error.[115,116] In Study IV, we concluded that there was a small increased risk of readmission due to CVD in the most disadvantaged SES groups, where the aRR was 1.44 [CI 0.78-2.64] when having the lowest income compared to the highest income. Had we merely looked at the confidence limits or done a test for significance, the conclusion would have been no association (as the CI includes one). Evaluating the biological interaction merely through an evaluation that addresses statistical interaction would only rely on an evaluation of a mathematical model assessing a product of two variables. This only applies if the model is an appropriate description of the relationship between the variables.[115] The evaluation would then purely be based on statistical significance and not on clinical significance.[115,116] To avoid this, we used the point estimate together with the width of the CI to evaluate the magnitude of effect size and degree of precision, concluding a small increased risk with limited precision.[115,116] We cannot, however, reject a null association or an association as large as a 164% increased risk, which further highlights the limited precision.

The study size is an important determinant of the precision of the results as a large size reduces random error. By using the DHR, we could include a relatively large cohort, ensuring an acceptable precision in the combined outcomes. However, when controlling for confounding and analyzing in the specified subgroups, the CI was wider and the precision was compromised.

6.2.6. Statistical considerations

The different statistical methods used in this thesis are all well described in the literature, however, some considerations should be elaborated on.

Hazard vs. risk

Although the use of Cox regression is widespread, the terminology and interpretation of the HR is often loose and sometimes incorrect.[79] As the Cox model does not take death as a competing risk into account, the one-to-one correspondence between the HR and the cumulative incidence is lost.[81] This resulted in contradicting results in our Study II regarding the HR and the cumulative incidence of revision.[44] A varying number of patients were at risk of revision over time due to differences in the mortality between the SES groups. Death as a competing risk is implicitly incorporated when modelling the cumulative incidence, while the Cox regression only considers the risk of revision among those still at risk.[82] The Cox regression only considers the momentary hazard rate for the event, whereas the cumulative incidence depends on both the hazard rate for the event and the hazard rate for the competing risk.[82] This leads to the paradox of our results in Study II, which hampers the interpretation, as the HR cannot be directly converted into a relative risk.[44] Further, when interpreting HR, the estimate should be interpreted as an average of the HR over the entire follow-up period and not as an HR at a specific time-point.[117]

Number of events

Even though a substantial number of individuals were included in our cohort, the number of events was small in some instances. In Study I, this was expressed by having small numbers when categorizing occupation in the age groups over 76 years.[43] The differentiation between the occupational groups was thereby lost, and we were left with the grouping of either being retired, working, or other. This hampered the opportunity of evaluating the effect of a potential lifetime workload. This could have been applied to our study by collecting SES from a different time-point, however, this was not done. In Study II, we were able to stratify according to age when evaluating the impact of income and liquid assets on the risk of revision and mortality.[44] This was done, as a large proportion of the population are senior citizens over the age of 65 years with a state pension, and evaluating SES by income in patients younger than 65 years and by liquid assets in patients over 65 years would thereby provide a more accurate estimate. However, due to too few events, this stratification was not applicable in Studies III and IV. This forced us to use income and liquid assets throughout all age groups, which hampers the level of detail of the association. In Study III, the number of events was too small when evaluating pneumonia. We were therefore not able to account for the effect of clustering in hospital units, as this resulted in problems with convergence. The same limitation was found in Study IV when stratifying for a history of previous CVD. Problems with convergence were discovered when fully adjusting the analysis of the risk of DVT and PE in individuals with a history of CVD. The small number of events in these subgroups therefore forced us to exclude the estimates for these outcomes. In addition, our original plan was to include heart failure as an outcome, but heart failure was removed from the study as there were too few events in the time period. We could have planned the study based on a power calculation. This would have increased the probability of detecting an effect.[118] Nevertheless, this calculation was not performed, as the study is based on complete registry data.

7. Main conclusions

7

With this thesis, we provide new knowledge on the impact of SES on THA. We found SES inequality in all four studies in varying degrees.

7.1. Utilization of THA (Study I)

We found considerable socioeconomic inequality in the THA utilization. Patients who were married, were cohabitating, patients with the lowest attained education, and patients with the lowest income had an increased risk of receiving a THA compared to patients who never married, were living alone, patients with the highest attained education, and patients with the highest income. The same higher risk was seen in patients who were self-employed, skilled workers, unskilled workers, and who were retired or retired early compared with patients who were a director or chief executive. We observed an age trend in which patients between 45-55 years had a higher risk of receiving a THA than patients of older age, when having attained the lowest educational level and having the lowest income. A time-dependent association was also present, when evaluating education, marital status, and income. The inequality decreased over time in relation to education; however, we found increased inequality over time in relation to marital status and income.[43]

7.2. Risk of revision and mortality (Study II)

We found socioeconomic inequality regarding revision and mortality after THA. An increased rate of revision and mortality was observed among patients living alone, patients with the lowest income, and patients with the lowest liquid assets after both 90 and 365 days following THA. Additionally, an increased mortality rate was found among patients with the lowest attained education. We showed a nearly uniform trend revealing the highest risk in low status groups to lowest risk in high status groups concerning revision due to any cause, due to infection, and due to fracture. The strongest determinants of THA revision and mortality were cohabiting status, income under the age of 65 years, and liquid assets over the age of 65 years.[44]

7.3. Risk of severe infections (Study III)

We found socioeconomic inequality related to readmission due to infections after THA. We observed an increased risk of readmission among patients living alone, patients with the lowest attained education, patients with the lowest income, and patients with the lowest liquid assets. There was a nearly uniform trend revealing the highest risk in low status groups to lowest risk in high status groups concerning any infection, pneumonia, and to a lesser extent UTI and PJI after both 30 and 90 days following THA.

7.4. Risk of cardiovascular events (Study IV)

Finally, we found that the increased risk of CVD after a THA had a socioeconomic gradient concerning all four SES markers. A small increased risk of CVD was evident when living alone, having attained the lowest level of education, having the lowest level of income, and having the lowest level of liquid assets after 90 days.

8. Clinical implications and future perspectives

8

As eliminating socioeconomic disadvantage from society is difficult, quantifying modifiable intermediate factors and targeting them could have important public health benefits.[94] The inequality described in this thesis, where SES is associated with the risk of complications following THA, contributes to healthcare disparities seen in society. This emphasizes the importance of a change in patient-, surgeon-, and policy practice concerning THA.

Even though cohabitation status is a non-modifiable risk factor, the marker has multiple options of intervention. On a patient level, the patients could be encouraged by healthcare professionals to get support from close friends or relatives to ensure early recognition of changes in health, to improve adherence, and further encourage healthy behaviors.[60] Trusted family members or friends could also give the patients more confidence to mobilize and alleviate some of the fears and obstacles associated with mobilization.[91] Mobilization is important, as prolonged immobilization affects almost every organ system increasing the risk of infection and CVD.[23]

SES is also an important factor in relation to surgeon practice. The thesis shows that SES may influence every aspect of the THA surgery, from the utilization of THA to the risk of adverse events after surgery. An evaluation of the patient's SES should therefore to a higher extent be incorporated as a standard when assessing patient frailty, patient suitability, patient involvement, and patient information. Further, the patient's SES should also be considered when assessing the indication for surgery, as SES influences the patient's risk profile.

A consideration to the patient's cohabitation status could also be an example regarding a change in policy practice. There are aspects of social support that could be targeted within the clinical setting by policy makers. Group-based rehabilitation could be offered to patients living alone, and is often positively received by the patients.[91] Group-based rehabilitation offers the opportunity to meet people at a similar stage of recovery and offers guidance from others with experience or role models, who motivate, all in all giving a sense of control.[36,91] This of course comes with a cost. However, it has been estimated that optimization of social care provision for patients living alone could lead to cost savings by reducing length of hospital stay and reducing rates of readmission.[91] More specifically, politically motivated targeted prevention strategies aimed at those identified here to be at greatest risk of e.g. pneumonia could include initial and ongoing education of the importance of coughing, deep-breathing exercises, and good pain control, which could have important public health benefits.[26]

We say that due to the national tax-supported healthcare there is guaranteed free access to hospitals.[61] This softens the effect of economic inequality by delivering high-quality care to all.[4] However, the guaranteed free access does unfortunately not guarantee equal usage of healthcare. Over the recent years, the Danish health system has been subject to significant reforms that have rationalized governance structure and embarked on major hospital reforms resulting in a reduction of the number of small hospitals.[119] The main objective of these reforms is to improve the quality of secondary and tertiary care while balancing economic priorities.[119] These cost reductions have consequences in other aspects. By closing small hospitals, the geographical accessibility to hospitals will as a consequence be worsened for patients living far from the larger hospitals.[120] This may challenge some socially disadvantaged patients creating an even larger barrier, resulting in larger inequalities. Further time-trend analyses are therefore relevant to evaluate the efforts made by the Danish government to guarantee equal access to healthcare irrespective of social position.

Future studies should examine which specific targeted prevention strategies should be implemented by investigating the impact of SES on patient compliance, shared decision making, optimization of risk factors prior to surgery, and differentiated rehabilitation and education after surgery.

We cannot change a patient's SES, but by developing these targeted intervention strategies, which may act as a prophylactic against the disparities in the risk of adverse events in patients identified here as the most vulnerable, and by changing policy practice, we may reduce the inequality and thereby close the health gap.

9. Summary

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Total hip arthroplasty (THA) is an effective procedure for reducing pain and improving quality of life for patients suffering from osteoarthritis in the hip joint. In orthopedic surgery, the quality of care and the outcomes after surgery are closely correlated to socioeconomic status (SES). Socioeconomic inequality in health is increasingly recognized as an important public health issue. However, previous research concerning utilization and postoperative complications after THA is limited by assessing SES only by a single marker, no distinction between outcomes, or area-based measurements.

In this thesis, we aimed to study the association between SES and the utilization of THA across different age groups and over time (Study I). Following the utilization of THA, we aimed to study whether SES was associated with revision and mortality rates after THA within 90 and 365 days (Study II) and whether SES was associated with the risk of hospitalization due to infections and cardiovascular disease after THA within 30 and 90 days (Studies III and IV).

In Study I, we conducted a population-based case-control study. We reported associations between SES and the risk of THA using odds ratios, and found that patients who were married, were cohabitating, patients with the lowest attained education, and patients with the lowest income had an increased risk of receiving a THA compared to patients who never married, were living alone, patients with the highest attained education, and patients with the highest income. Further, we found that the association between low level of education, low level of income, and higher risk of THA was observed among the youngest age group. This association decreased with increasing age. We found inequality in the risk of THA by education, and that this decreased over calendar time. The inequality found by income was, however, persistent.

In Study II, we conducted a cohort study and found that within 90 and 365 days, the adjusted hazard ratio for any revision was highest for patients living alone vs. cohabiting, was highest for patients with low income vs. high income among patients <65 years, and was highest for patients with low liquid assets among patients >65 years. We also found that living alone, low education, low income, and low liquid assets all were associated with increased mortality rate within both 90 and 365 days.

In Studies III and IV, we conducted a cohort study. The results show that living alone, low education, low income, and low liquid assets were all associated with higher risks of hospital-treated infections and cardiovascular disease after THA.

In conclusion, we found that the utilization of THA and the risk of severe postoperative complications after THA are associated with substantial socioeconomic inequalities. This was done by examining important SES markers all directly contributing to healthcare disparities. Our findings highlight that socioeconomic

disadvantage is a risk factor for inferior quality of care and inferior outcomes after surgery, emphasizing the importance of patient-, surgeon-, and policy practice when addressing inequalities in THA outcome.

10. Dansk resume (Danish summary)

Operation med indsættelse af en total hoftealloplastik er et effektivt indgreb i forhold til at reducere smerter, samt øge funktionsniveau og livskvalitet hos patienter med osteoartrose. Der er dog stor forskel på, hvor tilfredse patienterne er efter indgrebet, da nogle oplever bivirkninger eller får et utilfredsstillende resultat. Studier viser, at årsagerne til disse forskelligartede resultater skal finders i risikofaktorer, som enten knytter sig til patienten eller til det kirurgiske indgreb. Social ulighed i sundhed er velkendt og er et velbeskrevet emne af den danske Sundhedsstyrelse, men der er kun få, som har beskrevet social ulighed i forhold til tilbud om operation med hoftealloplastik og risikoen for revision, infektion og kardiovaskulære komplikationer efter operationen. Tidligere studier har været tvetydige og de har været begrænset af kun at bruge enkelte markører til at vurdere socioøkonomisk status (SØS) og ved at bruge områdebaserede estimater på SØS. Formålet med denne afhandling var at undersøge sammenhængen mellem SØS og tilbud om operation med en total hoftealloplastik (studie I). Desuden ønskede vi at undersøge, om der var sammenhæng mellem SØS og risikoen for revision og død (studie II) og risikoen for indlæggelseskrævende infektioner (studie III), samt til slut at undersøge, om der var sammenhæng mellem SØS og risikoen for indlæggelseskrævende kardiovaskulære sygdomme (studie IV) efter operationen med indsættelse af en total hoftealloplastik.

I studie I fandt vi en sammenhæng mellem SØS og tilbud om operation med en total hoftealloplastik, hvor det at være gift, at bo sammen med nogen, have et lavt uddannelsesniveau og have et lavt indkomstniveau var associeret med en højere risiko for at få tilbudt en protese. Ydermere så fandt vi, at det at have et lavt uddannelsesniveau og et lavt indkomstniveau var associeret med en højere risiko for at få tilbudt en protese hos de yngste aldersgrupper og at denne højere risiko forsvandt med stigende alder. Desuden var der social ulighed i forhold til uddannelsesniveau i de tidligste årrækker, men denne ulighed forsvandt hen over årene, hvorimod den ulighed fundet i forhold til indkomstniveau forblev uændret gennem studieperioden.

I studie II fandt vi en sammenhæng mellem SØS og risikoen for revision inden for 90 og 365 dage. Vi udregnede den justerede hazard ratio og fandt, at denne var højere blandt de patienter som boede alene, havde et lavt uddannelsesniveau, havde et lavt indkomstniveau hos patienter under 65 og havde et lavt formueniveau hos patienter over 65. Vi fandt desuden, at det at bo selv, have et lavt uddannelsesniveau, have et lavt indkomstniveau og have et lavt formueniveau var forbundet med en øget mortalitet inden for både 90 og 365 dage.

I studie III og IV fandt vi en sammenhæng mellem SØS og risikoen for både indlæggelseskrævende infektioner og indlæggelseskrævende kardiovaskulære sygdomme, hvor risikoen var højere blandt de patienter som boede alene, havde et lavt uddannelsesniveau, havde et lavt indkomstniveau og havde et lavt formueniveau.

Alt i alt fandt vi social ulighed i forhold til tilbud om operation med en total hoftealloplastik og risikoen for alvorlige komplikationer efter operationen. Det er derfor vigtigt at understrege, at der er social ulighed, og at de mest udsatte har højere risiko for bivirkninger eller et utilfredsstillende resultat efter en total hoftealloplastik.

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