The EMKAR-study: Epidemiology of multiply revised patients following knee arthroplasty.

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The project has been initiated by Anders Odgaard, Department of Orthopaedic Surgery, Copenhagen University Hospital, Rigshospitalet. Permission for data has been acquired by Julius Tetens Hald during employment at Department of Orthopaedic Surgery, Copenhagen University Hospital, Rigshospitalet. The project is associated with said department. Data is acquired from all public Danish Orthopaedic departments and available privately owned hospitals.

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Short project description

Knee replacement is one of the most frequently performed surgical procedure in Denmark. Over 10.000 procedures were performed in 2021. As with all surgical procedures, patients are at risk of developing ensuing complications. For some, the complications may lead to a downward spiral of repeated complications and repeated reoperations, or revisions. Ultimately some patients are treated with a salvage-procedure such as arthrodesis or amputation.

The clinical impression is that multiply revised patients develop serious functional impairments and chronic pain from their knee joint. However, there exists a paucity of information concerning the risk for multiply revisions and basic epidemiologic data, such as incidence and prevalence. From the literature, it is clear that this problem has been previously overlooked. It is fruitless to improve treatment without knowing the scale and size of the problem.

To fill this gap is the purpose of this project. The Danish Knee Arthroplasty Register (DKR) and Landspatientregisteret (LPR), which are the greatest databases for knee arthroplasty in Denmark, will be used for analysis. The following studies will be conducted:

Study 1: Incidence and prevalence for n-grade revision following knee arthroplasty in Denmark.

Study 2: Cumulative revision rates for n-grade revision following knee arthroplasty in Denmark and risk factors for n-grade revision.

Study 3: Lifetime risk for n-grade revision following knee arthroplasty in Demark.

Layman's protocol.

<u>Background</u>

Knee replacement is one of the most frequently performed surgical procedures in Denmark. Over 150.000 procedures have been performed over the last 20 years. However, as with all surgical procedures, an ensuing risk of developing complications exists. Examples of these include infection, loosening of the prosthesis from the bone or mechanical failure of the prosthesis. For some patients, the subsequent complications can lead to a negative spiral of repeated complications and repeated reoperations. In the worst cases, patients may end with a stiff knee joint or amputation. It is the general opinion of orthopaedic surgeons that patients who experience many reoperations, have severe functional impairments and chronic pain from their knee joint. However, this area of knee replacement has not been thoroughly scientifically investigated. It is known from register data in Denmark that 13 % of patients with a knee replacement undergo one reoperation in the span of 20 years. However, we do not know how many undergo two, three or more reoperations. We do not know if some patients are more likely to undergo reoperations. Additionally, it is not possible to inform patients of the risks of multiple reoperations later when undergoing knee replacement or reoperation. Finally, the fiscal requirements for future treatment of these patients cannot be assessed.

<u>Purpose</u>

The aim of the project is to investigate the occurrence, risk, risk factors, and lifetime risk of multiply reoperations after knee replacement.

<u>Methods</u>

This is a study of Danish registries concerning all knee replacement procedures performed from January 1st 1998 to December 31st 2021. Data is collected from the clinical databases Danish Knee Arthroplasty Register (DKR) and Landspatientregisteret (LPR). Information regarding patients' demographics, indication for primary procedure, indication for revision procedure, and procedure-related data will be obtained.

<u>Ethics and perspectives</u>

Personal data is processed in accordance with the General Data Protection Regulation Act. All patients are anonymized when presenting the project's results.

The project will create perspectives about the extent of the problem, which patients are at particular risk, as well as the future disease burden and thus the future need for resources. The project will generate ideas to improve treatment in the future and thus has the potential to improve the quality of life for patients in the future.

Publication

The project's results are planned to be published as a series of articles in peer-reviewed and international journals.

Economy and budget

The project is supported by Rigshospitalets Research Fund and "Danmarks" fund: "sundhedsdonationer".

Background

About knee arthroplasty and revisions.

Knee replacement or arthroplasty of the knee joint is performed in large numbers all over the world (1). The number of procedures performed has increased greatly in the last 30 years, both in Denmark and internationally (2). The first operation with the insertion of an endoprosthesis in the knee joint is called a primary knee replacement, and the term is used for the operation and the prosthesis. Primary knee arthroplasty is generally a safe operation that results in a significant improvement in the quality of life in the vast majority of patients, and more than 90% are satisfied with the result one year after surgery in Denmark (3).

In Denmark, over the past 20 years, more than 150,000 first-time knee replacement surgeries have been performed, and in 2020 alone, the number was approx. 10,500 operations (3). Many studies have been conducted in recent years with a focus on prevention and conservative treatment (1) of knee osteoarthritis. However, the need for operative intervention is increasing (2). The reason is presumably an increase in the proportion of elderly people in the population and greater expectations for a physically active old age without disease-related limitations. Furthermore, it is expected that the BMI of the population will increase, and that this will also increase the need for knee replacements (1).

As with all operative interventions, complications can occur after primary knee arthroplasty. Some of these complications lead to revision, which is defined as a reoperation in which a component of a knee prosthesis is inserted, removed or replaced.

Size of the problem

Since 1998, the Danish Knee Arthroplasty Register has registered knee replacements (both primary and revisions) performed in Denmark. Traditionally, the most important measure within register research of knee replacements has been the cumulative revision rate, which describes how many patients experience a revision after a given period of time. Around 13% of primary knee arthroplasties are revised for the first time within the first 20 years in Denmark. In the last 20 years, more than 20,000 revisions have been performed. In 2020, 1048 were performed (3).

As the number of performed annual primary procedures increases, so will the number of annual revisions. Upfill-Brown et al. examined the number of revisions in the United States in the period 2012 to 2019. The number of revisions increased by 29.6% per year (4). See **Figure 1**. Kurtz et al. and Pavel et al. have projected, on the basis of large national registries in the USA and England, containing several hundreds of thousands of patients, that the annual number of revisions after primary knee arthroplasty will increase over 300% in England and over 600% in the USA in 2030 compared to the number of revisions in 2005 (2, 5). See **Figure 2**.

Figure 1: Projection of the annual incidence of performed revisions in the United States.
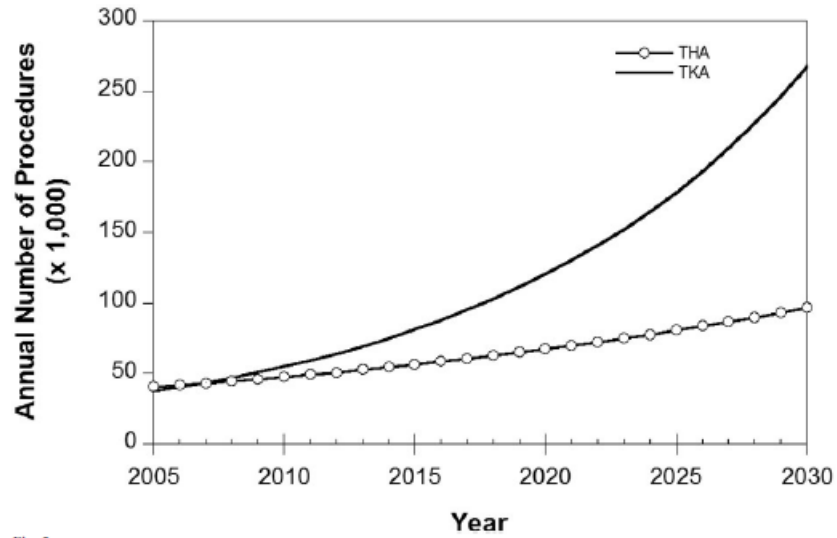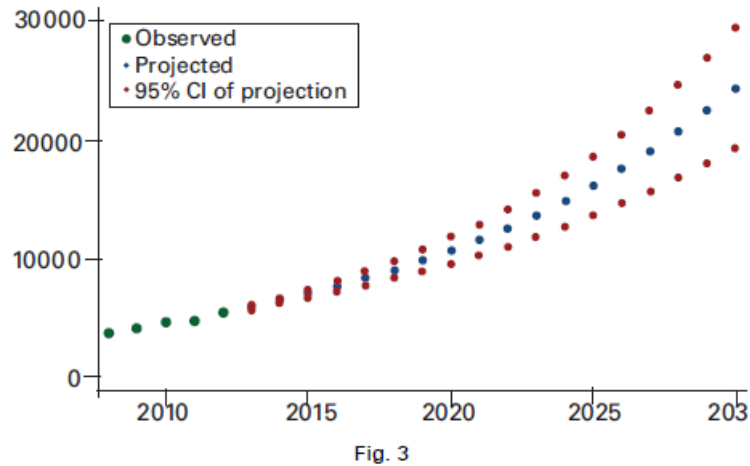
From Upfill-Brown et al.

Fig. 2

The projected number of revision total hip arthroplasty (THA) and total knee arthroplasty (TKA) procedures in the United States from 2005 to 2030.

Figure 2: Projection of the annual incidence of revisions carried out in England and Wales. From Patel et al.

Fig. 3

Graph showing the projected total number of revision knee arthroplasties in England and Wales between 2013 and 2030.
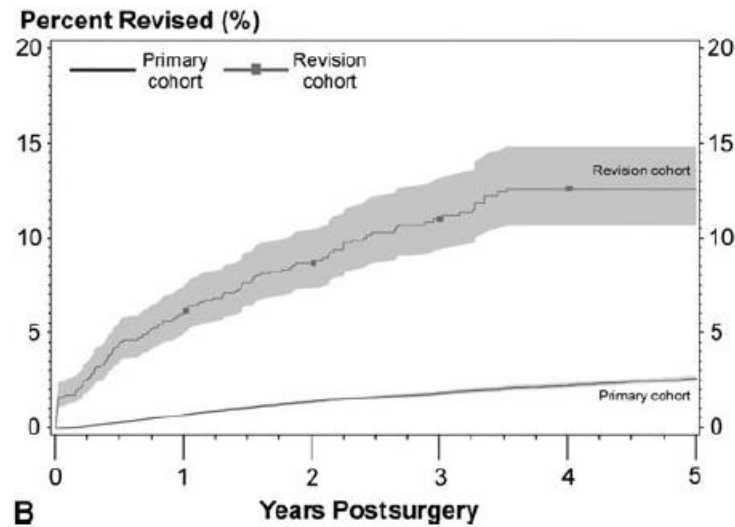
Re-revision

Unfortunately, even after revision, there is a risk of new complications, which may necessitate another revision (re-revision). In some patients, one complication follows another, and these patients may require several revisions. We use the term *multiply revised* when a patient experience at least three revisions of their knee replacement. In principle, there is no upper limit to the number of revisions in a knee, and some knees are revised more than 10 times. Some patients may end with an arthrodesis or amputation (6, 7).

There is a paucity of studies investigating multiple revised patients. Deere et al. investigated the subject in 2019, containing just over 30,000 patients from the English register NJR(8). The study found that 20% of those revised for the first time were revised a second time after 13 years. 20% of those were revised for the third time after 5 years, and 20% of those were revised again for the fourth time within 3 years. The risk of multiply revisions was higher in men and in younger patients. Also, the study found that the risk of revision increased as time between revisions decreased.

In 2010, Ong et al. investigated the risk of revision after primary and first revision after total knee arthroplasty (TKA) and total hip arthroplasty (9). The study contained data from 73,000 primary knee arthroplasties, and 1600 revisions performed between 1997 and 2006. The study found that the risk of a second revision was 6 times higher than the risk of a first revision. See **Figure 3**:

Figure 3: Graph illustrating risk of revision after primary and first revision. From Ong et al.

In 2021, Belt et al. investigated the association of the indication for revision and the risk of re-revision (10). The study found that the cumulative re-revision rate was 19% after 8 years (significantly higher than the cumulative revision rate after primary knee arthroplasty). Klasan et al. found that the re-revision rate after revision due to aseptic loosening was 12% over a 16-year period (1999-2015) in New Zealand (11). In 2018, Postler et al. examined a smaller population of 300 patients in a prospective, single-centre study (12). The study found that re-revisions were performed 4 years since the last revision, while first revisions were performed after 8 years since primary knee arthroplasty.

A Danish study was performed in 2022, by Arndt et al. which investigated rate of re-revision after revision for either "aseptic resolution" or "pain without resolution" (13). The study included data from 4299 revisions from 1997 to 2018 from the Danish Knee Arthroplasty Register. The study found a cumulative revision rate of 23% after 20 years for patients with pain without loosening. For patients with aseptic loosening, the cumulative revision rate after 20 years was 19%.

No study has investigated the cumulative revision rates stratified by number of previous revisions in a national population. It is not known how many patients live with a revision

knee or how many patients live with a n-grade revision in Denmark. The lifetime risk for multiply revisions is not known either.

Indications for revision and re-revision

There are several indications for revision of a knee replacement, such as aseptic loosening and infection (1). However, there is no consensus in the literature as to which cause is the most frequent, as aseptic loosening and infection are alternately stated as the most frequent cause(4, 10, 12, 14, 15). Discussion exists concerning whether infection will become the most frequent cause in the future(5, 12). Other causes are persistent pain, instability, periprosthetic fracture, metallosis and stiffness (1, 3).

Aseptic loosening is defined as the mechanical loosening of the prosthesis from the bone, and without ongoing infection around the prosthesis. Aseptic loosening typically occurs due to wear and tear of the prosthetic material or the polyethylene liner(1, 12, 14).

Infection around the prosthesis is the most feared complication, as bacteria form biofilms around the prosthetic material and break down the surrounding tissue prosthesis. Infection is very difficult to remove due to biofilm, and it often leads to structural complications as the infection weakens the tissue that will receive a new prosthesis(1). Typically, a deep infection is treated with either one-stage or two-stage revision, but prosthesis survival is generally low (16). Infection is believed to be the biggest cause of multiple revisions, precisely because of the low prosthesis survival compared to aseptic solution(10, 14, 17).

Risk factors for revision and re-revision

Several risk factors for revision after primary knee arthroplasty have been described. These are age, sex, BMI, previous surgery on the same knee, type of implant inserted and method of implantation, patient psychological factors and surgeon-related factors (1).

Older age is generally associated with lower risk of revision, and younger age is associated with higher risk of revision(1, 15, 18-22). Male sex, BMI >35 and previous procedures performed on the same knee have also been shown to be risk factors for revision(1, 12, 15, 23). The choice of inserted implant has also been shown to have an effect on the cumulative

revision rate. Unicompartmental prostheses generally have a lower prosthetic survival than total knee prostheses(3, 24). In the literature, it is described that non-cemented technique can theoretically reduce the incidence of aseptic loosening, due to osteolysis of bone related to bone cement. This has led to the development of several uncemented prostheses but these proved to have poorer prosthesis survival (1, 25, 26). However, more recent studies have shown equivalent results between cemented and uncemented prostheses after 5 years (21, 26).

Depression, medical comorbidities, relatively asymptomatic patients displayed by patient-reported-outcome-measures, and chronic back pain (1, 27-30) have been shown to increase dissatisfaction after primary knee arthroplasty and to increase revision rates. Most likely, a proportion of patients revised due to pain without reason belong to this category (3). In a study from Verbeek et al., it was found that the least symptomatic patients had the greatest risk of a poor outcome which suggests that revision should only be performed when the patient's symptoms are severe. This was confirmed by Quinn et al. which had the same finding (29, 30).

Hospital volume, meaning the number of operations performed in a hospital, has also been shown to influence revision rates. It is believed that the most experienced surgeons will generate the lowest revision rates (19, 31-35).

All these risk factors have been examined in relation to first revision, but only a few studies have investigated factors associated with a higher risk of multiple revisions. Previous revision, as well as male sex, age under 60, as well as revision of only one prosthetic part compared to replacement of the entire prosthesis, have been found to increase the risk of re-revision (10, 11, 29, 36). In the literature it is clear that the risk of re-revision is greater than expected, and that re-revisions is a cause for concern for every surgeon (37, 38).

Outcome after revision and re-revision

Complications after primary knee arthroplasty may lead to functional problems for patients (1). Scott et al. found that over half of revised patients either retired or had to transfer to

social care (39). It implies that most elderly people lose the ability to lead an independent life. See **Figure 4**.

Figure 4: Graph showing the job status of patients after revision arthroplasty. From Scott et al.

Quinn et al. found a lower prosthesis survival of 93.5% for revisions compared to primary knee arthroplasty after 2 years of follow-up, as well as a patient satisfaction of 85% (29). It was found that factors associated with a good patient reported postoperative outcome following revision were male sex and fewer previous revisions on the same knee (29). Verbeek et al. described a satisfaction rate of 53% after 5 years following revision (30). However, most patients report a satisfactory outcome after revision and that most patients improve postoperatively, as a meta-analysis by Saleh et al. showed (40-42).

The indication for revision has also been found to be important for the result after revision. Abram et al. and Yao et al. found in register studies, that for revision due to infection or fracture the mortality was significantly higher than for non-acute reasons for revision (43, 44).

In rare cases, some patients may end up with either an arthrodesis or amputation. These complications have been investigated in the Danish population by Gottfriedsen et al. In the

period 1997 to 2013, the cumulative incidence of primary knee arthroplasties that ended with an arthrodesis was found to be 0.26% (6). For transfemoral amputations, the cumulative incidence in the same period and for the same patient population was found to be 0.32% (7).

No studies examining functional outcomes after re-revision surgery were found. A Danish study by Lindberg-Larsen et al. studied a cohort of revision patients. It was found that Length-of-stay (LOS) >5 days were associated with previous revision. Reasons for prolonged LOS were pain, lack of mobilization and anaemia (40).

Klasan et al. found a lower risk of re-revision when all prosthetic parts were replaced, compared to exchange of only the femoral or tibial prosthesis (11). It was also found that patients with low ASA scores and longer time between primary TKAs had better OKS scores 6 months after revision.

Costs

Revision after knee arthroplasty is associated with significant financial costs for both the patient and society. For the patient, this is associated with a loss of ability to work, as described in the previous section. For Denmark's public health service, revision surgery is a significant financial burden. Revision surgery is more complex, requires longer operating time, more experienced surgeons, more advanced equipment and prostheses, and is usually performed in patients with comorbidities and who require more medication and a longer hospital stay (6, 45, 46). In addition, revision due to infection is more than 3 times as expensive as revision surgery for other reasons, which is a cause for concern as studies have found an increasing incidence rate of revisions due to infection (5, 12, 45-47). Gabor et al. conducted a prospective study in 2019 which suggested that centralizing revision surgery has the potential to limit costs (48).

Purpose

There is a need to prevent the complications that lead to repeated revisions, and there is a need to improve revision outcomes. Many unanswered questions are presented in the background section. Answers to these are needed in order to 1) predict the future need for

resources, 2) monitor the effects of changes in treatments and organization, and 3) give patients realistic expectations about the future when they undergo knee replacement surgery.

This research project aims to obtain new knowledge about the epidemiology of revisions after knee arthroplasty and to answer the following questions:

1. How many patients live with a multiple revision knee (i.e. prevalence) and how many multiple revisions procedures are performed (i.e. incidence)?
2. Are some demographic groups particularly at risk?
3. What is the risk of needing a revision after n-grade revision?
4. What future demands can be expected of surgeons and hospitals to provide care for patients needing revisions?
5. What is the lifetime risk of multiple revisions?

In order to answer the research questions, the research project is divided into 3 work packages.

WP-A1: Incidence and prevalence

The purpose of this work package (WP) is to determine the evolution of the incidence and prevalence of revisions of various degrees over the last two decades. We also aim to develop a mathematical model that predicts future incidence and prevalence based on demographic data as well as historical information of primary knee arthroplasty.

Research questions

1) What is the annual incidence of revisions of various degrees, and how has the incidence changed during the last 20 years?
2) What is the current prevalence of n-grade revisions, and how has the prevalence changed during the last 20 years?
3) What is the relationship between the annual incidence of revisions of n-grade with the incidence of primary procedures in the preceding years?

WP-A2: Cumulative Revision Rates (CRR)

The purpose of this WP is to determine the cumulative revision rate (CRR) for revisions of different grades (number of previous revisions) to generate information that can be used for informing patients preoperatively.

Research questions:

1. What is the CRR for n-grade revision?
2. Is CRR influenced by demographic and surgical variables such as sex, age, education, implant type, place of residence, income, operative technical conditions and the indication of revision such as infection, aseptic loosening, instability, pain without reason?

WP-A3: Lifetime risk of multiple revisions

The purpose of this WP is to determine the lifetime risk of revision of various grades as well as the lifetime risk of arthrodesis and amputation. These risks will be investigated in relation to demographic and surgical variables.

Research questions:

1. What is the lifetime risk that a patient with a given combination of demographic and surgical variables will need n-number of revisions after primary arthroplasty?
2. As above but with arthrodesis and amputation as the risk event.

Review of literature

To gather relevant background information for this protocol, MEDLINE via pubmed was searched to find relevant literature in the field. The MESH words "knee replacement" and "reoperation" were used. We wanted to identify articles that either described epidemiological findings regarding multiple revision knee arthroplasties or described risk factors associated with repeated revisions. There were no MESH words containing "rerevision", "multiply revisions" or "repeated revisions".

Articles found: 4350 results.

Based on the title, this number of abstracts were reviewed: 97

Of the abstracts, so many articles were reviewed and read: 65

Number of articles used in the protocol: 47.

Material and methods

Design

This study is a retrospective study using nationwide information from the Danish Knee Arthroplasty Register (DKR) and Landspatientregisteret (LPR), with an evidence level of level 3 in the evidence hierarchy. The registries are used to identify all patients with a primary knee arthroplasty and with a revision knee arthroplasty from January 1st 1998 to December 31st 2021. Information regarding surgery, patient demographics and surgical technique will be obtained for statistical analysis. Data will be stored briefly on a logged drive and then transferred to the servers of Danmarks Statistik, which are encrypted. Additionally, all data is anonymized when transferred to Danmarks Statistik.

The design was chosen as there is a limited number of revisions in Denmark, and even fewer cases of re-revisions. To produce meaningful results, it is necessary to collect as much data as possible. The study will include all patients operated in Denmark from 1998-2021, which will create the best possible basis for describing the population and calculating the incidence, prevalence, cumulative revision rates and lifetime risks.

Review

The project has been registered in the Knowledge Centre for Data Reviews in Region Hovedstaden (PACTIUS), as required.

Case number: P-2022-711

This is a registry study and there is no obligation to notify the scientific ethics committee.

Description of registers, acquisition of data and description of data

Danish Knee Arthroplasty Register

Danish Knee Arthroplasty Register (DKR) is a clinical database which has existed since January 1st 1997. Registration of all knee arthroplasty procedures has been mandatory from June 1st 2006 at all Orthopedic institutions in Denmark, including private hospitals. All primary and revision procedures are recorded including information regarding the patient, procedure, indication and equipment used. In general, the degree of completeness is high for the register, with a 97% completeness rate in 2014 (3).

Landspatientregisteret

Landspatientregisteret (LPR) is a national and clinical database administered by the Danish Health Authority since 1976. All information generated when a patient is treated by the public health service is reported here. In addition to information regarding procedures and admissions, the register contains information on residence, partner status, level of education, income, comorbidities and emigration amongst others. Operations are recorded according to the NOMESCO classification, while diagnoses are coded according to the ICD-10 classification.

Identification of primary procedures

We will determine the cohort of primary procedures from DKR (called P-DKR) by identifying all primary procedures performed from January 1st 1998 to December 31st 2021. P-DKR is then transferred to Danmarks Statistik (DS). Through DS, all primary procedures in the observation period will be identified using NOMESCO operation codes (KNGB*) and these will be collected in a cohort called P-SD. P-DKR and P-SD will be joined into a cohort called PRIM and this cohort will best describe all primary procedures performed in Denmark during the observation period.

Identification of revision procedures

The DKR cohort of revisions (R-DKR) will be identified by all registrations marked as revisions during the observation period. R-DKR I also transferred to DS. All revisions will be identified in DS as R-DS using the NOMESCO operation codes KNG* (knee procedure), KNGC* (revision of knee), KNGG* (arthrodesis) and KNFQ19 (femur amputation). The cohorts R-DKR and R-DS will be combined and called REV. This cohort will best describe revision procedures performed in Denmark during the observation period.

Insertion of cement spacers presents a special registration problem, as different registration practices exist. Some use KNGS codes (eg KNGC59A – Insertion of spacer in a knee joint in connection with revision). We intend to not consider spacer insertion as a revision. For example a two-stage revision will be considered as one revision.

Organization of data

A table (G) with PRIM and REV will be created. G will contain information on revisions, deaths, disappearances, emigration and the associated dates. For each knee joint in PRIM and for each date in the observation period, it will be possible to describe the status of the knee joint.

In the event of a discrepancy between data from DKR and DS, data from DKR will be chosen, but specific rules will be created for specific situations. In case of missing data for indication for revision (for example if a procedure is not registered in DKR), DS diagnosis codes will be used.

Data is obtained from both registers, as the degree of completeness is very high in both registers. By combining data a near-perfect data collection of the population is ensured.

Description of data from DKR

The Regions' Clinical Quality Development Program (RKKP) manages data from DKR. After receiving approval from PACTIUS, RKKP was queried for data-extraction. Data has since been acquired. Data consists of primary and revision procedures performed from January 1st 1998 to December 31st in 2021. The data includes information regarding:

CPR-number (personal identification number)

Sex

Hospital

Department

Laterality of procedure

Height

Weight

Revision (yes/no)

Indication for procedure

Operation date

Type of arthroplasty

Femur fixation (Cement, yes/no)

Tibia fixation (cement, yes/no)

Femur component

Tibial component

Patella component (yes/no)

Patella fixation (cement, yes/no)

Femur stem (yes/no)

Tibia stem (yes/no)

Operating room

Use of tourniquet (yes/no)

Use of drain

Number of previous revisions

Indication for revision

First revision date

Description of data from LPR

Danmarks Statistik contains many registers about the population in Denmark, including registers regarding place-of-residence, income, education, partner-status, as well as Landspatientregisteret, which contains all information created when a patient is admitted to a public hospital. DS also contains information regarding all treatments performed in privately owned hospitals.

An application has been submitted regarding the acquisition of data from primary and revision arthroplasties performed from January 1st 1998 to December 31st 2021. The requested variables are as follows:

Name

Social Security number

Address

Changes of residence, including information on movements, emigration, disappearance, death

Income

Diagnoses/comorbidities

Operations with operation code: KNGB*, KNGC*, KNGG* and KNFQ19

Level of education

Partner status

Employment status

Statistics

After extraction of data, pooling of data in DS, creation of the populations and tables as described in the previous section on data extraction, statistical analyzes will be carried out.

WPA1

In WP-A1 we want to calculate:

1) Annual incidence of revision arthroplasties.

   Incidence is calculated as the number of n-grade revisions performed in Denmark during a given year as a proportion of the current year's population. This is done for each level of revision.

   The incidence rate is also calculated:

$$IR = \frac{Number\ of\ n-grade\ revisions}{Number\ of\ person-years\ in\ observation period}$$

2) The continuous prevalence of revision knees.

Prevalence is calculated as the number of patients living with n-grade revision knee as a proportion of the current year's population. This is done for each level of revision.

3) The relationship between the annual incidence of n-grade revisions with the incidence of primary procedures in the preceding years.

$$rate\ ratio = \frac{IR\ for\ n - grade\ revision}{IR\ for\ primary\ procedures\ the\ previous\ year}$$

WPA2

The analyzes will be based on the population defined in WP-A1. We will estimate the cumulative incidence (risk) for the different levels of revision and examine whether factors such as patient demographics, implant type and other operative technical conditions influence the cumulative incidence.

$$risk\ for\ n - grade\ revision$$
$$= \frac{number\ of\ n - grade\ revisions\ in\ the\ observation\ period}{numbers\ with\ n - 1\ revisions}$$

To investigate whether patient demographics, implant type, indication for revision and other operative technical conditions have an effect on the subsequent incidence of revision, we will use regression analysis. It will be relevant to investigate possible confounding of the variables.

In addition, we will create "cumulative incidence plots" for each level of revision to illustrate prosthesis survival.

WPA3

The lifetime risk will be determined as a summation of the expected remaining life based on the CRR for the individual events (primary procedure and n-grade revision). As in WPA2, we will examine whether patient demographics, implant type and other operative technical conditions have an effect on the risk of revision. In addition, the lifetime risk of arthrodesis or amputation as an event will also be calculated. Thus, data from WP-A2 becomes the starting point for the calculations.

Applicant's duties

The applicant's duties consist of:

The overall responsibility for the execution of the project.

Obtaining necessary data approvals.

Acquisition of register data from RKKP and DS.

Analysis of register data.

Formulation of the results into scientific articles, meant for publication in peer-reviewed journals or by oral presentations at scientific conferences.

Ethics and perspectives

As this study is retrospective and examines register data, there are no present ethical issues. This study does not include clinical experiments or investigation of drugs. Thus, there is no obligation to notify or acquire approval from the Scientific Ethics Committee.

Personal data will be processed and stored in accordance with the General Data Protection Regulation Act. All included patients are anonymized when data is transferred to DS and when disseminating the project's results. Data is only stored on encrypted servers. The project has been notified to Region Hovedstadens Data Protection Agency (PACTIUS) and the project has been approved to receive register data (P-2022-711).

The perspective of the project is to gather new knowledge about a previously overlooked patient group and to draw attention to a significant burden for patients and health-care-

systems. The knowledge generated by this project will improve future treatment of patients and resource allocation by health-care-systems possible.

Publication

The three work packages are planned to result in at least 3 scientific articles. The articles will be submitted to international and peer-reviewed journals.

Economy and budget

The study is part of a Ph.D. project. The costs associated with the project are the salary of the main investigator and PhD-student (Julius Tetens Hald), data-extraction fees and tuition fee.

The project is partially financed through Rigshospitalets Research Fund, which has granted 610,000 DKK on 1/10 2022 over a 1-year period to the contact person Julius Tetens Hald. The project is also financed partly by a grant from sundhedsdonationer.dk (Sygesikring Danmark). This grant guarantees salary and tuition-fee. However as other applicants are included in the grant, and not the full requested amount was granted, it may be necessary to search for additional sources of funds.

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