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PhD Thesis

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Revisions of knee arthroplasties due to pain; survivorship, use of analgesics, patient-reported outcomes and validation of the indication

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Preface

The idea of conducting a PhD began, when I started my specialist training in orthopaedic surgery. I was inspired by other colleagues with a PhD degree, who seemed to have a comprehensive understanding of reading and conducting research and incorporate it into their clinical work. I wanted to improve my abilities as a specialist in orthopaedic surgery, by gaining an education in research. So, when my supervisor introduced me to the main idea of this PhD project, I considered pros and cons and finally decided to make a leave of absence in the middle of my specialist training and conduct the PhD.

The scope of this thesis is revision of painful knee arthroplasties. We hypnotise, that patients undergoing revision of a knee arthroplasty because of unexplained pain, do not benefit sufficiently from surgery. This is a sparsely investigated area, and the following papers brings valuable information about the topic. This is highly relevant for orthopaedic surgeons performing primary and revision knee arthroplasties, patients with unexplained pain after a knee arthroplasty, and possibly other interested parties as well.
We do not expect to get a clear answer for or against revision for unexplained pain, because this is an unexplored area of research. However, we do expect this thesis to by hypothesis generating.

Acknowledgements

This PhD would not have been possible without the support of several people. Firstly, I would like to thank my main supervisor **Martin Lindberg-Larsen** for giving me the opportunity to conduct this particular PhD and for contributing with great committed supervision all the way through. Secondly, I will thank my co-supervisors **Henrik Schrøder** and **Anders Troelsen**, who have actively contributed to this work throughout the entire process with great expertise.

Conducting a PhD midway through my specialist training in orthopaedic surgery was not a matter of course, so I would like to express my gratitude to the people making this leave of absence possible; **Lonnie Froberg, Søren Overgaard, Anders Jordy** and **Per W. Kristensen**.
Open Patient data Explorative Network (OPEN) has contributed with important professional sparring and REDCap services.

Thanks to **Gitte Havndrup** and **Louise D. Petersen**, secretaries at the Department of Orthopaedic Surgery and Traumatology OUH, for their help with many minor and major issues along the way.

I would also like to thank my fellow **PhD students** for their general support, social activities, sharing of ups and downs, and scientific and practical sparring. Without you, these years would have been less joyful.

A special thanks to my mother **Marianne**, who is always helpful with practical support and babysitting, and without whom, I would not be able to pursue my professional dreams.

And finally, a great thanks you to all the people I have not mentioned by name, who have also helped me along the way.

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This PhD project was funded by several donations. **The Danish Rheumatism Association** and **Grosserer Christian Andersen og hustru Ingeborg Andersens legat** funded operational costs. **The faculty of Health Sciences at the University of Southern Denmark** and **The PhD fund at the Region of Southern Denmark** provided a one year scholarship each. **The combined fund from Region Zeeland and Region of Southern Denmark** financed half a year of PhD stipend. Travel expenses related to international congresses were covered by **the Fund of the Danish Orthopaedic Society**.

List of papers

Study 1:
Kristine B. Arndt, Henrik M. Schrøder, Anders Troelsen, Mikkel R. Andersen, Lasse E. Rasmussen, Martin Lindberg-Larsen. Validation of the indication ”pain without loosening” for revision of knee arthroplasties in the Danish Knee Arthroplasty Register.
(Submitted to Acta Orthopaedica September 2022)

Study 2:
Kristine B. Arndt, Henrik M. Schrøder, Anders Troelsen, Martin Lindberg-Larsen. Prosthesis survival after revision knee arthroplasty for “pain without loosening” versus “aseptic loosening”: a Danish nationwide study. Acta Orthopaedica. 2022;93:103-10.
DOI:10.1080/17453674.2021.1999069
(Published 2021)

Study 3:
Kristine B. Arndt, Henrik M. Schrøder, Anders Troelsen, Martin Lindberg-Larsen. Opioid and Analgesic Use Before and After Revision Knee Arthroplasty for the Indications "Pain Without Loosening" Versus "Aseptic Loosening" - A Danish Nationwide Study. The Journal of arthroplasty. 2022; Apr;S0883-5403(22)00379-5.
DOI: 10.1016/j.arth.2022.03.077.
(Published 2022)

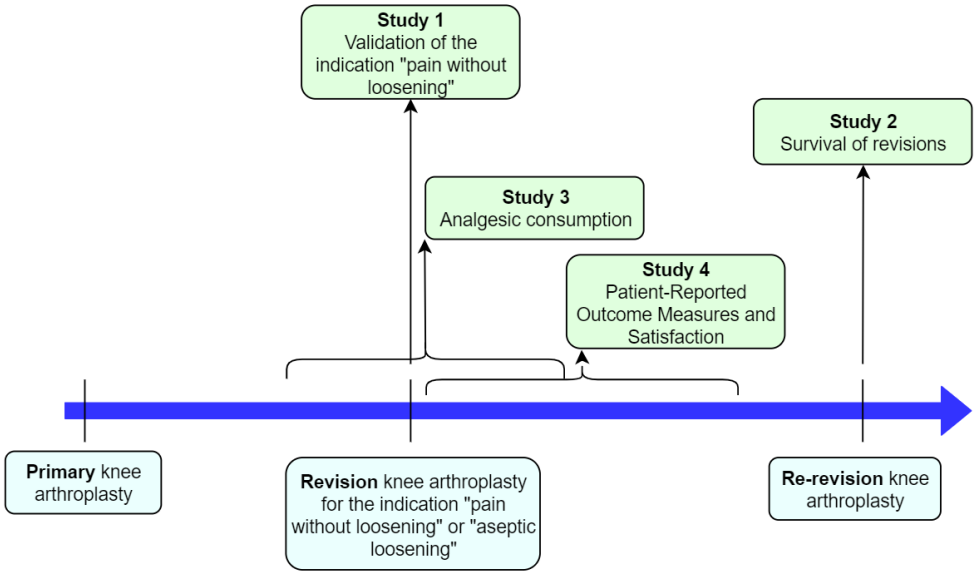
Study 4:
Kristine B. Arndt, Henrik M. Schrøder, Anders Troelsen, Martin Lindberg-Larsen. Patient-reported outcomes and satisfaction 1 to 3 years after revisions of total knee arthroplasties for the indications unexplained pain versus aseptic loosening. J Arthroplasty. 2022 Oct 17:S0883-5403(22)00939-1.
DOI: 10.1016/j.arth.2022.10.019.
(Published 2022)

Abbreviations

Abbreviation	Definition
ASA	American Society of Anesthesiologists
ATC	Anatomical Therapeutic Chemical code
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CPR	Civil Personal Register number
CRS	Civil Registration System
CT	Computerized Tomography
DKR	Danish Knee Arthroplasty Register
DNPR	Danish National Patient Register
EQ-5D-5L	EuroQol- 5 dimension- 5 level
FJS	Forgotten Joint Score
HR	Hazard Ratio
ICD-10	International Classification of Diseases
NPR	Danish National Prescription Registry
NSAID	Non-Steroidal Anti-inflammatory Drugs
OKS	Oxford Knee Score
OPEN	Open Patient data Explorative Network
PRO	Patient-reported outcome
PROM	Patient-reported outcome measure
RKKP	National Clinical Registries
ROM	Range of motion
TKA	Total Knee Arthroplasty
UKA	Unicompartmental Knee Arthroplasty
VAS	Visual Analogue Scale

Overview of the PhD project

Figure 1. The blue horizontal arrow represents the time-line of a revision knee arthroplasty patient. The four studies cover overlapping time-points of this time-line.



Summary – English

Background and aim

Up to 20% of patients experience persistent knee pain after insertion of a primary knee arthroplasty. Some patients are revised because of pain without any other obvious knee pathology present. It is unknown if these patients benefit from revision. Therefore, this thesis aimed to investigate ”pain without loosening” as indication for revision knee arthroplasties.

Methods

We identified 4,456 procedures of first time knee arthroplasty revisions for the indications “pain without loosening” and “aseptic loosening” in Denmark in 1997-2020 from the Danish Knee Arthroplasty Register (DKR). 1,825 revisions were performed for the indication “pain without loosening” and 2,631 revisions were performed for the indication “aseptic loosening”.

We conducted four studies based on data from the DKR. Study 1 validated the indication “pain without loosening” from medical records, radiographs, and computerized tomography (CT) scans. Study 2 investigated the re-revision rate of the pain revisions compared to the better established indication “aseptic loosening”. Study 3 investigated use of analgesics one year before and after revision for the indications “pain without loosening” and “aseptic loosening”. Data from the Danish National Patient Registry were used in study 2 and 3 and study 3 further required data from the Danish National Prescription Registry. Study 4 investigated patient-reported outcomes (PROMs) 1-3 years after revision comparing “pain without loosening” versus “aseptic loosening”.

Results

The indication “pain without loosening” covered knee arthroplasties revised because of pain in 99% of the investigated cases. We found hidden indications in 42% of these, with stiffness and prosthesis malposition occurring most frequently. We found similar re-revisions rates of about 23% (CI 20-25) and 19% (CI 18-21) for “pain without loosening” versus “aseptic loosening” with a 20-year follow-up. The analgesic consumption did not change considerably after revision for any of the indications. 9% and 8% of the revised patients for each indication respectively became new long-term users of opioids after revision. Patients revised for “pain without loosening” scored significantly worse on PROMs than patients revised for “aseptic loosening”, and a larger proportion of pain patients were unsatisfied with the result of the revision.

Conclusion and perspectives

The indication “pain without loosening” in the DKR identifies pain revisions, but a broad variety of other underlying indications were present as well. Stiffness and malposition of components lack as indication options in the DKR, and implementation of these indications would strengthen the register. Further, the register data would improve if pre- and postoperative PROMs were captured routinely.

Revision for “pain without loosening” performed similar to revisions for “aseptic loosening” regarding prosthesis survival and use of analgesics. A large proportion of long-term opioid users were generated after revision for both indications, but the pain revision patients scored worse on PROMs and were less satisfied.

Therefore, revising for the indication “pain without loosening” should be carefully considered, and in most cases avoided, when no obvious knee pathology is present.

Resumé – Dansk

Baggrund og formål

Vedvarende smerter er til stede hos op mod 20% af patienter, der får isat et kunstigt knæ. Nogle af disse patienter bliver genopereret på trods af, at der ikke er blevet fundet en oplagt årsag til smerterne. Det er uvist om disse genoperationer gavner patienterne. Derfor er formålet med denne afhandling at undersøge ”smerter uden løsning” som årsag til genoperation af kunstige knæ. I flere af studierne sammenlignes med en kontrolgruppe af genoperationer udført på grund af ”aseptisk løsning”, der udføres når det kunstige knæ har løsnet sig fra knoglen og derved medfører gener.

Metode

4.456 patienter, der har fået foretaget en førstegangs-genoperation af deres kunstige knæ på baggrund af ”smerter uden løsning” og ”aseptisk løsning” i perioden 1997-2020 i Danmark, blev identificeret fra Dansk Knæalloplastikregister (DKR).

Vi udførte 4 studier baseret på data fra DKR. Det første studie var et valideringsstudie, der undersøgte ”smerter uden løsning” som årsag til genoperation via gennemgang af journaler, røntgenbilleder og scanninger. Dette var med henblik på at finde ud af om ”smerter uden løsning” var den rigtige årsag til operationen og/eller om der var andre årsager til stede samtidig. Det andet studie undersøgte patienternes risiko for at skulle igennem yderligere genoperationer af deres knæ. I studie 2-4 blev smertepatienter blev sammenlignet med patienter, der blev genopereret på grund af ”aseptisk løsning”, som er en mere veletableret årsag til genoperation. I det tredje studie blev forbruget af smertestillende medicin undersøgt et år før og et år efter genoperation. Data fra Landspatientregistret blev anvendt i studie 2 og 3. I studie 3 blev der desuden anvendt data fra Lægemiddelstatistikregistret. I det fjerde studie blev der foretaget en spørgeskemaundersøgelse 1-3 år efter genoperationen.

Resultater

Indikationen ”smerter uden løsning” som årsag til genoperation er korrekt angivet i DKR i 99% af tilfældene, men vi fandt også skjulte indikationer i 42% af tilfældene. De hyppigste skjulte indikationer var stivhed af knæet samt fejlplacering af det kunstige knæ. Risikoen for yderligere genoperationer var overordnet ens for de to grupper af patienter opereret på grund af ”smerter uden løsning” og ”aseptisk løsning”. Forbruget af smertestillende medicin ændrede sig ikke betydeligt for nogen af grupperne efter genoperationen, men 9% og 8% af patienterne i de to grupper udviklede et nyt langtidsforbrug af morfinpræperater efter genoperationen. Smertepatienterne scorede markant værre på de forskellige

spørgeskemaparametre end patienterne, der blev genopereret pga. ”aseptisk løsning”. Desuden var en større andel af smertepatienterne utilfredse med det endelige resultat af genoperationen.

Konklusioner og perspektiver

Indikationen ”smerter uden løsning” i DKR identificerer patienter, der har fået genopereret deres knæ på grund af smerter, men der gemmer sig også andre skjulte årsager til genoperation i denne kategori. Fejlstilling af komponenter og stivhed mangler i DKR, og registret forbedres, hvis disse årsager til genoperation bliver inkluderet. Desuden kan standardiserede knærelevante spørgeskemaer med fordel inkluderes i registret for at give mulighed for løbende at følge den patient rapporterede effekt af operationerne.
Risikoen for yderligere genoperationer samt forbrug af smertestillende var ens for patienter, der blev genopereret på grund af smerter sammenlignet med ”aseptisk løsning”. Men der blev dannet en stor andel af langtidsforbrugere af morfin i begge grupper og smertepatienterne var mindre tilfredse med resultatet af operationen.
Derfor skal en behandlingsstrategi, hvor man undgår kirurgi grundigt overvejes, når man ikke kan finde noget god forklaring på smerterne på trods af grundig undersøgelse.

Background

Epidemiology of knee arthroplasties

9,616 primary knee arthroplasty procedures and 933 revision procedures were reported to the Danish Knee Arthroplasty Register in Denmark in 2021 (1). The mean age at primary procedure was 68 in the Danish population. 56% of the patients undergoing primary knee arthroplasty in 2021 in Denmark were women. Future increases in both primary and revision knee arthroplasties are expected. Projections of increases in primary and revision knees have been made for other populations (USA, England and Wales, Germany), and similar trends for the Danish population might occur as well (2, 3). Following these projections, the amount of revisions performed annually are expected to increase around 30% by 2030. This puts a pressure on the resources of the health care systems. Especially revision procedures are comprehensive and costly and the results are not always as good as for primary procedures (4). To achieve the best possible results and avoid unnecessary procedures it is of great importance to select the right candidates for revision surgery.

Nationwide knee arthroplasty registers

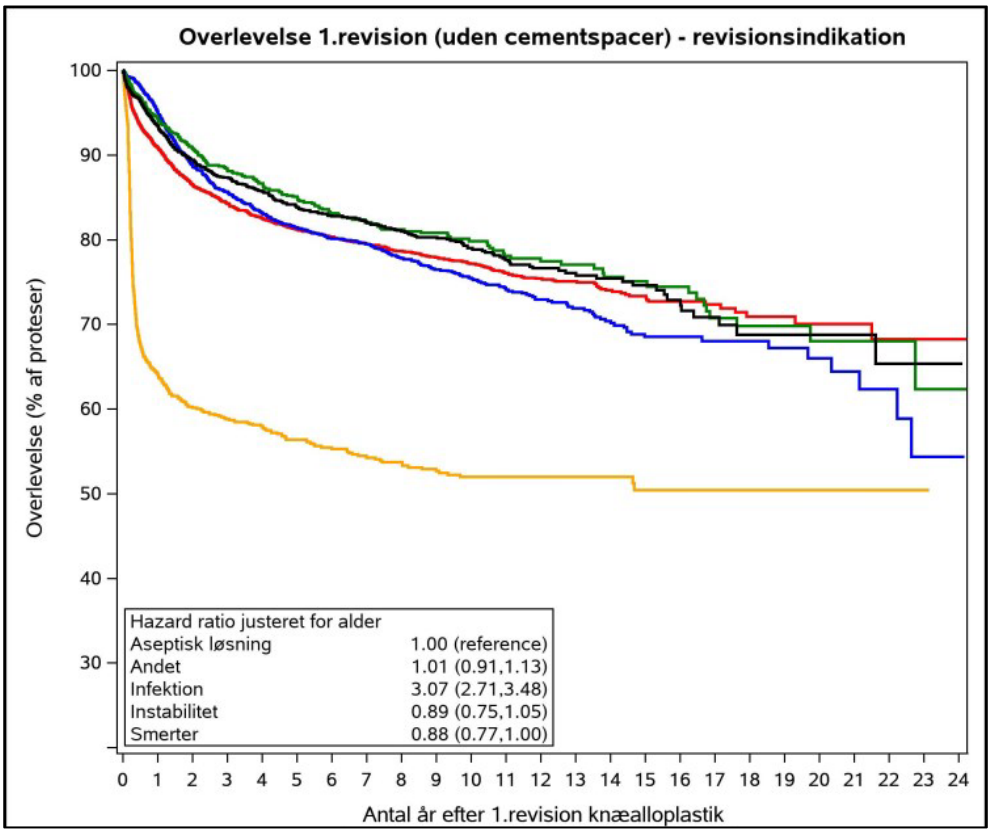
Several countries have well established knee arthroplasty registers to observe the epidemiology of procedures performed and to facilitate improvement of surgery outcomes (5). Norway, Sweden, Finland, the Netherlands, UK and Australia all have nationwide knee arthroplasty registers resembling the DKR (6-11). This enhances comparisons of research and collaborations, though the respective registers are not identical.
A register needs to be of high quality to be valuable and form a solid basis for research. A high level of completeness of a register is important in order for data to be valid (5, 12). The completeness of the DKR was 97% for primary procedures and 96% for revisions procedures in 2021 (1). The goal of completeness is >90% for each Danish hospital including private hospitals, thus the DKR is well performing though improvements are possible. The validity of entered data is essential for the database to be of high quality. The indications for revisions analyzed in this thesis are not previously validated and neither are any of the other indications. Validations of indications for revisions are also lacking in other national registers.

Revisions

The risk of revision after primary knee arthroplasty is well investigated, but the knowledge about re-revisions is sparse. Revisions have higher failure rates than primary procedures, and the risk of re-revision increases the more revisions performed (1). Dyrhovden et al. investigated 3,151 revisions from the Norwegian knee arthroplasty register in 2017. The

survival of TKAs was 91% and 94% over two consecutive 10-year periods. The survival for UKAs was 80% and 81%. The risk of revision decreased for unexplained pain and aseptic loosening from the early period to the late. Much similar to this, a 10-year survival of 94.8% and a 20-year survival of 85% is estimated in the DKR (1). Yapp et al. found a 10-year survival of 88.6% for aseptic revisions (13). Higher rates of re-revision have been associated with lower volume revision centers and other proposed risk-factors for re-revision are male sex, younger age, high BMI and previous revisions (13, 14). Studies concerning re-revisions and indications are lacking.

Figure 2. Kaplan-Meier plot presenting the survival of revisions performed for the indications aseptic loosening, infection, instability, pain and other. (The figure is from the annual report of DKR, 2021 (1)).



Aseptic loosening (blue), infection (yellow), instability (green), pain (black) and other (red).

Gredanius et al. found inferior quality of life after revision compared to primary knee arthroplasty in a cohort of 265 patients (15). Indications were not considered. Baker et al. investigated a cohort of 24,190 patients in 2012 and found inferior improvements in specific knee scores and quality of life in revision patients compared to patients undergoing primary knee arthroplasty (16). Baker et al. also investigated indications for revisions and unexplained pain performed worse than the other indications, whereas revisions for the indication “aseptic loosening” showed the best results (16). They found a mean post-revision OKS of 26.4 for unexplained pain and 27.8 for aseptic loosening/lysis, with no significant difference between groups. They found mean post-revision EQ-5D scores of 0.48 for unexplained pain and 0.56 for aseptic loosening/lysis.

Persistent pain after primary knee arthroplasty

About 20% of patients experience persistent pain after a primary knee arthroplasty (17-19). The amount of patients experiencing persistent pain after a revision is probably higher, but this is sparsely investigated (20). Petersen et al. found 47% of patients experiencing persistent pain 3 years after revision in a cohort of 99 patients opposed to 19% after primary surgery. This study was conducted by the collection of questionnaires with ratings of pain, satisfaction and the Osteoarthritis research Society Questionnaire 3 years after surgery. Several predictors for development of persistent pain after knee arthroplasty have been detected and can be taken to consideration, when selecting patients for surgery. Pain catastrophizing prior to surgery is a strong predictor of increased risk of persistent pain afterwards (21, 22). Mental health, anxiety, depression, pain at other sites, higher weight, younger age and other comorbidities also predicts persistent pain after knee arthroplasty surgery (18, 22).

Pain revisions

Patients experiencing persistent pain after a primary knee arthroplasty might request a new surgery in the hope of a better result. The effect of revisions performed solely because of pain without any other obvious knee pathology present is questionable and they are not recommended (18, 23). However, this is a sparsely investigated area and the true outcome of these revisions is unknown.

The amount of revisions performed because of pain in Denmark have decreased over the past few years comprising 120 (10.7%) of revisions performed in 2017 to 90 (7.66%) in 2020. The frequency was 12.5% of revisions performed in the entire duration of the register (1997-2020). It is unknown why the numbers are decreasing, but the growing knowledge about the unsatisfying outcomes is a possible explanation. The frequency of pain revisions in other countries varies, but 10-22% has been reported (6, 8, 10, 11). Pain is not available

as indication option in all registers and are probably recorded under “other” indications if they are performed anyway.

Figure 3. Revisions for “pain without loosening” presented as frequency of the total number of revisions performed per year. Data from the DKR (1, 24).

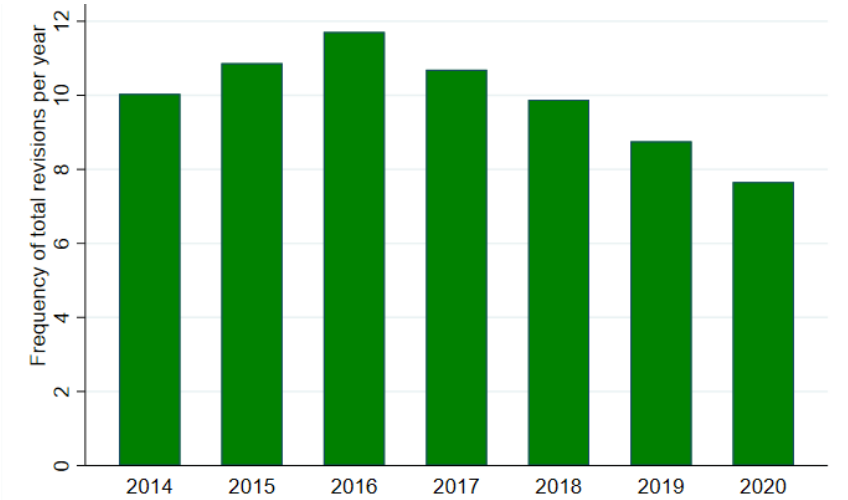
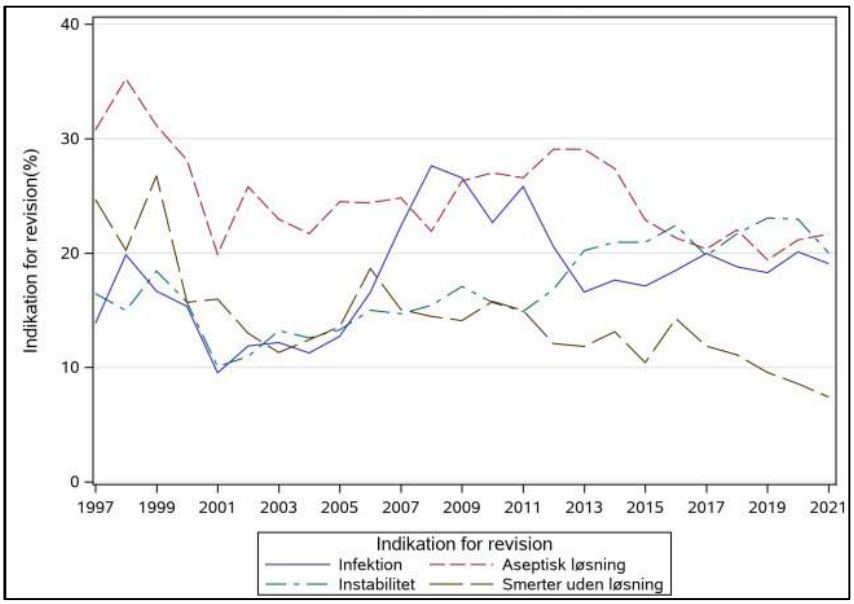


Figure 4. Indications for revision of knee arthroplasties reported to the DKR from 1997 to 2021 (The figure is from the annual report of DKR, 2021 (1)).



Aseptic loosening

Aseptic loosening is the loosening of one or more of the components of the prosthetic joint without the presence of infection, and is mostly caused by implant wear. 22.9% of revisions captured by the DKR are performed for the indication aseptic loosening (1). This makes aseptic loosening the most common cause for revision and studies of other populations shows similar trends (25, 26). Several diagnostic modalities for aseptic loosening exists including standard radiographs, computed tomography (CT) scans, and bone scintigraphy (27-29), but the final diagnosis is made perioperative.

Aseptic loosening is not validated in any knee arthroplasty register. However, aseptic loosening as indication for revision of knee arthroplasties is well understood and well established. Other indication groups might be less understood, such as the indication "other", which possibly covers many different indications. Therefore, revisions performed for the indication aseptic loosening were considered the most appropriate for comparison to revisions performed for the indication pain in this thesis.

Motivation for this thesis

The safety of revision procedures of knee arthroplasties is similar to that of primary procedures regarding readmissions, complications and mortality even in a fast track setting (30-32). However, considering the inferior patient-reported outcomes after revision versus primary surgery, the high failure rate of revisions, the cost for the health care system and the huge inconvenience for the patient of going through additional major surgeries the indication for revision should be carefully thought through and unnecessary revisions avoided. Revisions for the indication unexplained pain are controversial, but the knowledge about the outcomes of these revisions is sparse and it is important to investigate this topic further. Knowledge about the outcomes will help the surgeons and the patients in the process of shared decision making when surgery is considered. This evidence will be valuable in the selection of the right candidates for surgery and thereby improve the outcomes afterwards. Whereas patients who a less likely to benefit from further surgeries are better off with a well-planned non-operative treatment strategy.

Aims

The overall aim of this thesis was to investigate ”pain without loosening” as indication for revision knee arthroplasties.

The aims of each of the four studies were as follows:

Study 1:
The aim of this study was to investigate the indication “pain without loosening” in the DKR, and screen for other possible indications hidden in this category.

Study 2:
The primary aim of this study was to investigate the survival rates of knee arthroplasties revised for the indication ”pain without loosening” compared to the indication ” aseptic loosening”. Secondary aims were to investigate the survival rates in four surgical subgroups (TKA-TKA, partial revision, unicompartmental knee arthroplasty (UKA)-TKA, secondary patella button) and investigate the survival rates over two time-periods 1997-2009 and 2010-2018.

Study 3:
The objectives of this retrospective cohort study on patients having a knee arthroplasty revised in the period 1997 to 2018 for the indication “pain without loosening” compared to the control group “aseptic loosening” were:

1. To investigate the consumption of opioids, paracetamol, non-steroidal anti-inflammatory drugs, antidepressants, anticonvulsants, and other analgesic drugs one year before and after revision.
2. To investigate the development in long-term use of opioids before and after revision.
3. To determine if age, sex, Charlson comorbidity score, surgical subgroup, opioid-related comorbidities, and preoperative use of analgesics are predictors for development of new postoperative long-term opioid use.

Study 4:
The aim of this study was to compare patient-reported outcomes 1-3 years after revision of knee arthroplasties for the indications “pain without loosening” versus “aseptic loosening”.

Methods

Study designs

Study 1 was a validation study of prospectively collected data from the DKR, medical records, radiographs and CT scans. We followed the guidelines from Benchimol et al. for validation of health administrative data (33).
Study 2 and 3 were retrospective cohort studies of nationwide collected data. The RECORD guidelines for the reporting of routinely collected observational data were followed (34).
Study 4 was a cross-sectional nationwide case-control study conducted in accordance with the COSMIN reporting guideline for PROM studies (35).

Registers

The Danish Knee Arthroplasty Register

The DKR is a clinical database administered by the National Clinical Registries (RKKP) that has prospectively collected data on all primary and revision knee arthroplasties performed in Denmark since January 1, 1997. All orthopaedic departments, including private hospitals, report pre- and intraoperative data to the database. The register contains information on hospital, time of surgery, type of prosthesis, components inserted, primary or revision procedure, and indication for surgery etc. The register does not include PROMs. Inclusion of patients for all four studies were based on datasets obtained from the DKR.

The Danish Civil Registration System

The Danish Civil Registration System (CRS) is an administrative register established in 1968 (36). Persons registered in the CRS are assigned a 10-digit Civil Personal Registration (CPR) number, which encodes date of birth and gender and enables linkage to all Danish registers. The data in the register is complete and validated. Variables in the register are; address, civil status, status of residence in Denmark, and vital status etc.

The Danish National Patient Register

The Danish National Patient Register (DNPR) is a national administrative register collecting information on all inpatient hospital contacts in Denmark since 1977 and all outpatient hospitalizations and emergency room visits since 1995. It is mandatory for all hospitals in Denmark to report data to the DNPR to receive reimbursement from the Danish health authorities, which insures a completeness of >99% (37). Variables in the DNPR are; CPR number, dates of admission and discharge and up to 20 discharge diagnoses classified

according to the International Classification of Diseases (ICD) (Eighth edition (ICD-8) until the end of 1993, and Tenth edition thereafter (ICD-10)).

The Danish National Prescription Registry

The Danish National Prescription Registry (NPR) is a nationwide database collecting information on all reimbursed drugs for administrative purposes in Denmark since 1995 (38). The register contains 46 variables (e.g. ATC-codes, amount, strength, pharmacy) concerning reimbursed prescriptions.

Study population

Inclusion of patients

Patients for all four studies were identified from the DKR. We obtained a dataset supplied by the RKKP with all DKR variables of patients revised for the indications “pain without loosening” and “aseptic loosening” in Denmark in 1997 to 2018. The time-period equaled the lifespan of the DKR at the time of data collection. We further obtained an extension of the dataset to include patients revised in 2019 to 2020 for Study 4.

We identified 5,829 revisions in the initial dataset for the indications “pain without loosening” and “aseptic loosening”. Some of the revisions had other indications registered in addition to “pain without loosening” or “aseptic loosening”, as it is possible for the surgeon to select multiple indication options. We included revisions without other additional indications. Revisions for “pain without loosening” including other indications were analyzed in a sensitivity analysis in study 2, but they were excluded in all the other studies. 1,111 revisions for “pain without loosening” and 2,514 revisions for “aseptic loosening” were available for analyses when relevant surgical subgroups (see section below) and revisions with more than one indication were removed for study 2 to 4. Flowcharts for the individual studies are presented in the individual Papers (Papers, page 55). In study 3, considering analgesic consumption, we excluded bilaterally revised patients (n=281), because it could not be determined if one or both knees gave rise to use of analgesics.

Study 1 included pain revisions performed in 2016 to 2018. Revisions for “aseptic loosening” were not relevant for this study, as it validated the indication “pain without loosening” (11). Study 4 required a more recently revised population, because time from revision to PROM should not exceed 1 to 3 years. A larger timespan would make PROM’s less accurate due to recall bias. We included revisions from 2018 to 2020 in this study.

Surgical subgroups

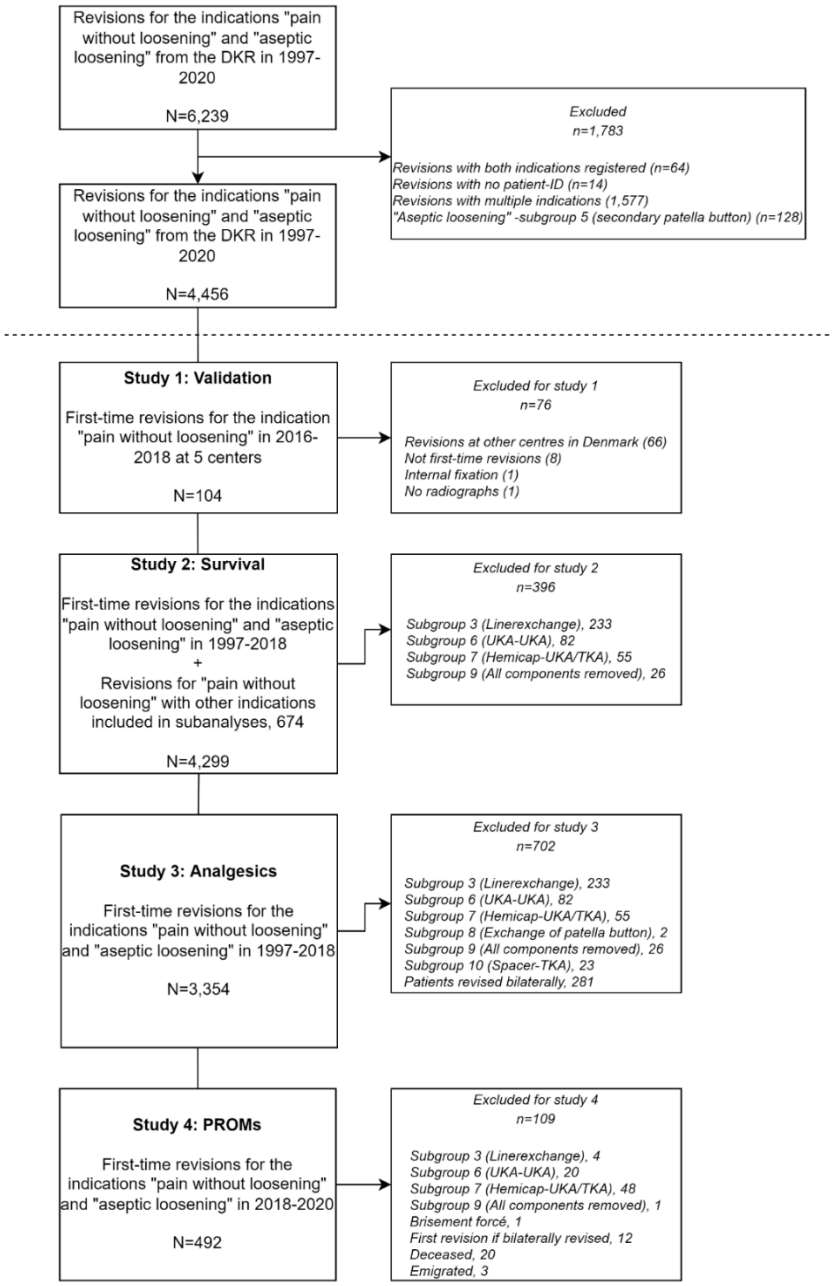
We defined surgical subgroups according to the type of prosthesis removed and the type of prosthesis inserted at the revision in all four studies. The DKR supplies this information. It

was used as demographic information to compare indication groups and for sensitivity analyses in study 2, 3, and 4. The surgical subgroups were:

1. TKA to TKA
2. Partial revision (change of femoral or tibial component, not both)
3. Liner exchange
4. UKA to TKA
5. Secondary patella button
6. UKA to UKA
7. Hemicap to TKA/UKA
8. Exchange of patella button
9. All components removed
10. Spacer to TKA

We included subgroup 1 (TKA-TKA), subgroup 2 (partial revision) and subgroup 4 (unicompartmental knee arthroplasty (UKA)-TKA) in all four studies. In study 1, we included all groups besides group 9.
Surgical subgroup 3 was excluded from study 2 to 4, because components were not exchanged. We found the effect of change of components in pain revisions highly relevant in our studies to estimate the true effect on pain relief. In study 2 to 4, we considered a "true" revision a surgery with change of components.
Surgical subgroup 5 was unclear. TKAs with patellar resurfacing have shown better results than TKAs without resurfacing, but it is still a debatable topic (39, 40). 21.8% of primary TKAs reported to the DKR are performed without patellar resurfacing. Secondary patella buttons are very relevant in pain revisions, as some patient experience pain when the patella is not resurfaced primarily. However, secondary patella button is not meaningful in revisions for aseptic loosening without revision of the femoral or tibial components, as the insertion of a patella button does not solve the issue of a loose component. Patients registered for the indication "aseptic loosening" in surgical subgroup 5 were therefore considered misclassified in the register and excluded from all analyses.
Surgical subgroups 6 to 8 were excluded in study 2 to 4. These groups consisted of few patients, making subanalyses weak and the groups represented patients with other problems than for example TKA-TKA. Patients with focal metallic cartilage resurfacing components (HemiCAP/UniCAP) constitute a group that should by analyzed of their own, because these prostheses are very different from TKAs and UKAs. They are therefore excluded from 3 of the studies in this thesis. Likewise, surgical subgroup 9 and 10 represents small groups of patients with other problems than the larger groups of this investigation. These types of revisions are mainly performed as part of the eradication of infections.

Figure 5. Flowchart of patients included in the thesis.



Data collection

Study 1

Data were collected from medical journals, radiographs, and CT-scans. CT-scans were reviewed for those patients, who have had one performed. KBA collected all data from medical journals and radiographs and reported to the database set up in REDCap electronic data capture tools hosted at Open Explorative Patient data Network (OPEN) (41, 42).
All radiographs were reviewed by KBA, and in case of doubt also by MLL. All CT-scans were reviewed by KBA and MLL. Data were collected from 5 centers included in the study; Hvidovre Hospital, Gentofte Hospital, Odense University Hospital, Naestved Hospital and Vejle Hospital.

Study 2

Data were collected from the nationwide databases DKR, CRS and DNPR. DKR data were supplied by the RKKP. The Danish Health Data Authority supplied data from CRS and DNPR, which were processed on their secure IT-platform “Forskermaskinen”.

Study 3

Data were collected from the nationwide databases DKR, CRS, DNPR and NPR. The handling of data was carried out as mentioned above (Study 2). The Danish Health Data Authority also supplied NPR data.

Study 4

A questionnaire was set up in REDCap. The questionnaire contained the PROMs listed in the next section. All patients included in study 4 received an email with a link to the electronic questionnaire in a secured digital mailbox, which linked to the patient’s Danish personal registration number. If the questionnaires were not answered within 2 weeks, two reminder emails were sent with a 2-week interval. The system identified patients, who were not registered to the digital mailbox. A paper version was constructed for these patients including a prepaid reply envelope, which was sent by postal mail. One patient requested a postal questionnaire instead of the digital version, and this request was granted. 493 questionnaires were sent out electronically and 76 were sent out by postal mail. 23 patients did not receive a questionnaire because they had emigrated or passed away.

Outcome variables

Study 1

We collected information on age, sex, previous knee surgeries, type of arthrosis (primary/secondary), American Society of Anesthesiologists (ASA) physical Status Classification System Score, medically treated psychiatric disorder at the time of revision, and other treatment strategy prior to revision (cast, physiotherapy, weight loss, analgesics, brisement forcé, steroid injection and other) from medical charts. The examination of radiographs and CT-scans is described in detail in the manuscript (Paper I, page 55).

Study 2

The primary outcome of study 2 was re-revision of knee arthroplasty revisions for the indication “pain without loosening” versus “aseptic loosening”. We obtained information on all index procedures and following procedures from the DKR. We obtained further procedures registered in the DNPR on the procedure codes KNGU0-1 and KNGC0-9 to ensure complete follow-up and we identified 20 additional procedures. The occurrence of re-revisions were reported in tables as frequencies with confidence intervals and in a Kaplan-Meier plot. The frequencies were accumulated over 2, 5, 10, 15 and 20 years. Frequencies of re-revision were presented for 3 indication groups, “pain without loosening” without other indications, “pain without loosening” with other indications and “aseptic loosening” without other indications. The frequencies were also presented for the four surgical subgroups 1, 2, 4, and 5.

The secondary outcome was re-revision over the two time-periods 1997-2009 and 2010-2018 comparing the two indications of investigation. These outcomes were presented as frequencies with confidence intervals (CI) and a Kaplan-Meier plot.

The Cox proportional hazards regression calculated risk factors for re-revision as hazard ratios. We evaluated the variables sex, age groups, Charlson Comorbidity Index (CCI), and surgical subgroups.

We also presented a table with the indications for re-revisions provided as counts and frequencies though it was not an aim of the study. We included this table as a sensitivity analysis to visualize, that re-revisions for one of the indications were not overrepresented, as this would be interesting to investigate further if it was the case.

Charlson Comorbidity Index: The CCI was calculated and used as a descriptive measure and in regression analyses in study 2 and 3. We used this score to estimate the load of comorbidities (43-45). To obtain meaningful group sizes for analyses, we divided patients

into 3 levels of comorbidity burdens based on the CCI. CCI of 0 (low), CCI of 1-2 (medium) and CCI of 3 or more (high).

Study 3

The outcome of study 3 was the use of analgesics one year before and one year after revision. We includes six categories of drugs (opioids, paracetamol, non-steroidal anti-inflammatory drugs (NSAID), anticonvulsants, antidepressants, and other analgesics). Detailed information on ATC-codes of all included drugs are listed in the paper (Paper III, page 80). We obtained information on all reimbursed prescriptions and time of reimbursement for the included drugs from the NPR.

We divided the year before and the year after revision into four quarters each (-Q4, -Q3, -Q2, -Q1, Q1, Q2, Q3, Q4) and presented the users of the six drug categories as counts and frequencies for each of the eight quarters. A patient was considered a user of a drug in a given quarter if the patient had a reimbursed prescription of the drug in that given quarter. We did not perform calculations on dosages, strength, or type of drug. We did not know if the patients actually consumed the drugs and we did not find detailed calculations meaningful to perform without this knowledge, because of the lack of precision.

Long-term users of opioids were an outcome of this study. We defined a long-term opioid user as a user in four consecutive quarters before or after revision. A new long-term opioid user was a user in the four postoperative quarters, who were not a long-term user prior to revision. We thought that one year was a clinically relevant amount of time to define a long-term user, because postoperative pain requiring analgesic consumption and healing processes are over at that time-point. When a patient requires opioids after a year, other circumstances are present such as persistent pain of the revised knee or drug addiction.

Predictors of new long-term opioid use were an outcome of study 3. We investigated age, sex, CCI, surgical subgroup and other analgesic-requiring diagnoses and procedures. Other analgesic-requiring diagnoses and procedures was a composed variable from ICD-8/10 diagnosis codes and procedure codes from the DNPR that often represent painful conditions requiring the use of opioids (46). The specific codes of this variable are listed in the supplementary table 5 in paper III (Paper III, page 80).

Study 4

The outcomes of study 4 were PROM's. We collected information on OKS, EQ-5D-5L, FJS, Copenhagen Knee ROM and supplementary questions about pain, satisfaction, and reason for revision 1-3 years after revision.

Patient-reported outcome measures

The Oxford Knee Score

The OKS is a validated 12-item questionnaire developed in 1998 by Dawson et al. to measure outcomes after TKA (47). It is a joint specific instrument aiming to minimize the influence of comorbidity. It was translated into Danish in 2009, but has not been validated (48). The questionnaire produces scores of 0-48, with 48 being the best outcome after TKA. The developers of the OKS estimates the minimal important change (MIC) in OKS after TKA to be about 3-5 (49). A Danish study found MIC to be 8 after TKA (50).
Each response to an item is scored between 0 and 4. In the online version of the questionnaire, missing an item is not an option and neither are multiple responses to one item. Unanswered items are possible in the paper version. If an item is left unanswered, the mean value of the other responses is entered. If two or more responses for one item are selected, the worst response is adopted. If more than two items are left unanswered, the questionnaire should be discarded (49).

EQ-5D-5L

EQ-5D-5L consists of a 5-item questionnaire and the EQ visual analoque scale (EQ VAS) designed to measure health state. It was developed by the EuroQol Group Association with the present edition being available since 2009. A validation of the Danish edition was performed in 2021 (51). The EuroQol Group Association provides specific instructions on how to use and interpret the questionnaire (52). The questionnaire covers 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and each dimension has 5 levels. Each item was scored between 1 to 5 (no problems = 1, slight problems = 2), moderate problems = 3, severe problems = 4, unable to/extreme problems = 5). A total score could be calculated – the EQ Index. To generate the EQ Index, the score for each item is multiplied with a value from the value set estimated by van Hout et al. (53). The EQ index is the sum of the 5 values. The value set by van Hout (UK value set) was estimated from a large sample from 6 countries including Denmark. No specific value set for the Danish population has been estimated yet.
The EQ VAS visualizes the patients self-reported health state on a scale from 1 to 100 with 1 being ”The worst health you can imagine” and 100 being “The best health you can imagine”.

The Forgotten Joint Score

The Forgotten Joint Score (FJS) is a 12-item joint specific questionnaire developed in 2012 by Behrend et al. and was later on translated and validated in Danish (54, 55). A total score of 0-100 is calculated. High scores indicate high degree of “forgetting” the artificial joint. The

FJS is an efficient tool for evaluation of small differences in knee performance after surgery. The MIC value for improvement in the FJS is 14 (50).
Responses are scored between 0 and 4 (never = 0, almost never = 1, seldom = 2, sometimes = 3, mostly 4). Answers “not relevant for me” are treated as a missing value. To calculate the total score, all responses are summed and divided by the number of completed items. This value is multiplied by 25 and substracted from 100. The questionnaire is discarded if more than four items are left unanswered or answered with “not relevant for me”.

Copenhagen Knee ROM

Copenhagen Knee ROM Scale was developed and validated in 2018 for patients to self-estimate passive range of motion (ROM) of their knee after a knee arthroplasty (56). The patients reported ROM from the 2-item scale with 11 illustrations of knee motion. The ability of flexion is selected from picture 0 to 6, where 0=impossible to flex the knee 60° or less and 6=135° flexion or more. Extension ability is selected from 5 pictures, where 0 represents 45° or less and 5 represents -15° or more. We considered the flexion pictures 0-4 to represent estimations of flexion deficits (<60°-105°) and the extension pictures 0-3 to represent extension deficits (<45°-15°).

Pain, satisfaction and reason for revision

In addition to the standardized questionnaires mentioned above, we asked additional questions about pain and satisfaction, which were originally developed for knee arthroplasty patients treated at Hvidovre Hospital.

Pain

- “What was your average pain level the last month on a 0-100 scale”
  (0= no pain; 100= worst pain imaginable).

Satisfaction

- “How satisfied are you with the result of the surgery on a 0-100 scale”
  (0= very satisfied; 100= not satisfied).

- “How are your knee problems now compared to prior to your operation?
  (Better, an important improvement/ Somewhat better, but enough to be an important improvement/ Very small change, not enough to be an important improvement/ About the same/ Very small change, not enough to be an important improvement/ Somewhat worse, but enough to be an important deterioration/ Worse, an important deterioration).

- “Do you find your present situation acceptable considering your daily level of function?”

- “Do you think the treatment has failed?”
  (Only asked to patients, who answered “no” to the previous question4).

- “Would you go through the surgery again?”

Statistics

Descriptive statistics were presented with means and standard deviations (SD) for normally distributed continuous variables and median and interquartile range (IQR) for non-normally distributed continuous variables. Distributions were inspected for normality via QQ-plots. Frequency counts and percentages were provided for categorical variables. Pearson’s Chi-square test was used to test for statistical differences between categorical measures. Wilcoxon Rank Sum test was used to test non-normally distributed continuous variables for statistical differences.
Study 1: The Cohen’s kappa was calculated to evaluate the intraobserver agreement and radiographs measurements from double examination of 20 randomly selected radiographs included in the study (57). A value of 0.81-1 indicated almost perfect correlation and a value of 0 indicated no agreement. The intra-observer level of agreement for the radiographic examinations was high, with Cohen’s kappa of 0.95.
Study 2: We performed a survival analysis calculated by the Cox proportional hazards regression model to estimate the effect of the exposure “indication”, and estimates were presented as hazard ratios. Following covariates were included in the model: sex, age groups, Charlson Comorbidity Index, and surgical subgroups. Kaplan-Meier curves presented the survival of revision knee arthroplasties for the two indications of investigation.
Study 3: A multivariable logistic regression was performed to estimate the effect of proposed predictors for new long-term opioid use given as odds ratios.
Study 4: Missing data of PROMs were handled according to the recommendations from the developers of the individual PROMs (49, 52, 54).

Statistical significance was set at the 5% level. For all analyses, we used Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.

Ethical considerations

All the studies were approved by the Danish Data Protection Agency (Journal no. 19/14416 and 19/45734).
Approval to access medical records and radiographs for study 1 was obtained from the Danish Patients Safety Authority (Journal no. 31-1521-249).
Permission to contact patients for the inclusion in study 4 was obtained by gathering consent from Head of Departments from the respective departments performing the revisions (cf. BEK no. 585 “Bekendtgørelse om indberetning til godkendte kliniske kvalitetsdatabaser og videregivelse af data til Sundhedsdatastyrelsen”.
Approval Ethical approval was not needed, as the studies were non-interventional.
The studies were conducted in accordance with the Declaration of Helsinki.
The PhD student and co-authors had no conflicts of interest to declare regarding this project.

Results

For all of the four studies, the inclusion of patients, flowcharts and demographic data as well as tables and figures, which are referred to in the results below, are presented in detail in the specific papers (Paper I-IV, page 55).

Study 1

Hidden indications

103 (99%) of 104 patients were revised because of “pain without loosening”, and 1 patient was revised because of “aseptic loosening”. We found an additional indication in 44 (42%) of the cases.

Table 1. Hidden indications assessed from medical charts, radiographs, and CT scans.

Hidden indication	Total N=44 (42%)	TKA n=27 (26%)	mUKA n=14 (13%)	Hemicap n=3 (1%)
Stiffness	**13**	12	1	
Patella maltracking	**13**	12	1	
Malposition of components (assessed from radiographs)	**6**		6	
Dislocated bearing	**1**		1	
Instability (medial ligaments)	**3**	2	1	
Progression of arthrosis	**6**		3	3
Aseptic loosening	**1**	1		
Residual cement	**1**		1	

TKA=Total Knee Arthroplasty; mUKA=medial Unicompartmental Knee Arthroplasty.

Kellgren-Lawrence grades prior to primary surgery

The Kellgren-Lawrence arthrosis grades prior to primary knee arthroplasty were 1-2 in 31% of the patients and 3-4 in 69% of the patients.

Radiographic assessment

The components were in general not considerably displaced. All measurement are presented in the Appendix of paper I (Page 55).

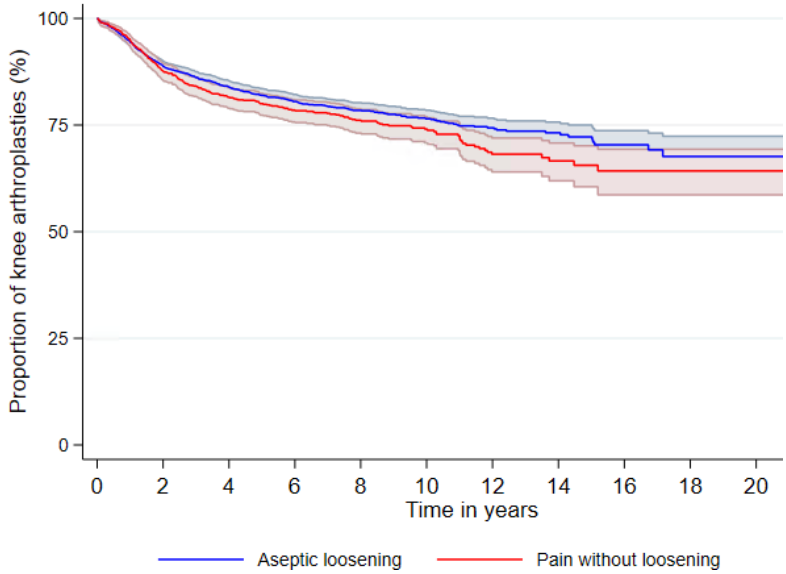
Study 2

The inclusion of patients, flowchart and demographic data are presented in the paper as well as tables and figures, which are referred to in the results below (Paper II, page 74).

Survival over a 20-year time-period

The overall frequency of re-revisions after 20 years was 23% (95% CI (20-25)) for “pain without loosening” and 19% (95% CI (18-21)) for “aseptic loosening”. The confidence intervals were overlapping at any time-point in the study period.

Figure 6. Kaplan-Meier survival curves for the indications “pain without loosening” and “aseptic loosening” presenting the survival of revisions over a 20-year period (The figure is published in paper II(58)).



A similar analysis of cumulated frequencies over the 20-year study period compared the two indications of investigation at surgical subgroup level. There were no differences between groups.

We performed a Cox regression adjusting for the covariates sex, age group, CCI and surgical subgroup. The adjusted hazard ratio (HR) for risk of re-revision for “pain without loosening” vs “aseptic loosening” were 1.03 (95% CI 0.87-1.2)), p=0.7. Male sex, age<60 years and surgical subgroup 2 (partial revision) increased the risk of re-revision.

Survival over two time-periods, 1997-2009 and 2010-2018

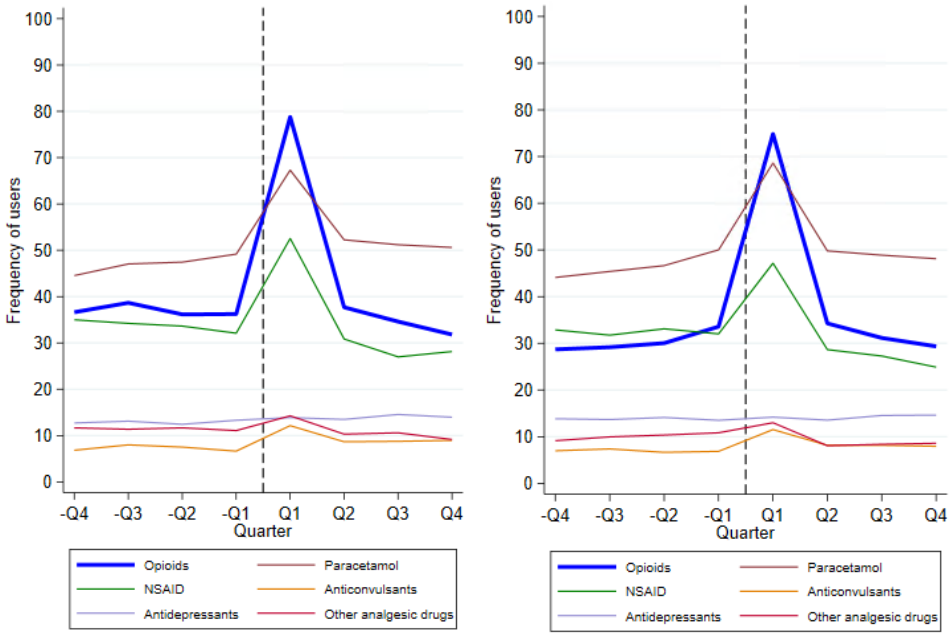
We analyzed the frequency of re-revision over the two time-periods 1997-2009 and 2010-2018. Revisions for both indications showed improved revision rates in the later time-period, though the differences were not significant in the Cox regression.

Study 3

Use of analgesics one year before and after revision

We investigated the use of analgesics in the four quarters before and after revision. The frequencies of opioid users in –Q4 versus Q4 for patients revised for "pain without loosening" were 37% versus 32%, p=0.021. There was no change for patients revised for "aseptic loosening". The use of NSAID lowered significantly for both indications from –Q4 to Q4. We did not find any changes in the use of other drugs or within the surgical subgroups.

Figure 7.A and 7.B. Users of all drugs presented as frequencies of patients revised for the indication "pain without loosening" (n=1,037) and "aseptic loosening" (n=2,317) (The figures are published in paper III (59)).



Development in long-term users of opioids
18% of the patients revised for “pain without loosening” were long-term users of opioids before revision versus 22% afterwards, p=0.029. Corresponding frequencies for patients revised for “aseptic loosening” were 18% and 21%, p=0.003. The amount of new long-term users of opioids were 9% for “pain without loosening” and 8% for aseptic loosening.

Predictors of new long-term opioid use
We investigated possible predictors for becoming a new long-term opioid user after revision. CCI≥3, other opioid-requiring diagnoses or procedures within the first postoperative year and preoperative long-term use of NSAID or other analgesics predicted new long-term opioid use.

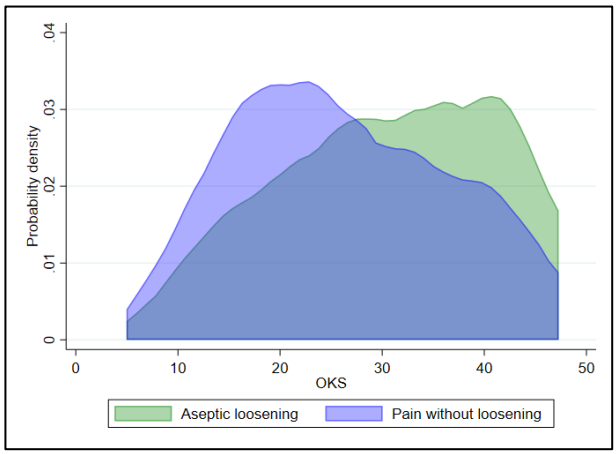
Study 4

Due to a reviewer request in the publication process, the publication only contain analyses of surgical subgroup 1 and 2 (TKA-TKA and partial revision). This results section also includes surgical subgroup 4 and 5 (UKA-TKA and secondary patella button for pain revisions). The results of this study with all subgroups included (1, 2, 4, and 5) are presented in Appendix I (Appendix I, page 100).

The total response rate in questionnaires was 69%. 66% and 70% for revisions for “pain without loosening” versus “aseptic loosening” respectively.

Patient-Reported Outcome Measures
The scores for the OKS, EQ-5D-5L Index, EQ VAS and Copenhagen Knee ROM were significantly lower for patients revised for the indication “pain without loosening” than “aseptic loosening”. Median OKS was 26 (IQR 17) versus 31 (IQR 16) 1-3 years after revisions for “pain without loosening” versus “aseptic loosening”, p=0.001. Median EQ-5D-5L was 0.7 (IQR 0.4) versus 0.8 (IQR 0.3) for “pain without loosening” versus “aseptic loosening”, p<0.001. Median FJS was 48 (IQR 9) versus 50 (IQR 15) for “pain without loosening” versus “aseptic loosening”, p=0.406 (Appendix I, Table 3, page 100).
We found no differences within the two indication groups in the sensitivity analyses comparing the same scores 1-2 years after revision vs 3-<4 years after revision.

Figure 8. OKS for the indications of revision "pain without loosening" and "aseptic loosening" presented as kernel curves.



Pain

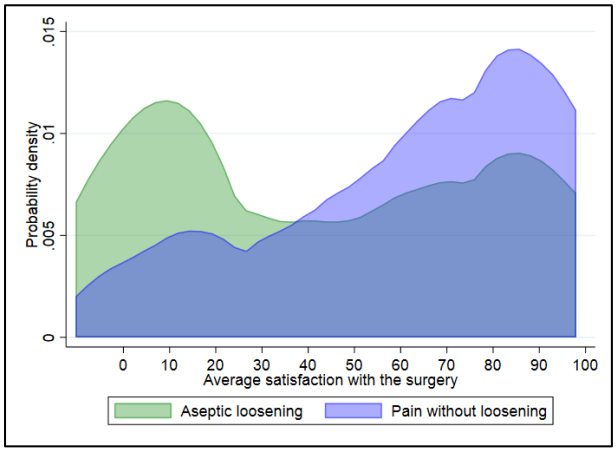
The median pain score was 62 (IQR 48) for "pain without loosening" and 40 (IQR 55) for "aseptic loosening", p=0.001, on a scale from 0 to 100, with 100 representing the worst pain imaginable (Appendix I, Table 4, page 101).

Satisfaction

The median score for satisfaction with the result of the surgery was 72 (IQR 39) for "pain without loosening" and 50 (IQR 73) for "aseptic loosening", p<0.001, on a scale from 0 to 100 (0=very satisfied and 100=not satisfied) (Appendix I, Table 4, page 101).

A smaller proportion of patients revised for "pain without loosening" considered their knee problem importantly improved after revision than patients revised for "aseptic loosening", 65% versus 78%, p=0.042.

Figure 9. Average level of satisfaction with the surgery (0=very satisfied; 100=not satisfied) presented as kernel curves of revisions for "pain without loosening" and "aseptic loosening".



Discussion

Indications

The indications for revision in the DKR have never previously been validated. Nor have they been validated in any other knee arthroplasty register or in corresponding registers of other arthroplasty areas such as hip and shoulder. This makes further investigations warranted, and not only for “pain without loosening”, but also for other indications as well. Thus the validation of the pain indication in this thesis is highly relevant. We compare “pain without loosening” to “aseptic loosening”, because “aseptic loosening” is better understood and more acknowledged as an indication, whereas “pain without loosening” is controversial (18, 19). It must be taken into consideration that “aseptic loosening” has not been validated as well, and it is unknown what it actually covers.

When peroperative data are reported to the DKR, the surgeon can chose an unlimited number of indication options simultaneously. Though several indications can be selected because they were present peroperative in combination, it makes further analysis less consistent and more difficult to interpret. We chose to analyse revisions with only one indication recorded, to avoid the influence of other revision causes. The Australian Orthopaedic Association developed the Australian Hierarchy of indications for revision in 2009 (Appendix II) (60). If more than one indication for revision of a knee arthroplasty is present, the highest-ranking indication represent the dominant problem. Pain is inferior to all other indications of revision in this hierarchy. Thus, it should be investigated on its own to exclude influence from other indications on the outcome variables of investigation. The same is applicant for “aseptic loosening”, though this indication ranks considerably higher. We used this hierarchy, because it seemed appropriate. The low ranking of pain as an indication for revision supports the general belief that it is an indication of exclusion. Potential analytic conflicts may arise from the possibility of choosing more than one indication for revision. Nevertheless, it is a strength of the register to have this option, because it provides the possibility for the surgeon to report the correct indications, in cases where several indications were in fact present peroperative. The Australian Hierarchy or other relevant hierarchies of indications can be used for analytic purposes in order to avoid exclusion of revisions with more than one indication.

Hidden indications

We found several hidden indications in the validation study of “pain without loosening” (Paper I, page 55). 42% of the revisions registered in the DKR for the indication “pain without loosening” alone had additional indications recorded in the medical charts. Most

dominant were stiffness and malposition of components including malrotation. The evidence for these indications are discussed in the paper (Paper I, page 55). The definitions of these indications are lacking and the diagnostic measures and thresholds of measurements are inconsistent. In many of the cases, the reviewers of medical charts and radiographs were unable to recover the hidden indications established by the surgeons. Especially regarding the cases of stiffness and malrotation. However, the reviewers did not have the opportunity to perform clinical examinations, which are very important to the overall picture. Even when the reviewers did not recover the hidden indications in some of the cases, the hidden indications were still assessed as important problems for the patients. The problems were considered important enough to justify revisions by the respective surgeons.
We found several cases of malrotation of components resulting in patella malalignment. This is a well known association, that can be properly handled with a revision (61). CT scans are the appropriate investigation to verify malrotation. However, there are various ways to perform measurements for malrotation on CT scans and they are difficult to perform, which results in varying inter-observer variability (62). We found cases of suggested malrotation, in which there were no patella malalignment and where the reviewers could not recover the malrotation from CT scans. It is unclear if a mechanical problematic were present for these revisions in addition to the pain indication. The use of CT scans varied across the different centers. Some centers CT scanned the majority of their patients and some used it sparsely. We are not familiar with the cause of this difference. Possibly, the protocols for investigations of patients were varying among centers, or some centers registered revisions for malrotation under another indication such as “Other”, or did not perform this type of revisions at all. Guidelines for the assessment of malrotation are warranted to improve the identification of this type of malposition and streamline the indication for revision on a nationwide basis. No clear-cut definition of malrotation is present at this time point (Paper I, page 55) (63). Likewise, a threshold for stiffness is desirable.

Timing of primary knee arthroplasty – arthrosis grade and age

We found that patients revised for “pain without loosening” were younger than the average knee arthrosis patients at the time of primary arthroplasty. The mean age at primary knee arthroplasty was 60 years (Paper II, page 74). The mean age at primary knee arthroplasty for Danish patients is 68, which is considerably higher (1). We also found a large proportion of pain patients with low arthrosis grades at the time of primary knee arthroplasty (Paper I, page 55). 31% had a Kellgren-Lawrence arthrosis grade of 1 or 2. A systematic review confirmed that the severity of arthrosis grade and satisfaction after TKA was correlated and Kellgren-Lawrence grades of 3 to 4 should be present when a TKA was performed (64). A Finnish study from 2021 found patients with low Kellgren-Lawrence grades of 1-2 to be less

satisfied (28.6%) after TKA than patients with high Kellgren-Lawrence scores of 3-4 (8.7%) (65). They also found increased risk of persistent pain after primary TKA when Kellgren-Lawrence grades were low (65). The lower age and lower Kellgren-Lawrence grades of pain patients in our studies are probably not a coincidence. Possibly, some of the patients had received their knee arthroplasty at a too early stage of their arthrosis development, where it was not the appropriate treatment and a conservative treatment strategy would have been more appropriate. At least some portion of their pain might have emanated from other structures of the knee, which was not cured by the insertion of a prosthesis. If this was the case, a revision performed because of unexplained pain might be equally ineffective.

Risk of re-revision

Revisions for the indication “pain without loosening” performed similar to revisions for “aseptic loosening” regarding prosthesis survival. The re-revision risks were 23% (20-25) for “pain without loosening” and 19% (18-21) for “aseptic loosening” over a 20-year period. An improvement in re-revision risk over 8 years from 22% to 18% for “pain without loosening” and 22% to 14% for “aseptic loosening” was found.

Re-revisions risks have been estimated by other register studies. Yapp et al. reported a 20-year re-revision risk of 15.5% for aseptic re-revisions reported to the Scottish Arthroplasty Project Dataset from 1998-2019 (13). Belt et al. found an 8-year re-revision risk of 19% of revisions performed for any indication in a study based on data from the Dutch Arthroplasty Register from 2010-2018 (66). Meyer et al. found an 8-year re-revision risk of 16.6% for aseptic revisions based on data from the New Zealand Joint Registry from 2003-2016. These re-revision risks are consistent with the findings of Study 2, and the risk of re-revision in Denmark does not seem to be elevated compared to those of other countries. However, the risk of re-revision is considerably elevated compared to the risk of revision after primary surgery. The 10 year risk of revision of primary knee arthroplasty is 7% reported by the DKR (1).

The improvement in re-revision risk over time is very encouraging. This can probably be attributed to the improvements in knee arthroplasty surgery in general. The decline in re-revisions in the later period (2010-2018) was only significant for “aseptic loosening”, which supports the assumption, that this is a more appropriate indication for revision than pain. If the problem of pain was not mainly related to the prosthesis, improvements in knee surgery will not be sufficient in helping these patients.

Analgesics

The amount of opioid users in the first quarter of the year up to revision (-Q4) was high for both indications; 37% for “pain without loosening” and 29% for “aseptic loosening”. The use of opioids in –Q4 was considerably higher for the patients included in Study 3, than the use in the Danish population in general. The estimated number of Danish citizens with chronic non-malignant pain is 20% (67). Of these, 12% report a use of opioids to some extent. This discrepancy indicates a causal link between increased pain levels for these knee patients compared to the general population and a need for analgesic treatment and ultimately revision. We cannot however, confirm this association with the register data available for this thesis. If revisions performed because of pain were effect full, the level of pain should decrease afterwards and result in decreased levels of opioid use, possibly resembling the use of the average population. However, this did not happen. The opioid use had fallen to 32% for pain patients in the fourth postoperative quarter. This proportion of users was still way above the proportion of users in the general population and the decline of 5% is of questionable clinical relevance. The use of opioids for patients revised because of “aseptic loosening” did not change.

Long-term opioid use can be defined in various ways as discussed in the introduction of Study 3 (Paper III, page 80). We defined long-term opioid use as a consecutive use of opioids in four quarters, because this time frame was clinically meaningful. A patient has reached the final result after surgery 1 year postoperatively, and residual postoperative pain is very unlikely to be present after a year. If the patient still experiences knee pain 1 year after revision, this pain might be persistent and could potentially be the cause of long-term opioid use. 3-5% of Danish citizens have a long-term opioid use (67, 68). We found 22% and 21% long-term opioid users after a year in patients revised for “pain without loosening” and “aseptic loosening” respectively. These proportions are very high compared to those of the average population. Other studies have investigated long-term opioid use after major surgery. In a study of 892 patients undergoing adult spinal deformity surgery, about 30% of the patients were long-term opioid users postoperatively (69). The proportion of long-term users only decreased 2% after surgery. A study regarding 19,251 hip and knee arthroplasty patients from New Zeeland found 31% of patients with a preoperative use of opioids to be long-term opioid users postoperatively (70). A large Canadian study from 2022 of 49,638 primary hip and 85,558 primary knee arthroplasty patients found 24% and 29% of patients to be opioid users 1 year after surgery respectively. Because definitions of long-term users vary across different studies, direct comparisons are inaccurate. However, it is clear that proportions of long-term opioid users of various definitions are excessive after major surgery. Knee arthroplasty revisions for unexplained pain does not differ from other

categories in any particular way. It is therefore obvious, that patients revised for unexplained knee pain are of equally elevated risk of being long-term opioid users after surgery than patients undergoing major surgery for other reasons.

Patient-Reported Outcomes Measures

PROMs and Satisfaction

Patients revised for “pain without loosening” had lower scores than patients revised for “aseptic loosening” on the included PROMs in Study 4. PROMs have been investigated sparsely for revision patients, and we only found one study considering the specific indications of investigation in this thesis. This study investigated PROMs on a cohort of 996 revision patients from 2008 to 2010 recorded by the National Joint Registry for England and Wales (17). Mean post-revision OKS was 26.4 for unexplained pain and 27.8 for aseptic loosening/lysis, with no significant difference between groups. The finding of lower PROM scores for pain patients were in line with those of our study, though we found a significant difference between groups. The discussion of included PROMs is further elaborated in Paper IV (Paper IV, page 91).

Satisfaction rates were also lower for patients revised for “pain without loosening” than “aseptic loosening”, which is consistent with the findings of other studies (Paper IV, page 91) (17, 71). On the 0-100 scale (0= very satisfied; 100= not satisfied) of “how satisfied are you with the result of the surgery” the pain patients reported a median of 72, meaning the vast majority of the patients were poorly satisfied with the treatment. 65% of the pain patients considered the result an important improvement. These poor outcomes on questions of satisfaction is consistent with the low PROM-scores. Overall, these results are not satisfactory. Some carefully selected patients might benefit from revisions because of unexplained pain, but overall the patient-reported outcomes from the patients revised due to pain are unacceptably low.

Strengths

This thesis explores an area of research that is not well investigated, but still highly relevant. A broad spectrum of research considering knee arthroplasty revisions are existing, but focus on indications and unexplained pain in particular is lacking. Thus, the results from the thesis are new and important.

Nationwide registers forms the solid basis of this thesis. The DKR is a valuable tool for the assessment of quality of knee arthroplasty surgery and for research purposes. The possibility to combine data with other nationwide databases via the patients’ social security numbers is a great strength of Danish registers. The DNPR has a completeness of almost

100%. This linked system gives access to a broad variety of data with a very high completeness. In study 2, we get a follow-up of 100% on re-revisions, because of the completeness of the LPR. These resources ensures that studies based on the nationwide registers are of very high quality.
Specific strengths of the studies included are listed in each individual paper (Papers, page 55).

Limitations

There are limitations to the studies of this thesis as well. The completeness of data in the DKR are varying, but well above 90% at most time points. As these data forms the basis of all four studies, we cannot account for the missing registrations of index revision procedures to the DKR. This can possibly screw data, but we do not expect this to happen, as the level of completeness is adequate for research purposes. The DKR aims to contain a 90% completeness.
The lack of validated indications limits the interpretation of the results. We have no knowledge of studies validation the indications for revision. Therefore, we chose the best option for comparison, which was “aseptic loosening”. It is possible that both groups of investigation consists of mixed indications. However, we believe the surgeons reporting to the register have a certain understanding of indications and that registrations are overall valid. As we can see in Study 1, the pain indication does indeed represent pain revisions, though other indications were present too in some cases. To avoid this possible bias, all cases included in 2-4 could have been investigated as in study 1. This would however, be a comprehensive task, and undermine the research qualities of the DKR itself. Further, this strategy would exclude all the revisions performed in the earlier time-period, as proper access to medical records and diagnostic imaging is not available.

Incorrect reporting of indications to the DKR limitation

We identified two combinations of indications/subgroups we considered misclassified in the register, as they were not meaningful. We observed 64 revisions for “pain without loosening” and “aseptic loosening” in combination. Though patients revised for “aseptic loosening” often experience pain, it is not possible for the prosthesis to be loose and not loose at the same time. Even if only one of the components were loose, the indication “aseptic loosening” should be used. As we do not know which indication was the true indication for revision of these patients, we excluded them from all analyses.
We identified 128 revisions for “aseptic loosening”, who were classified as surgical subgroup 5; Secondary patella button. No exchange of components were recorded for these patients. Insertion of a secondary patella button will not solve the issue of a loose prosthesis. Either

the exchange of components was incorrectly reported to the DKR or the wrong indication was chosen. As we could not identify and correct the error with any of the data available for the studies in this thesis, these patients were excluded from all analyses.

Specific limitations of the studies included are listed in each individual paper (Papers, page 55).

Perspectives

DKR

The DKR is a highly resourceful database, but continues improvements to the database is mandatory for the database to remain its high standards on an international level.
Based on the work of this thesis, we suggest two specific improvements;

1. **Adding stiffness and malposition of components as indication options**
   We found several hidden indications in addition to the indication "pain without loosening" in study 1 (Paper I, page 55). Stiffness and malposition of components were widely used. Patella maltracking was also a frequently used hidden indication. It was often present because of malrotation of components, which sorts under malposition. We therefore suggest, that the indications stiffness and malposition of components are added as indication options for revision in the DKR. The expansion of indication options will improve the precision of future research regarding revisions for individual indications. This will ease the process of finding specific groups of patients, conduct studies regarding these, and to monitor the overall quality of revision knee arthroplasty surgery on a more detailed level. Furthermore, the indications stiffness and malposition of components are present in several other nationwide registries, thus collaborative research possibilities will be improved as well (Appendix II).
2. **Inclusion of pre- and postoperative PROMs**
   PROMs are essential to evaluate the performance of knee arthroplasties – both for primary and revision knees. Individual Danish departments have their own collection of pre- and postoperative PROMs with variations in type of PROMs and completeness. Incorporating PROMs directly in the DKR will straighten the value of PROMs used and improve the completeness of data collection because it will be mandatory. Furthermore, the data will be nationwide, which is a great strength for future studies.

Pain revisions in the future

This thesis investigates pain as indication for revision of knee arthroplasties. Though it does not cover all imaginable aspects concerning these revisions, it does form a coherent picture;

- The indication covers other hidden indications, some of which are also controversial.
- The revisions perform as well as other revisions considering re-revision risk.
- The analgesic consumption does not decrease considerably after revision and a lot of new long-term opioid users are generated.
- Many patients are not satisfied after the revision.

Consequently, the revisions for unexplained pain are probably not more risky than revisions for other indications, but it seems that the patients does not improve enough. Their analgesic consumption remain high and their satisfaction low. These important parameters should reverse if the revisions were truly beneficial.

We cannot determine which of the pain revisions were beneficial for the patients. The evidence from this thesis is valuable for surgeons in the decision process of the treatment of a patient with unexplained pain. The choice of surgery will still be a decision made by the individual surgeon and patient together. However, the surgeon should carefully be aware of other options than revision and in the majority of cases chose a conservative treatment strategy.

Many of the patients revised for “aseptic loosening” also experienced some level of pain, but, they also had a mechanical problem, which hopefully have been solved. On the one hand, patients revised for “aseptic loosening” have a mechanical problem of a loose prosthesis, which can be solved with a revision, as the results of this thesis also implies. On the other hand, the patient is applied the risks of a major surgery, which may or may not result in persistent pain afterwards. The choice of revision for either indication is therefore a balancing of pros and cons, which the surgeon and the patient must make.

Conclusion

Study 1

The indication “pain without loosening” covered patients revised because of pain, but other hidden indications were present. Stiffness and malposition of components were hidden indications and lack as indication option in the DKR and other registers.
The relative high frequency of low arthrosis grade (Kellgren-Lawrence 1-2) prior to primary knee arthroplasty may explain the need for revision of a painful knee in cases without any other pathology present.

Study 2

We found similar risk of re-revision for patients having a knee arthroplasty revision for the indication of “pain without loosening” compared with that of “aseptic loosening.” We also did not find any differences at surgical subgroup level. However, we found a small improvement of prosthesis survival rates after revisions for both indications from 1997–2009 to 2010–2018, which we interpret as an improvement in the performance of revision knee arthroplasties.

Study 3

The consumption of opioids decreased slightly after knee arthroplasty revision for the indication “pain without loosening”, but not for “aseptic loosening”. The amount of new long-term opioid users increased for both indications.

Study 4

Patients undergoing revision for the indication of unexplained pain had worse results on PROMs than those revised for aseptic loosening. Likewise, patients revised for unexplained pain were less satisfied compared to patients revised for aseptic loosening. This information is valuable to both surgeons and patients when candidates for revision surgery are selected, in order to obtain the best possible outcomes.

Conclusion of the thesis

The indication “pain without loosening” in the DKR identifies pain revisions, but a broad variety of other underlying indications were present as well. Stiffness and malposition of components lack as indication options in the DKR, and implementation of these indications

would strengthen the register. Further, the register data would improve if pre- and postoperative PROMs were captured routinely.

Patients revised for “pain without loosening” have similar risks regarding survival and use of analgesics as patients revised for “aseptic loosening”. A large proportion of long-term opioid users were generated after revision for both indications. The pain patients scored worse on PROMs and were less satisfied after revision than patients revised for “aseptic loosening”. Therefore, revising for the indication “pain without loosening” should be carefully considered, and in most cases avoided, when no obvious knee pathology is present.

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Paper I

Validation of the indication "pain without loosening" for revision of knee arthroplasties in the Danish Knee Arthroplasty Register.

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Abstract

Background and purpose

13% of revisions of knee arthroplasties registered in the Danish Knee Arthroplasty Register (DKR) are for the indication "pain without loosening". We aimed to investigate "pain without loosening" as indication for revision knee arthroplasties, and screen for other possible indications hidden in this category in order to improve future registration and data quality.

Materials and methods

We included 104 patients undergoing first-time revision knee arthroplasty for the indication "pain without loosening" from January 1, 2016 to December 31, 2018 at five Danish centers. Medical records and radiographs were reviewed for all patients and CT scans for those available.

Results

The primary knee's were 68 total knee arthroplasty's (TKA), 28 medial unicompartmental knee arthroplasty's (mUKA), 3 patellofemoral prostheses and 5 hemicaps. The Kellgren-Lawrence arthrosis grades prior to primary knee arthroplasty were 1-2 (31%) and 3-4 (69%). In 103 of 104 (99%) cases we could confirm "pain without loosening" as indication for revision. We found other hidden indications in 44 (42%) cases; malposition of components (n=19), stiffness (n=13), progression of arthrosis (n=6), instability (n=3), liner dislocation (n=1), residual cement (n=1) and aseptic loosening (n=1).

Interpretation

The indication "pain without loosening" covered patients revised because of pain, but other hidden indications were present. Stiffness and malposition of components were hidden indications and lack as indication option in the DKR and other registers.

The relative high frequency of arthrosis grade 1-2 prior to primary knee arthroplasty is concerning and may explain the need for revision of a painful knee in cases without any other pathology present.

Introduction

Nationwide arthroplasty registers provide valuable information enabling high quality research. The quality is dependent on the validity of the register in terms of coverage, completeness and accuracy of variables (1). Several countries have well established knee arthroplasty registers (2-6). The validity of the Danish Knee Arthroplasty Register (DKR) is high, but some variables needs further examination such as the indications for revisions (7). To our knowledge, indications for revisions have not been validated in any national register.

Revision of knee arthroplasties because of pain with no obvious knee pathology present is generally not recommended and may not result in pain relief (8-10). Nevertheless, pain revisions are still performed, as the registers confirm. The indication is controversial and not existing in all nationwide registers. It is existing as indication in knee arthroplasty registers from Denmark, Norway, Australia, UK and Finland, but not in registers from Sweden and the Netherlands (2-6, 11, 12). Pain revisions account for 13% of all revisions in Denmark and 22% in Norway, 11% in Australia, 10% in UK and 10% in Finland (2-4, 11, 13). The assortment of indications for revisions in the registers varies considerably. E.g., the register from Finland has 6 indications and the register from the Netherlands has 14 indications (3, 6). The variation generates the question of how well the indications in the registers show the true reasons for revision. Though "other" is present in most registers to assemble unlisted indications, "pain" might also be used as the best fit when available. It is uncertain if the indication "pain without loosening" covers other unknown indications. Therefore, the aim of this study was to investigate the indication "pain without loosening" in the DKR, and screen for other possible indications hidden in this category in order to improve future registration and data quality.

Methods

This is a validation study of prospectively collected data from the DKR, medical records and radiographs. The guidelines from Benchimol et al. for validation of health administrative data were followed (14).

Patients and data sources

We identified patients undergoing first-time knee arthroplasty revision for the indication "pain without loosening" in the time period January 1, 2016 to December 31, 2018 at five centers from the DKR. The DKR is a clinical quality control database that prospectively collects data on all primary and revision knee arthroplasties performed in Denmark since 1997. The completeness of the register for the included centers in the study period was 92% for revision arthroplasties and >99% for primary arthroplasties (2).

We defined surgical subgroups by the type of prosthesis removed and type of prosthesis inserted at the revision (Figure 1). Subgroup 1 (Total Knee Arthroplasty (TKA)-TKA), subgroup 2 (Liner exchange), subgroup 3 (Unicompartmental Knee Arthroplasty (UKA)-TKA), subgroup 4 (Secondary patella button) and subgroup 5 (Hemicap).

Data collection

A single observer (KBA) reviewed medical charts. Study data were collected and managed using REDCap electronic data capture tools hosted at Odense Explorative Patient data Network (OPEN) (15, 16). Data on following variables were collected; indication for revision, the surgeons description of radiographs and computed tomography (CT) scans, age, sex, previous knee surgeries, type of arthrosis (primary/secondary), American Society of Anesthesiologists (ASA) score, medically treated psychiatric disorder at the time of revision, other treatment strategy prior to revision; cast, physiotherapy, weight loss, analgesics, manipulation under anesthesia, steroid injection and other.

Radiographic evaluation

Radiographs prior to revision were available for all included patients and prior to primary arthroplasty for 79% of the patients. A single observer reviewed all radiographs (KBA). In cases of doubt, a second observer (MLL) also assessed the radiographs. The pre-revision computed tomography (CT) scans were reviewed by two observers (KBA and MLL) when available (28% of cases). Radiographic evaluation of TKA followed the criteria from Gromov et al. (17). If the component placement deviated from the recommended criteria, it

was registered as deviating from optimal placement. The criteria were as follows; placement and size of femoral component relative to coronal angle 2°-8° valgus, flexion/extension angle 0°-3° flexion, overhang less than 3mm, posterior fit <2mm; placement and size of tibial component relative to coronal angle should strive neutral alignment (90°), 0°-7° posterior slope. Tibial overhang in mm was estimated. No clear cut-off points for overhang exists, but >3mm overhang was considered excessive (18, 19). Rotation of femoral components were assessed from CT scans by the surgical transepicondylar axis (sTEA) method. This method estimated the angle between the line from the medial femoral sulcus to the lateral femoral epicondyle and the component posterior condylar line. The femoral component should be placed in 2°-5° of external rotation. Tibial tubercle axis (TTA); 18° of internal tibial implant rotation in relation to the tibial tuberosity was considered neutral. The tibial component should be placed in <10° of internal rotation and <5° external rotation.

Radiographic evaluation of medial UKA followed the criteria used by Hurst et al. and were as follows (20); position and size of the femoral component relative to the femur with varus/valgus angle -10°-10°, medial/lateral placement central and posterior fit <4 mm overhang; position and size of the tibial component relative to the tibia with varus/valgus angle -5°-5°, a posterior slope of 7° (+/-5°), medial and posterior fit flush or with ≤2mm overhang, anterior fit flush or <5mm short, lateral fit flush with no gap; the x-ray marker central and parallel central to the tibial component; depth of tibial saw cuts appropriate with minimal ingress of cement; no subsidence.

Position of patellofemoral prostheses were evaluated according to recommendation from Lustig et al. (21). Affected compartments and arthrosis grade of the worst affected compartment were estimated by Kellgren-Lawrence classification on radiographs prior to the primary procedure and in lateral compartments of knees with a medial UKA prior to revision (22).

The intra-observer level of agreement for the radiographic examinations was high with Cohen's kappa of 0.95. The Cohen's kappa was estimated from double examination of 20 randomly selected radiographs included in the study.

Statistics

Categorical data were presented as counts and proportions. Continuous data were inspected for normal distribution with Q-Q plots and presented with median and range or mean and 95% confidence interval. Statistical significance was set at the 5% level. For all analyses, we used Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Danish Data Protection Agency (Journal no. 19/14416). Approval to access medical records and radiographs were obtained from the Danish Patient Safety Authority (Journal no. 31-1521-249). The authors had no conflicts of interest to declare.

Results

104 patients were included in the study (Figure 1). The primary arthroplasties were 68 TKA, 28 medial UKA (mUKA), 3 patellofemoral prostheses and 5 hemicaps. Table 1 presents patient characteristics obtained from medical charts.

103 (99%) of 104 patients were revised because of "pain without loosening", and 1 patient was revised because of "aseptic loosening". The observers found an additional indication in 44 (42%) of the cases (Table 2). The majority of the additional indications were stiffness (n=13), patella maltracking (n=13) and malposition of components (n=6). All arthroplasties revised for malposition of components were UKA's. The majority of revisions for patella maltracking were TKA-revisions. In 5 (38%) of these cases, malrotation of the components was found. The remaining 8 cases were not CT scanned. The surgeons found malrotation in 14 cases of which we could not recover deviations from standard recommendations.

The extension deficit of patients revised because of stiffness was 16° (95% CI 9-22) and flexion ability was 92° (95% CI 81-103).

All radiographic measurements of TKA's and UKA's prior to revision were presented in Appendix A and B. Deviations from optimal component placement were present in 62% of all the cases, in 47% of cases revised for pain without other hidden indications and in 68% of cases where another indication was present.

The distribution of Kellgren-Lawrence arthrosis grade up to the primary knee arthroplasty were grade 1 (4%), grade 2 (27%), grade 3 (49%) and grade 4 (20%). The distribution of Kellgren-Lawrence grades and the presence of hidden indications are presented in Table 3.

Figure 2-5 showed histograms of some of the most important measurements. Table 4 presents the presence of radiographic deviations in groups with the presence or non-presence of other indications.

Discussion

This validation study of the indication "pain without loosening" as indication for revision of knee arthroplasties included 104 patients. 103 of 104 patients underwent revision because of "pain without loosening", but we found valid hidden indications in 44 (42%) of the cases. The majority of the hidden indications were stiffness and malposition of components in addition to pain.

Hidden indications

Our study demonstrated the presence of hidden indications in addition to the registered indication "pain without loosening" in the DKR. Some of the additional indications already existed in the DKR (instability, progression of arthrosis, aseptic loosening).

13% of the revisions in our study were performed because of stiffness in addition to pain. Stiffness is a controversial indication, but not infrequently used. It does not exist in the DKR, but it is seen in other national arthroplasty registers (6, 12). Stiffness after TKA is not consistently defined, but flexion ability <70° is considered a severe deficit and extension deficit of >15° affects the gait (23). Manipulation under anesthesia and/or arthroscopic lysis may be recommended at first and revision surgery secondly to those who fail the other treatment strategies (24). In our study, we did not identify a consistent attempt to try

non-revision procedures first and there was no consensus of severity of range of motion (ROM) to indicate a need for revision. However, our study material for this particular indication was very small and the ROM was not estimated in a standardized manor.

We could recover patella maltracking in 13 cases (13%), where malrotation was evident in 5 of them. The DKR does not provide any indications relevant to malrotation or malposition of components. Malalignment is implemented in other national registers and our data confirm the need of an indication for revision of an incorrectly inserted prosthesis (4, 6, 12). There is no consensus of cut-off point for malrotation or CT assessment of surgical landmarks, which makes interpretation of malrotation debatable (25, 26). Internal rotation of the femoral component above 3-6° has been associated with poorer outcomes in some studies, whereas other studies could not find any correlation (27). Internal rotation of the tibial component >10° has been associated with inferior outcomes, pain and stiffness (26). External rotation of the femoral and tibial component does not correlate with inferior outcomes (27). In this study, we considered the optimal placement of the femoral component 2-5° of external rotation and placement of the tibial component <10° of internal rotation and <5° external rotation (17). The malposition of prostheses exceeding these limits might be causing pain or other problems. Some studies suggest a correlation between rotational malalignment and patella maltracking, though the evidence is non-consistent (28, 29). Rotational malalignment was present in 5 (38%) of the cases revised for patella maltracking. We cannot estimate any association with this study.

We found 6 (6%) cases of revision performed because of malposition of components, and the radiographic measurements of malposition did exceed the recommendations for optimal placement. They were not remarkably displaced compared to the other prostheses in this study, of which 62% deviated from the optimal recommendations.

Radiographic assessment

Although radiographic deviations from standard recommendations for optimal prosthesis component placement were present in 62% of all cases, the placement of components were not excessively displaced

compared to TKA`s of other investigations (18, 30). Ritter et al. found a mean femoral alignment of TKA's of 3.7°±3.3° and a mean tibial alignment of 90.4°±2.4° (30). Nielsen et al. observed 18% with medial overhang, 32.2% with lateral overhang and 5.8% with anterior overhang of the tibial component in a cohort of 323 TKA patients, with overhang defined as any measurement above 0mm (18). Deviations from optimal placement of components are to be expected in standard series of TKA's, which does not necessarily cause clinical symptoms leading to a need for revision. Achievement of optimal femoral and tibial component alignment is important to the long-term survival of TKA's (30). The femoral components in our study were overall well placed, but 30% of the tibial components were placed in varus position, which is associated with increased failure rates.

The findings from the radiographic evaluation of UKA's in our study, were comparable to assessments from other studies (31, 32).

Arthrosis grade and age prior to primary surgery

It is well established, that preoperative radiographic severity of knee arthrosis is correlated with higher postoperative levels of satisfaction and improved pain scores after TKA (33, 34). Preoperative Kellgren-Lawrence arthrosis grades of >3 is associated with better pain scores after TKA than grades ≤2, where a larger portion of pain might not emanate from arthrosis, but rather from the periarticular soft tissues. Patients with preoperative Kellgren-Lawrence grades ≥3 were more satisfied after TKA (33). In our study, 31% of the patients had a Kellgren-Lawrence grade ≤2. This is a larger portion than reported from three previous single center studies where portions of grades 0-2 were 3-13% in consecutive series of osteoarthritis patients receiving TKA´s (35-37). It supports the correlation between severity of arthrosis and improved pain scores after TKA. Possibly, some of the patients included in our study received their primary knee arthroplasty at a too early state.

The mean age at the time of revision is 60 years in this study population. This is considerably lower than the average age for primary TKA/UKA, which is 68 years for Danish patients (2). It substantiates the suspicion that some patients might have received their TKA/UKA at an early state of their arthrosis development.

Perspectives

We found the indication "pain without loosening" in the DKR to be correctly registered in 99% of the cases of investigation. However, we found hidden indications as well. Though stiffness and malrotation are controversial indications for revision, they are commonly used. Implementing these indications in the register would enhance possibilities for correct registration for the surgeons and improve data quality. Furthermore, an alignment of indications in registers across countries could potentially enhance collaborations and improve future investigations even further.

Strength and limitations

This is the first study to validate pain as indication for knee arthroplasty revision in a nationwide register. Medical records were thoroughly investigated, but we can only account for data entered to the records, and might be missing some unrecorded observations. Furthermore, data might be entered differently by the surgeons e.g. estimation of ROM, instability etc., making comparisons inaccurate. The radiographic assessment has its limitations. Long radiographs and calibration ball were missing in most cases, which limits the precision of radiographic measurements. CT-scans had only been performed for a limited number of the patients and the interobserver reliability for measurements is well known to be low concerning estimations of rotation of components. However, the precision was improved by two observers agreement.

Conclusion

The indication "pain without loosening" covered patients revised because of pain, but other hidden indications were present. Stiffness and malposition of components were hidden indications and lack as indication option in the DKR and other registers.

The relative high frequency of low arthrosis grade (Kellgren-Lawrence 1-2) prior to primary knee arthroplasty is concerning and may explain the need for revision of a painful knee in cases without any other pathology present.

Author contributions

KBA, HMS, AT, and MLL designed the study protocol. The analyses were planned by KBA, HMS, AT, MRA, LER and MLL and conducted by KBA and MLL. KBA drafted the manuscript, which was critically revised first by MLL and later by HMS, AT, MRA and LER.

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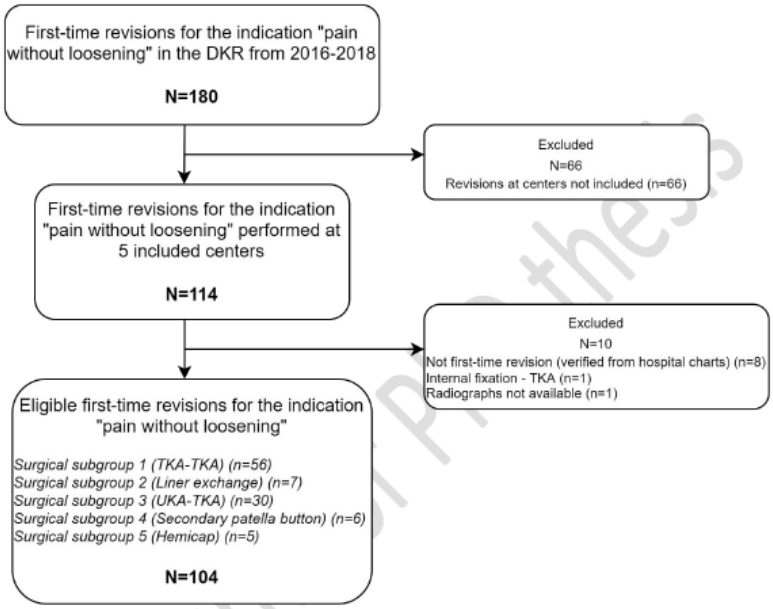
352 ## Figures

353 **Figure 1. Flowchart of included patients.**



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355 *DKR=Danish Knee Arthroplasty Register; UKA=unicompartmental knee arthroplasty; TKA=total knee*
356 *arthroplasty*

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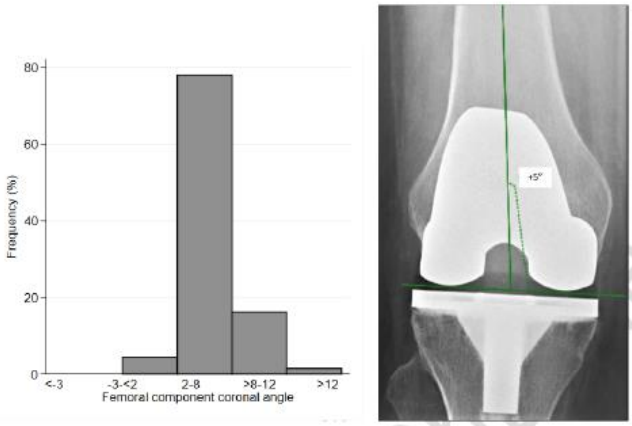
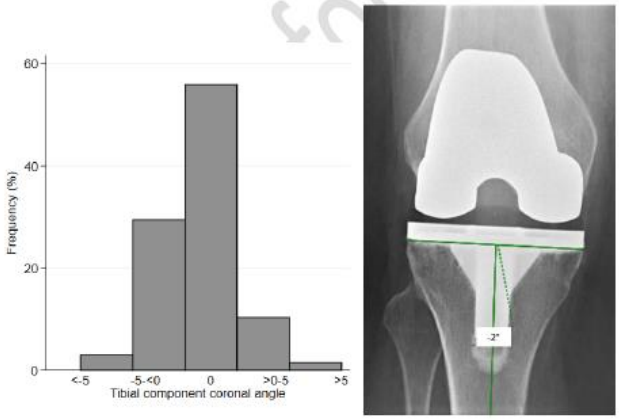
Figure 2a and 2b. Total knee arthroplasty: Coronal angle of femoral component.



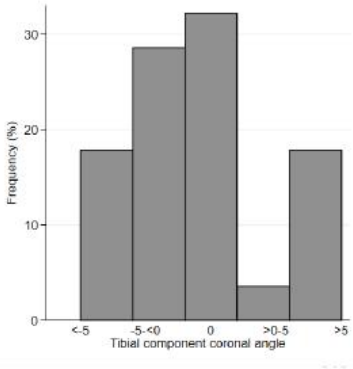
2°-8° is the optimal angle for placement of the femoral component. <0° indicates varus position and >0° indicates valgus position.

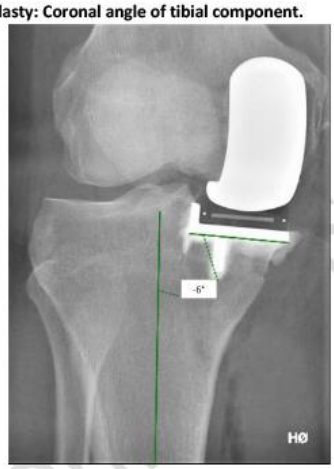
Figure 3a and 3b. Total knee arthroplasty: Coronal angle of tibial component.



Neutral alignment (0°) is the optimal placement of the tibial component. <0° indicates varus position and >0° indicates valgus position of the tibial component.

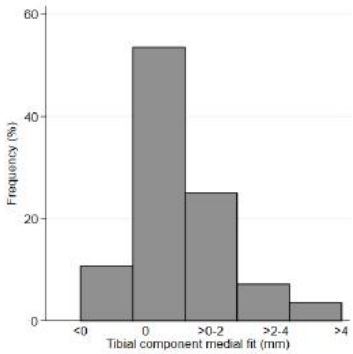
Figure 4a and 4b. Unicompartmental knee arthroplasty: Coronal angle of tibial component.

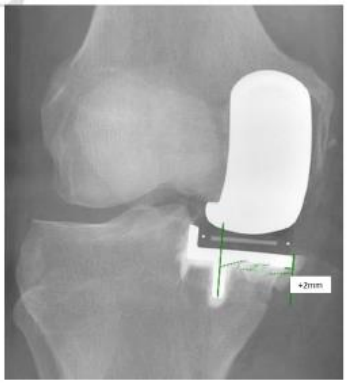




-5°-5° is the optimal alignment of the tibial component. <-5° indicates varus position and >5° indicates valgus position of the tibial component.

Figure 5a and 5b. Unicompartmental knee arthroplasty: Tibial component medial fit.





<2mm lateral overhang is the optimal placement of the tibial component.

Tables

Table 1. Characteristics of included patients.

Characteristic	N=104 (%)
Sex (female)	61 (59)
Age at primary surgery (median, range)	60 years (25-86)
Age at revision (median, range)	65 years (29-88)
Time from primary surgery to revision	4.3 years (CI 3.3-5.1)
Previous knee surgeries	
None	24 (23)
Arthroscopy	37 (36)
Other	5 (5)
Unknown	38 (36)
Type of arthrosis	
Primary	54 (52)
Secondary	16 (15)
Unknown	34 (33)
ASA at time of revision	
1	26 (25)
2	65 (63)
3	13 (12)
Medically treated psychiatric disorder at time of revision	5 (5)
Other treatment strategy prior to revision	
Cast/bandage	1 (1)
Physiotherapy	10 (10)
Analgesics	8 (8)
Manipulation under anesthesia	9 (9)
Steroid injection	6 (7)
Radiographic evaluation prior to primary knee arthroplasty	
Knee compartments affected from arthrosis before primary surgery	
Patellofemoral	2 (2)
Medial	33 (41)
Lateral	2 (2)
Medial and patellofemoral	10 (12)

Medial and lateral	5 (6)
Three compartments	30 (37)
Missing radiographs (n=22)	
Kellgren-Lawrence classification of arthrosis before primary surgery (worst affected chamber)	
1. Doubtful narrowing of joint space and possible osteophytic lipping	3 (4)
2. Definite osteophytes and possible narrowing of joint space	22 (27)
3. Moderate osteophytes, definite narrowing of joint space, possible deformity of bone	40 (49)
4. Large osteophytes, marked narrowing of joint space, sclerosis and deformity of bone	17 (20)
Missing radiographs (n=22)	

Table 2. Hidden indications assessed from medical charts and radiographic assessment.

Hidden indication	Total N=44 (42%)	TKA n=27 (26%)	mUKA n=14 (13%)	Hemicap n=3 (1%)
Stiffness	13	12	1	
Patella maltracking	13	12	1	
Malposition of components (assessed from radiographs)	6		6	
Dislocated bearing	1		1	
Instability (medial ligaments)	3	2	1	
Progression of arthrosis	6		3	3
Aseptic loosening	1	1		
Residual cement	1		1	

TKA=Total Knee Arthroplasty; mUKA=medial Unicompartmental Knee Arthroplasty.

Table 3. Presence of other hidden indications and Kellgren-Lawrence grades prior to the primary knee arthroplasty.

Verification of the indication "pain without loosening"	n	Kellgren-Lawrence grade prior to primary arthroplasty	
		1-2	3-4
No other indications present	35	13 (37%)	22 (63%)
Other indications for revision were present	47	12 (26%)	35 (74%)
Total	82	25 (30%)	57 (70%)

Table 4. Radiographic deviations from optimal component placement in correlation the presence of the indication "pain without loosening" with and without other indications.

Indications	n	Deviation from optimal component placement	
		Yes N (%)	No N (%)
"Pain without loosening" and no other indication	43	20 (47)	23 (53)
"Pain without loosening" and other indication	60	41 (68)	19 (32)
Other indication	1	1 (100)	0 (0)
Total	104	62 (60)	42 (40)

Paper II

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Prosthesis survival after revision knee arthroplasty for "pain without loosening" versus "aseptic loosening": a Danish nationwide study

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Background and purpose — Patients having a knee arthroplasty revision for the indication "pain without loosening" may have a higher risk of re-revisions than patients revised for other indications. The primary aim of this study was to compare the survival of knee arthroplasties revised for "pain without loosening" compared with "aseptic loosening." The second was to investigate the prosthesis survival rates in 3 surgical subgroups (total knee arthroplasty (TKA)–TKA; partial revision (revision of tibial or femoral component); unicompartmental knee arthroplasty–TKA) and to compare the prosthesis survival rates for 1997–2009 and 2010–2018.

Patients and methods — 4,299 revisions were identified in the period 1997–2018 from the Danish Knee Arthroplasty Register. Of these, 1,111 (26%) were performed due to "pain without loosening" without any other indications, 674 (16%) due to "pain without loosening" combined with other indications, and 2,514 (59%) due to "aseptic loosening". Survival analysis was performed by a Cox multivariate analysis and Kaplan–Meier curves were presented.

Results — The cumulated proportions of re-revision after 2, 5, and 20 years were 12% (95% CI 10–14), 18% (CI 16–20), and 23% (CI 20–25) for "pain without loosening" versus 11% (CI 9.3–12), 16% (CI 14–17), and 19% (CI 18–21) for "aseptic loosening." There were no statistically significant differences between the 2 indications in repeated analyses for each of the surgical subgroups. The hazard ratio for re-revision comparing "pain without loosening" with "aseptic loosening" was 1.03 (CI 0.87–1.2). The 8-year risk of re-revision for "pain without loosening" was 22% (CI 19–26) versus 22% (CI 20–25) for "aseptic loosening" in the period from 1997–2009, and 18% (CI 15–22) versus 14% (CI 13–16) in the period from 2010–2018.

Interpretation — The risk of re-revision was similar for patients having a knee arthroplasty revision for the indication "pain without loosening" compared with "aseptic loosening." However, we observed a slight improvement of prosthesis survival rates after revisions for both indications from 1997–2009 to 2010–2018. We cannot recommend for or against revision in cases with "pain without loosening" based on these data alone.

The number of primary knee arthroplasties—and the number of revisions—is expected to increase over the next decades (1). Up to 20% of patients experience some degree of knee pain after a primary total knee arthroplasty (TKA) and an even higher proportion after revision knee arthroplasty (2–6). Petersen et al. reported persistent pain in 47% of patients after a revision TKA for any indication compared with 19% after a primary TKA (6).

Revision TKA on the grounds of unexplained pain is generally not recommended (3,6,7). Revision TKA in the absence of knee pathology may not relieve pain, and it may result in worse outcome and higher rates of re-revision than for TKA revision for more established indications such as "aseptic loosening." Re-revision TKA rates of 12–27% have been reported (8–11), but survival rates after revision TKA for various indications are unknown. Pain is available as an indication for TKA revision in most national orthopedic registries.

Although the number of TKA revisions is expected to increase, better outcomes are also expected due to improvements in revision surgery because of organizational changes in the healthcare system, including enhanced recovery programs, greater surgical experience with revision surgery, and technical developments such as improved bone substitution and fixation (12).

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The primary aim of this study was to compare the prosthesis survival rates after TKA revision for the indication "pain without loosening" versus the indication "aseptic loosening." Secondary aims were to investigate the prosthesis survival rates in four surgical subgroups (TKA–TKA, partial revision, unicompartmental knee arthroplasty (UKA)–TKA, secondary patellar button) and to compare the prosthesis survival rates for 1997–2009 and 2010–2018.

Patients and methods

This study is a nationwide retrospective cohort study of prospectively collected data from the Danish Knee Arthroplasty Register (DKR) and the Danish National Patient Register (DNPR). The RECORD guidelines for reporting of routinely collected, observational data were followed.

Data sources

Data on all knee arthroplasty revisions registered for the indications "pain without loosening" or "aseptic loosening" in the period January 1, 1997 to December 31, 2018 was collected from the Danish Knee Arthroplasty Register (DKR). DKR is a nationwide clinical database that has collected data on primary and revision knee arthroplasties in Denmark since 1997 (13). All hospital orthopedic departments (including private hospitals) report pre- and intraoperative data to the database. In 2018, the completeness of the register was 98% for primary arthroplasties and 95% for revision arthroplasties (14).

We obtained information on diagnosis and procedure codes from the Danish National Patient Registry (DNPR) for 1987 to 2018. The DNPR is an administrative registry established in 1977 that holds information on all hospital contacts in Denmark (15,16). Patients can be identified by their social security number—a personal unique 10-digit code that also enables linkage between registries. Information on patient characteristics including age, sex, and Charlson comorbidity index (CCI) were obtained from the DNPR (Table 1). The burden of comorbidities for each patient was estimated by the CCI, using the DNPR ICD-8 and ICD-10 diagnostic codes for the 10-year period up to the date of the first revision (Table 2, see Supplementary data). We classified patients into 3 groups according to their burden of comorbidities: CCI of 0 (low), CCI 1–2 (medium), or CCI ≥ 3 (high).

Table 1. Characteristics of TKA revisions for 2 selected indications between 1997 and 2018. Values are count (%) unless otherwise specified

	Pain without loosening without other indications	Pain without loosening with other indications	Aseptic loosening	Total
TKA revisions	1,111 (26)	674 (16)	2,514 (58)	4,299 (100)
Female sex	709 (64)	428 (63)	1,533 (61)	2,670 (62)
Mean age at 1st revision (range)	63 (29–92)	65 (32–88)	66 (22–96)	65 (22–96)
Age groups				
≥ 80 years	60 (5)	62 (9)	259 (11)	381 (9)
70–79 years	275 (25)	200 (30)	736 (29)	1,211 (28)
60–69 years	362 (33)	217 (32)	882 (35)	1,461 (34)
50–59 years	277 (25)	137 (20)	486 (19)	900 (21)
< 50 years	137 (12)	58 (9)	151 (6)	346 (8)
Mean age at primary knee arthroplasty (CI)	60 (60–61)	62 (61–63)	62 (61–62)	61 (61–62)
Charlson Comorbidity Index				
0 (low risk)	839 (76)	508 (76)	1,513 (60)	2,860 (66)
1–2 (medium risk)	239 (21)	137 (20)	812 (32)	1,188 (28)
≥ 3 (high risk)	33 (3)	29 (4)	189 (8)	251 (6)
Surgical subgroups				
1. Total revision TKA–TKA	365 (33)	283 (42)	1,649 (66)	2,297 (53)
2. Partial revision	127 (11)	67 (10)	480 (19)	674 (16)
4. UKA–TKA	477 (43)	140 (21)	385 (5)	1,002 (23)
5. Secondary patellar button	142 (13)	184 (27)	–	326 (8)
Total number of re-revisions	252 (23)	128 (19)	476 (19)	856 (20)
Years from 1st to 2nd revision (CI)	3.4 (2.9–3.8)	4.5 (3.8–5.3)	2.9 (2.6–3.2)	3.3 (3.1–3.6)

TKA = total knee arthroplasty; UKA = unicompartmental knee arthroplasty.

Participants

The study cohort comprised patients undergoing first-time TKA revision for the indications "pain without loosening" or "aseptic loosening" (control group). Patients who underwent bilateral revision were included in the study.

We defined surgical subgroups according to the type of prosthesis removed and the type of prosthesis inserted at the first revision. We included subgroup 1 (TKA–TKA), subgroup 2 (partial revision), subgroup 4 (unicompartmental knee arthroplasty (UKA)–TKA), and subgroup 5 (secondary patellar button). The included subgroups comprised numbers of revisions appropriate for further analysis and the types of revisions all included change of components, which is considered relevant for this study. We excluded subgroup 3 (liner exchange), subgroup 6 (UKA–UKA), subgroup 7 (hemicap), subgroup 8 (exchange of patellar button), subgroup 9 (all components removed), and subgroup 10 (spacer–TKA). The excluded subgroups comprised small numbers of revisions or did not include change of components, and were therefore not considered relevant to compare with the other subgroups. Furthermore, we excluded subgroup 5 (secondary patellar button) in combination with the indication "aseptic loosening" as these cases were considered to be misclassified in the register.

After exclusion of surgical subgroups and removal of duplicate records, 4,299 revisions were included in the study. Of these 1,111 (26%) were included on the indication "pain without loosening" without any other indications, 674 (16%) on

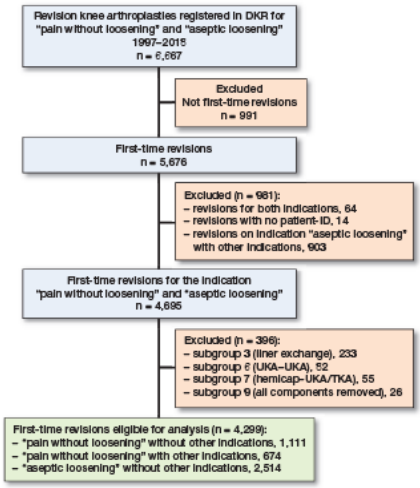

Figure 1. Flowchart of TKA revision cases identified and included in the study analysis.

the indication "pain without loosening" combined with other indications, and 2,514 (58%) on the indication "aseptic loosening" without any other indications.

For survival rate analysis TKA revisions were divided into 2 time groups, 1997–2009 and 2010–2018. 2009 was set as the cutoff point in order to have 2 almost equal sizes of groups for the analysis.

Outcomes

We extracted data from the DKR on all the re-revisions that were undertaken. Re-revisions registered in the DNPR on the procedure codes KNGU0-1 and KNGC0-9 were also obtained to ensure complete follow-up.

Statistics

The risks of re-revision at 2, 5, 10, 15, and 20 years are presented as cumulated proportions calculated as percentages with 95% confidence intervals (CI). The proportion were calculated both by indication ("pain without loosening" with and without other indications and "aseptic loosening") and by surgical subgroups (for "pain without loosening" without other indications and "aseptic loosening").

Survival analysis was performed using the Cox regression model to estimate the effect of the primary exposure variable "indication" on the outcome crude failure of revision knee arthroplasties, with adjustment for the covariates age groups, CCI, sex, and surgical subgroups. The estimates are presented

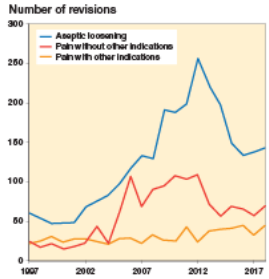

Figure 2. Incidence of TKA revision surgery for indications of "pain without loosening" with and without other indications and "aseptic loosening" without other indications. Data source = Danish Knee Arthroplasty Register, 1997–2018.

as hazard ratios. To meet the model assumptions, data must be independent. The data of the unilaterally revised patients were assumed to be independent, but the data of bilaterally revised patients were assumed to be dependent. We adjusted for dependency by applying adjustment of the standard error for clustered data to our model. The model was tested for proportionality of hazards.

We used a Cox model to estimate the effect on the outcome "re-revision" for the secondary covariates age group, CCI, sex, and surgical subgroups when controlled for the primary exposure "indication" by the regression, calculated as hazard ratios. We present survival of knee arthroplasties as Kaplan–Meier curves. The level of statistical significance was set at 0.05 for all analyses.

The statistical software package Stata version 16.0 was used (StataCorp, College Station, TX, USA).

Ethics, funding, and potential conflicts of interest

The study was approved by the Danish Data Protection Agency (Journal no. 19/14416). Ethical approval was not needed as the study was non-interventional. The study was conducted in accordance with the Declaration of Helsinki. The study was funded by the Danish Rheumatism Association. The authors have no competing interests to declare.

Results

6,667 TKA revisions for the selected indications were identified in the DKR between 1997 and 2018 (Figure 1). The revisions were performed on 4,183 patients. 116 patients were bilaterally revised. The mean patient age for TKA revisions undertaken for "pain without loosening" (63 years; 29–92) was lower than that for TKA revisions undertaken for "aseptic loosening" (66 years; 22–96), $p < 0.001$, but the proportion of men and women was broadly similar (Table 1). 856 knees had

Table 3. Cumulated proportion of TKA re-revision after 2, 5, 10, 15, and 20 years by surgical indication. Values are count and percentage (CI)

Indication	n	2 years	5 years	10 years	15 years	20 years
"Pain without loosening" without other indications	1,111	12 (10–14)	18 (16–20)	21 (19–23)	23 (20–25)	23 (20–25)
"Pain without loosening" with other indications	674	9 (7–11)	12 (10–15)	17 (14–20)	19 (16–22)	19 (16–22)
Aseptic loosening without other indications	2,514	11 (9–12)	16 (14–17)	18 (17–20)	19 (17–20)	19 (18–21)

Table 4. Cumulated proportion of TKA re-revision after 2, 5, 10, 15, and 20 years by surgical subgroup and indications of "pain without loosening" (without other indications) and "aseptic loosening" (without other indications). Values are count and percentage (CI)

Subgroup	n	2 years	5 years	10 years	15 years	20 years
1: TKA–TKA	2,014					
"Pain"		11 (8–15)	16 (12–20)	19 (15–23)	20 (16–24)	20 (16–24)
"Aseptic loosening"		9 (8–10)	14 (12–15)	15 (14–17)	16 (14–18)	16 (15–18)
2: Partial revision	607					
"Pain"		14 (9–21)	20 (14–28)	24 (17–32)	26 (19–34)	27 (20–35)
"Aseptic loosening"		14 (11–17)	22 (19–26)	27 (23–31)	28 (24–32)	28 (24–32)
4: UKA–TKA	862					
"Pain"		12 (10–16)	19 (16–23)	22 (18–26)	24 (20–28)	24 (20–28)
"Aseptic loosening"		13 (10–17)	17 (14–21)	19 (16–24)	19 (16–24)	20 (16–24)
5: Secondary patellar button	142					
"Pain"		9 (5–14)	18 (12–25)	21 (15–29)	23 (16–30)	23 (16–30)
"Aseptic loosening"		–	–	–	–	–

TKA = total knee arthroplasty; UKA = unicompartmental knee arthroplasty.

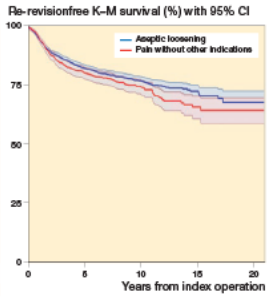

Figure 3. Kaplan–Meier survival curves with 95% confidence interval for the indications "pain without loosening" (without other indications) and "aseptic loosening" (without other indications).

undergone re-revision; 836 of these were identified from the DKR and 20 from the DNPR. The proportion of re-revisions after TKA revision was for "pain without loosening" without other indications (n = 252, 23%), "pain without loosening" with other indications (n = 128, 19%), and "aseptic loosening" (n = 476, 19%).

The number of TKA revisions for "pain without loosening" increased from 2004 to 2012 and decreased thereafter, while revisions for "aseptic loosening" increased from 2001 to 2012 and decreased thereafter (Figure 2).

The cumulated proportions of re-revision after 2, 5, 10, 15, and 20 years are presented in Table 3. The proportion of re-revision after 20 years was slightly higher for "pain without loosening" without other indications (23%) than for "aseptic loosening" (19%), with overlapping confidence intervals at all follow-up times. This finding was unchanged when the analyses were repeated for each of the 4 surgical subgroups (Table 4 and Figure 3).

The adjusted hazard ratio (HR) risk of re-revision for "pain without loosening" without other indications compared with "aseptic loosening" estimated by Cox regression was 1.03 (CI 0.87–1.2). Table 5 shows the effects of the covariates on the risk of revision adjusted for the effect of the primary exposure "indication." The Charlson Comorbidity score did not influence the risk of re-revision. Subgroup 2 (partial revision) had increased risk of re-revision compared with subgroup 1 (TKA–TKA) with an HR of 1.52 (CI 1.26–1.83), $p < 0.001$. Male sex and age below 60 years increased risk of re-revision.

To estimate changes in risk of TKA re-revision over time, the cases were divided into 2 time-periods of 1997–2009 and 2010–2018 (Tables 6, 7, and Figure 4). For both indications, the 8-year risk of re-revision was higher in the first period (both 22%) than in the second period (14–18%).

A Cox regression was performed to explore any differences between the time-periods. HR for "pain without loosening" without other indications comparing the later time-period with

Discussion

In this study on prosthesis survival after total knee arthroplasty (TKA) revision, we found a slightly higher, but not statistically significant risk of re-revision after TKA revision for the indication "pain without loosening" without other indications compared with the indication "aseptic loosening". Analyses for 3 surgical subgroups showed the same tendency. To our knowledge, this is the first study to report re-revision rates after TKA revisions performed because of unexplained pain. Our study findings oppose the general belief that revisions for pain should be avoided, as the risk of re-revision was not significantly elevated. However, many other aspects than re-revision rates should be considered. The threshold for performing a re-revision is possibly higher in patients who were initially revised due to pain than in those revised due to aseptic loosening, resulting in lower rates of re-revision for patients with persistent pain. Furthermore, we cannot draw any conclusions about whether patients experienced pain relief or improved quality of life after the revisions.

The indication "pain without loosening" can be combined with other indications when surgeons record the event in the DKR. According to the Australian Hierarchy of Indications, pain is inferior to all other indications for revision (17), thus the highest ranked indication is the dominant problem. This may explain why "pain without loosening" combined with other indications had a lower re-revision risk than "pain without loosening" without any other indications. The reason we include data for the indication "pain without loosening" without other indications is to provide estimates that are unbiased by other indications.

We investigated the risk of re-revision after TKA revision for the indications "pain without loosening" and "aseptic loosening" over the 2 time-periods 1997–2009 and 2010–2018. We observed an overall reduction in the proportion of re-revision on both indications in the later time-period compared with the earlier period, although the difference for "pain without loosening" was less pronounced than for "aseptic loosening." The overall reduction in re-revision risk between time-periods was not statistically significant by the Kaplan–Meier estimates for either indication group. However, the 8-year cumulated proportion of re-revisions for TKA-to-TKA revisions (subgroup 1) changed from 20% in the earlier period to 12% in the later period for "aseptic loosening." Encouragingly, this may be interpreted as an improvement over recent years in the performance of revision knee arthroplasties, especially for TKAs revised because of aseptic loosening.

There are limitations to this study. We are not able to present data on all index revisions performed nationwide as the completeness of revisions in the DKR is 89%, but a complete follow-up on re-revisions was ensured by using data from both DKR and DNPR (completeness > 99%) (15). We have no reason to believe that the lack of index revisions would bias our results in any way. The study may not have enough sample-size power to identify a statistically significant difference in the re-revision rates between the 2 indications, and no pre-study power calculation was performed as we included all available procedures.

The indication "pain without loosening" was itself associated with limitations. No validation of the indication has been done. It may be an exclusion indication chosen by the individual surgeon performing the surgery when there are no other obvious indications. No clear-cut definition of this indication exists, and it might cover a broad spectrum of patients who may or may not have a similar underlying problem.

Further investigations of the validity and use of this indication are warranted as well as clinical results after revisions performed on the basis of this indication.

In conclusion, we found similar risk of re-revision for patients having a knee arthroplasty revision for the indication of "pain without loosening" compared with that of "aseptic loosening." We also did not find any differences at surgical subgroup level. However, we found a small improvement of prosthesis survival rates after revisions for both indications from 1997–2009 to 2010–2018, which we interpret as an improvement in the performance of revision knee arthroplasties. We cannot recommend for or against revision in cases with "pain without loosening" based on these data alone.

Supplementary data

Table 2 is available as supplementary data in the online version of this article, http://dx.doi.org/10.1080/17453674.2021.1999069

KBA, HMS, AT, and MLL designed the study protocol. The analyses were planned by KBA, HMS, AT, and MLL and conducted by KBA. KBA drafted the manuscript, which was critically revised first by MLL and later by HMS and AT.

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Paper III

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Revision Arthroplasty

Opioid and Analgesic Use Before and After Revision Knee Arthroplasty for the Indications "Pain Without Loosening" Versus "Aseptic Loosening" – A Danish Nationwide Study

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ABSTRACT

Background: It is uncertain if patients undergoing revision knee arthroplasty for "pain without loosening" are relieved of pain. This study aimed to compare pre- and postoperative analgesic consumption by patients undergoing revision for "pain without loosening" versus "aseptic loosening" and to determine predictors for postoperative long-term opioid use.
Methods: A retrospective nationwide study of 1,037 revisions for "pain without loosening" and 2,317 revisions for "aseptic loosening" during 1997-2018 from the Danish Knee Arthroplasty Register was carried out. Analgesic use was defined by prescription reimbursement, and long-term opioid use by prescription reimbursement in 4 consecutive quarters.
Results: In the preoperative year, 37% and 29% of patients revised for "pain without loosening" and "aseptic loosening" were opioid users compared to 32% and 30% in the postoperative year. Non-steroidal anti-inflammatory drug (NSAID) use was significantly lower postoperatively for both indications (35% versus 28% for "pain without loosening" and 33% versus 25% for "aseptic loosening"). Use of other analgesics was unchanged. Long-term opioid use increased postoperatively by 4% for patients with "pain without loosening" ($P = .029$) and by 3% for "aseptic loosening" ($P = .003$). New long-term opioid users (without preoperative long-term use) were 9% for "pain without loosening" and 8% for "aseptic loosening". Predictors of new long-term opioid use were other opioid-requiring diagnoses or procedures within the first postoperative year, Charlson Comorbidity Index (CCI) ≥3, and preoperative long-term NSAID use.
Conclusion: The consumption of opioids decreased slightly after knee arthroplasty revision for the indication "pain without loosening", but not for "aseptic loosening". The amount of new long-term opioid users increased for both indications.

The well-established indication "aseptic loosening" is one of the most common reasons for revision of total knee arthroplasty (TKA) [1,2]. Some revisions are performed for the indication "pain without loosening" to relieve unexplained knee pain with no obvious pathology, but revision for this indication alone is not commonly recommended [3,4]. About 20% of patients have persistent pain after TKA, and its prevalence after revision knee arthroplasty is presumably higher [5,6].

Postoperative pain after TKA is primarily treated with short-term opioid therapy, but some patients become long-term users (>3-12 months) [7,8]. Long-term opioid therapy after primary TKA is 3%-8% in patients without preoperative opioid use, but 14%-53% in patients with preoperative opioid use [9–11]. The same trend of opioid

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consumption exists after revision knee arthroplasty [12]. It is concerning that about 30% of the patients using opioids for 31 days or more are still users after a year [13]. Long-term opioid therapy can lead to nausea, constipation, and somnolence as well as drug tolerance, physical dependence, addiction, and sudden death [7]. Predictors of long-term opioid use after TKA are preoperative opioid use, young age, female sex, high body mass index (BMI), anxiety, depression, and catastrophizing [9,14]. The evidence regarding long-term opioid therapy after revision TKA is sparse. Importantly, it is unknown if patients revised due to unexplained pain go on to experience less pain afterward with reduced need for analgesic therapy.

The objectives of this retrospective cohort study on patients having a knee arthroplasty revised in the period 1997-2018 for the indication "pain without loosening" compared to the control group "aseptic loosening" were:

1. To investigate the consumption of opioids, paracetamol, non-steroidal anti-inflammatory drugs, antidepressants, anticonvulsants, and other analgesic drugs one year before and after revision.
2. To investigate the development in long-term use of opioids before and after revision.
3. To determine if age, sex, Charlson comorbidity score, surgical subgroup, opioid-related comorbidities, and preoperative use of analgesics are predictors for development of new postoperative long-term opioid use.

Patients and Methods

The study was a retrospective cohort study of nationwide collected data. The RECORD guidelines for the reporting of routinely collected, observational data were followed [15].

Data Sources

All knee arthroplasty revisions performed for the indications "pain without loosening" and "aseptic loosening" in the period January 1, 1997 to December 31, 2018 were identified from the

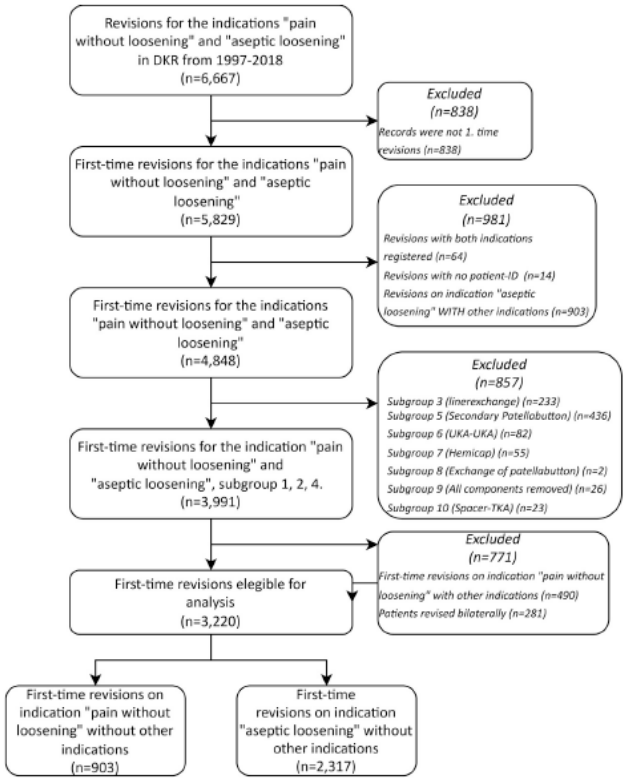

Fig. 1. Flowchart of patients included and excluded in this study.

Table 1
Demographic Data for Patients Undergoing Revision for the Indications "Pain Without Loosening" or "Aseptic Loosening".

Characteristic	Pain without Loosening	Aseptic Loosening
n (%)	1,037 (31)	2,317 (69)
Male/female, n (%)	374/663 (36/64)	921/1,396 (40/60)
Mean age at revision (y)	63 (CI 62.4-63.7)	66.5 (CI 66-66.9)
Age groups, n (%)		
≥80 y	58 (6)	248 (11)
70-79 y	258 (25)	687 (30)
60-69 y	340 (33)	794 (34)
50-59 y	254 (24)	452 (19)
<50 y	127 (12)	136 (6)
Charlson Comorbidity Index, n (%)		
0 (low risk)	783 (76)	1,699 (73)
1-2 (medium risk)	223 (21)	514 (22)
>3 (high risk)	31 (3)	104 (5)
Mean BMI (kg/m^2) (Missing: 1,773)	28.7 (CI 28.3-29.1)	29.4 (CI 29-29.5)
Subgroup, n (%)		
1. Total revision TKA-TKA	341 (33)	1,507 (65)
2. Partial revision	117 (11)	441 (19)
4. UKA to TKA	445 (43)	369 (16)
5. Secondary patella button	134 (13)	-

BMI, body mass index; TKA, total knee arthroplasty; UKA, unicompartmental knee arthroplasty; CI, confidence intervals.

Danish Knee Arthroplasty Register (DKR). The DKR is a clinical database that has prospectively collected data on all primary and revision knee arthroplasties performed in Denmark since 1997. The completeness of the register in 2018 was 95% for revision arthroplasties and 98% for primary arthroplasties [2].

Data on reimbursed prescriptions one year before and one year after revision were retrieved from the Danish National Prescription Registry (NPR), which is a nationwide database collecting information on all reimbursed drugs in Denmark [16]. The drugs were identified by Anatomical Therapeutic Chemical (ATC) codes and grouped according to category. The following ATC codes were included; N01AH and N02A (opioids), N02BE01 (paracetamol), M01A and N02B anti-steroidal anti-inflammatory drug (NSAID), N03A (anticonvulsants/antiepileptics), N06A (antidepressants), and other analgesic drugs including methadone and codeine (see Supplementary Table 3 for all included ATC codes). All opioids, anticonvulsants, and antidepressants require a prescription in Denmark, and the NPR holds complete information on the reimbursement of these drugs. Paracetamol and NSAID have required prescriptions for packages larger than 10 tablets since 2013, thus the NPR does not hold complete information on these drugs. Registries were cross-matched using the patient's social security number (CPR number), which is a unique number assigned to every citizen in Denmark.

The Danish National Patient Register (DNPR) is a national administrative register collecting information on all hospital contacts in Denmark from 1977, with a completeness of >99% [17]. We obtained information on somatic diagnosis, procedure

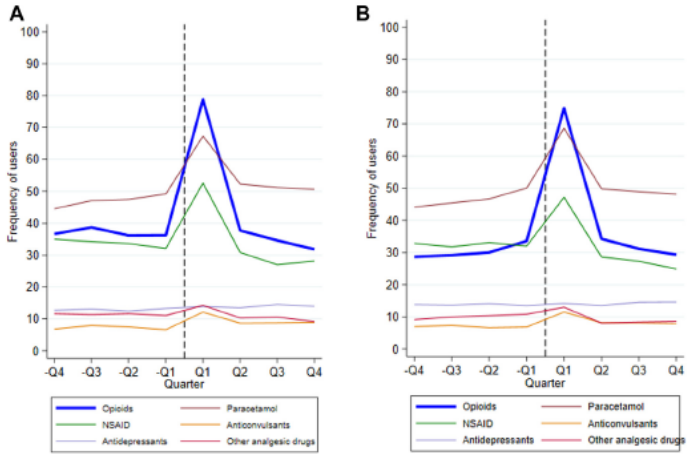

Fig. 2. (A) Users of all drugs presented as frequencies of patients revised for the indication "pain without loosening" (n = 1,037). (B) Users of all drugs presented as frequencies of patients revised for the indication "aseptic loosening" (n = 2,317).

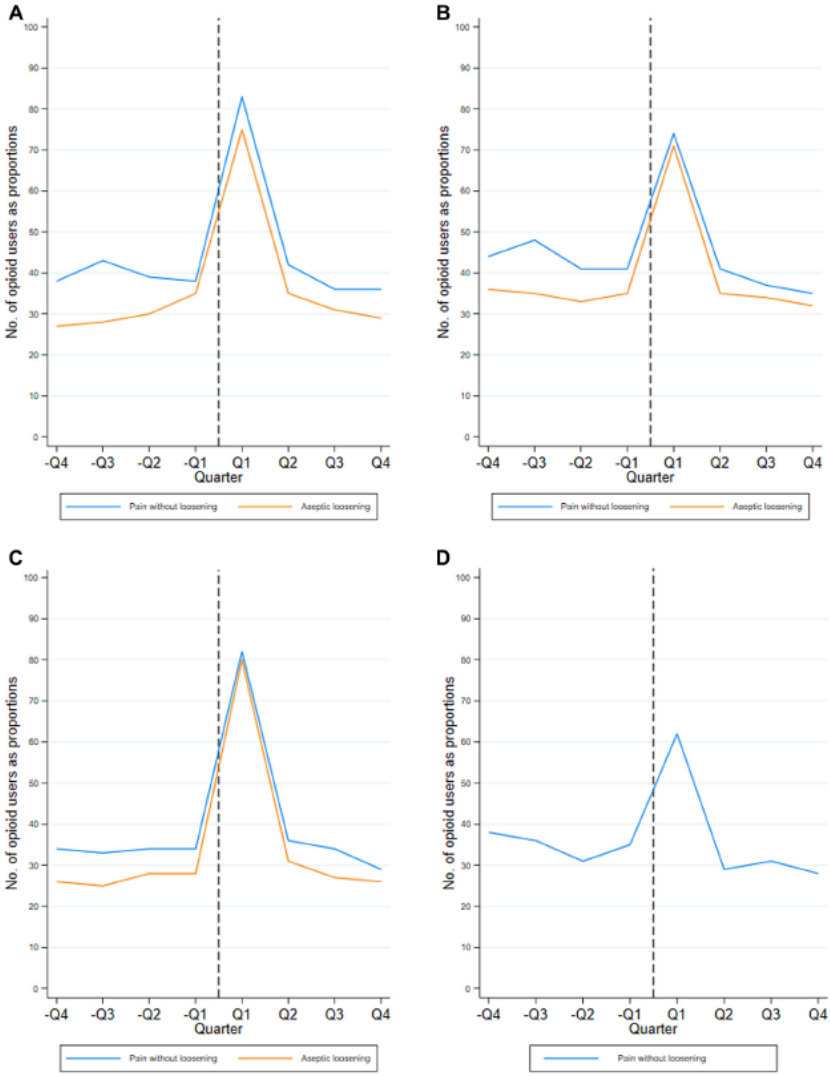

Fig. 3. (A) Proportion of users of opioids for surgical subgroup 1 (TKA-TKA). ("Pain without loosening" n = 341; "aseptic loosening" n = 1,507). (B) Proportion of users of opioids for surgical subgroup 2 (Partial revision). ("Pain without loosening" n = 117; "aseptic loosening" n = 441). (C) Proportion of users of opioids for surgical subgroup 4 (UKA-TKA). ("Pain without loosening" n = 445; "aseptic loosening" n = 369). (D) Proportion of users of opioids for surgical subgroup 5 (Secondary patellabutton). ("Pain without loosening" n = 134).

Table 2
Development in Long-Term Opioid Users 1 y After Revision for the Indications "Pain Without Loosening" and "Aseptic Loosening".

Subgroup	Indication	n	Preoperative Long-Term User (-Q4, -Q3, -Q2, -Q1) n (%)	Postoperative Long-Term User (Q4, Q3, Q2, Q1) n (%)	New Long-Term Users n (%)	Change in Total Number of Chronic Users n (%)	*P*-Value (χ^2; Difference Between Pre- and Postoperative Long-Term User)
Total	Pain without loosening	1,037	191 (18)	231 (22)	94 (9)	40↑ (4)	.029
	Aseptic loosening	2,317	407 (18)	486 (21)	178 (8)	79↑ (3)	.003
1: TKA-TKA	Pain without loosening	341	74 (22)	86 (25)	33 (10)	12↑ (3)	.278
	Aseptic loosening	1,507	266 (18)	325 (22)	123 (8)	59↑ (4)	.007
2: Partial revision	Pain without loosening	117	20 (17)	24 (21)	12 (10)	4 ↑ (4)	.503
	Aseptic loosening	441	89 (20)	98 (22)	32 (7)	9 ↑ (2)	.458
4: UKA-TKA	Pain without loosening	445	74 (17)	96 (22)	42 (9)	22↑ (5)	.061
	Aseptic loosening	369	52 (14)	63 (17)	23 (6)	11↑ (3)	.264
5: Secondary patellabutton	Pain without loosening	134	23 (17)	25 (19)	7 (5)	2↑ (2)	.750
	Aseptic loosening	-	-	-	-	-	-

TKA, total knee arthroplasty; UKA, unicompartmental knee arthroplasty.

codes, age and sex from the DNPR. The burden of comorbidities for each patient was estimated by the Charlson Comorbidity Index (CCI) [18]. The CCI was calculated from ICD-8 and ICD-10 codes for the 10-year period up to the date of revision [19] (see Supplementary Table 4 for ICD-8 and ICD-10 codes). The burden of comorbidities were classified into 3 levels: CCI of 0 (low), CCI of 1-2 (medium), and CCI of 3 or more (high). We obtained other analgesic-requiring diagnoses and procedure codes within the first year postoperatively from the DNPR, such as fibromyalgia, cancer, back pain, neck pain, peripheral neuropathy, and insertion of any other arthroplasty [7] (see Supplementary Table 5 for all included diagnoses and procedure codes).

Study Population

First-time knee arthroplasty revisions performed for the indication "pain without loosening" in 1997-2018 were included in the study cohort. Revisions for the indication "aseptic loosening" performed in the same period were included as control group. We identified 6,667 revisions for the 2 indications from the DKR (Fig. 1). A study on the survival of revision arthroplasties has previously been performed on the same cohort [20]. A total of 3,354 patients were included in the final analysis: 1,037 for the indication "pain without loosening" and 2,317 for the indication "aseptic loosening". The time from primary surgery to first revision for "aseptic loosening" was 2.6 years (0-20.7). Patient demographics are presented in Table 1.

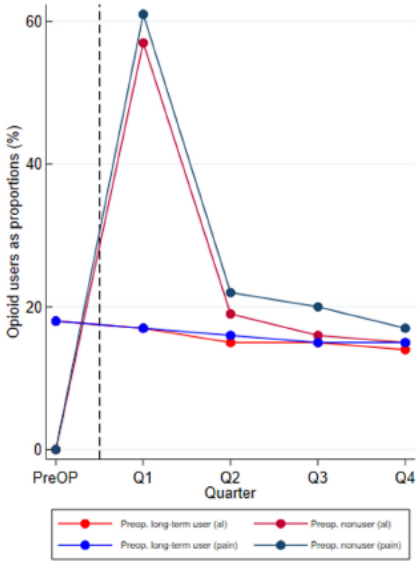

Fig. 4. Proportion of opioid users each quarter after revision in preoperative long-term users and nonusers for the indications "pain without loosening" and "aseptic loosening".

Table 3
Predictors for New Long-Term Users of Opioids 1 y After Revision Knee Arthroplasty Estimated by Multiple Logistic Regression.

Predictors	Odds Ratio	95% CI	*P*-Value
≥80 y	0.599	0.353-1.015	.057
70-79 y	0.690	0.487-0.978	.037
60-69 y	1	-	-
50-59 y	1.063	0.752-1.504	.728
<50 y	1.569	0.996-2.469	.052
Male sex	0.998	0.764-1.303	.988
Female sex	1	-	-
CCI = 0	1	-	-
CCI = 1-2	1.116	0.806-1.544	.510
CCI ≥ 3	1.944	1.087-3.476	.025
Subgroup 1: Total revision TKA-TKA	1	-	-
Subgroup 2: Partial revision	0.894	0.624-1.281	.541
Subgroup 4: UKA to TKA	0.889	0.649-1.218	.464
Other opioid-requiring diagnoses or procedures within the first postoperative year	2.529	1.885-3.394	<.001
Preoperative long-term NSAID user	1.564	1.101-2.222	.012
Preoperative long-term antidepressant user	1.386	0.706-2.720	.343
Preoperative long-term anticonvulsants user	1.401	0.894-3.196	.141
Preoperative long-term user of other analgesics	1.924	1.158-3.198	.012

CCI, Charlson comorbidity index; TKA, total knee arthroplasty; UKA, unicompartmental knee arthroplasty, NSAID, non-steroidal anti-inflammatory drug; CI, confidence interval.

We divided the revisions into surgical subgroups defined by the types of prostheses removed and inserted at surgery (Fig. 1). The excluded surgical subgroups were not considered relevant for analysis for the indication of pain, and the number of revisions in most of the excluded groups were too low to perform a meaningful analysis. We excluded subgroup 5 (secondary patellar button) in combination with the indication "aseptic loosening" as these cases were considered misclassified in the register.

Variables

The primary outcome variable was the frequency of patients receiving opioids one year before and one year after revision. The use of paracetamol, NSAID, anticonvulsants, antidepressants, and other analgesic drugs was also reported. The year before and the year after revision were divided into 4 quarters of 91 days (-Q4, -Q3, -Q2, -Q1, Q1, Q2, Q3, Q4). We classified patients as drug-users in one quarter if a prescription was reimbursed in that quarter, regardless of the total number of reimbursed prescriptions or the strength of the drug. Likewise, we classified patients as non-users if no prescriptions were reimbursed in a quarter. We defined preoperative and postoperative long-term opioid users as patients with reimbursed opioid prescriptions in all 4 preoperative quarters (-Q4, -Q3, -Q2, -Q1) or postoperative quarters (Q1, Q2, Q4, Q4), respectively [21].

Statistics

Users of analgesics in each quarter were reported as counts and frequencies. Normally, distributed variables were reported as means with 95% confidence intervals. The data were tested for normal distribution with Q-Q plots. Categorical measures were compared using Pearsons Chi-square test. A multivariable logistic regression was performed to estimate the effect of proposed predictors for new long-term opioid use, given as odds ratios (OR) with a 95% confidence interval. The model held its assumptions of independency of events and was tested with a goodness of fit test. Statistical significance was set at the 5% level. We used the statistical software package Stata version 17.0 for statistical analyses.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Danish Data Protection Agency (Journal no. 19/14416). Ethical approval was not needed as the study was non-interventional.

Results

As above, 3,317 patients undergoing first-time revision for the indications "pain without loosening" or "aseptic loosening" were included in the study (Fig. 1).

The frequencies of patients receiving opioids, paracetamol, NSAID, anticonvulsants, antidepressants, and other analgesics are presented in Figure 2A and B. The frequency of opioid users one year before (-Q4) and after (Q4) surgery for the indication "pain without loosening" was 37% versus 32%, $P = .021$, and for "aseptic loosening" 29% versus 30%, $P = .285$ (Supplementary Table 1). The use of NSAID was significantly lower one year postoperatively (Q4) for both indications: 35% users before and 28% after revision for "pain without loosening" ($P = .001$) and 33% before and 25% after revision for "aseptic loosening" ($P < .001$). We did not find any significant change in the use of paracetamol, anticonvulsants, antidepressants, or other analgesic drugs for either of the indications. There were no significant changes in the frequencies of opioid users for the indications "pain without loosening" and "aseptic loosening" within the surgical subgroups (Fig. 3A-D, Supplementary Table 2).

The overall frequency of long-term opioid users increased by 4% for "pain without loosening" and by 3% for "aseptic loosening" (Table 2). The frequencies of new long-term opioid users postoperatively were 9% and 8%. We performed a sensitivity analysis of early (less than 2 years following primary arthroplasty) and late (more than 2 years from primary arthroplasty) revisions for "aseptic loosening", which has similar results as the primary analysis (Supplementary Table 6). Figure 4 shows the postoperative frequency of opioid users for preoperative users and nonusers.

Other opioid-requiring diagnoses or procedures within the first postoperative year, CCI ≥ 3, and consumption of NSAID and other analgesics predicted development of new long-term opioid use after revision (Table 3).

Discussion

In this retrospective nationwide register study of patients undergoing revision of total knee arthroplasty, we found that the 1-year postoperative consumption of opioids decreased for patients

revised for the indication "pain without loosening" but not for patients revised for "aseptic loosening". The consumption of NSAID decreased for both indications in the first postoperative year. No changes were detected for paracetamol, antidepressants, anticonvulsants, or other analgesic drugs. The proportion of long-term opioid users increased for both indications postoperatively, and a large proportion of patients became new long-term opioid users. Other opioid-requiring diagnoses or procedures within the first postoperative year, CCI $\geq$ 3, and consumption of NSAID and other analgesics predicted development of new long-term opioid use.

Opioid Consumption

The 5% decrease in opioid consumption in patients revised for "pain without loosening" indicate a decrease in pain after surgery, but the clinical relevance of this small change is questionable. The consumption did not change for patients revised for "aseptic loosening", but hopefully their mechanical problem was solved. Our data suggests that patients revised for "aseptic loosening" cannot be expected to decrease their opioid consumption postoperatively and hence experience pain reduction. Our study did not have the strength to detect changes at surgical subgroup level. The average consumption of opioids in Denmark for non-malignant pain is 3%-5% and the consumption has decreased since 2015 [22]. The consumption of opioids of patients in this study is highly above the general population and hence very likely related to knee pain.

New Long-Term Opioid Users

The total proportion of long-term opioid users increased postoperatively by 4% for "pain without loosening", but 9% new long-term opioid users were generated. This increase in new long-term opioid users cannot be considered acceptable for patients undergoing revision aiming to achieve pain relief, considering the exposure to surgical risk and potential harmful side effects of persistent opioid consumption. Patients revised for "aseptic loosening" had similar outcomes, but they were potentially relieved of their mechanical problem. Early and late revisions for "aseptic loosening" are potentially 2 very different groups of patients, but our sensitivity analysis did not prove any differences in the development of new long-term opioid use. Our results are consistent with the findings of other studies. One study found an increase in new long-term opioid users of 20% after revision knee arthroplasty compared to 10% after TKA [23]. A study of opioid use after spinal surgery found 10% new long-term users postoperatively [21]. Hence, the risk of patients becoming new long-term opioid users after major surgery should be taken into consideration at the preoperative stage.

Predictors

We found other opioid-requiring diagnoses or procedures within the first postoperative year, CCI $\geq$3, and consumption of NSAID and other analgesics to predict postoperative long-term opioid use. This finding is consistent with other studies. Other proposed predictors are young age, female sex, and depression, but we could not show any impact from these variables [14,24].

Strengths and Limitations

To our knowledge, this is the first study to analyze the analgesic consumption of patients undergoing revision knee arthroplasty for the indications "pain without loosening" versus "aseptic loosening". The data are nationwide and over 95% complete [2]. There are limitations to this study. The indications "pain without loosening" and "aseptic loosening" has not been validated in the DKR. It is subjectively chosen by the surgeon, and it might cover a broad spectrum of other hidden indications. We lack information on the dosage and actual consumption of each prescribed drug. The indications for prescriptions are not available in the register, and this is a major limitation to the study because the prescription might have been for reasons other than knee pain. We do not have information on over-the-counter sale of NSAID or paracetamol, though most patients receiving extensive amounts of these drugs usually get them prescribed, making the influence on our results limited. Furthermore, this study does not include health-related quality of life measures, and this must be included in the overall assessment of the possible beneficial effects of revision knee arthroplasty surgery.

Conclusion

The consumption of opioids decreased slightly after knee arthroplasty revision for the indication "pain without loosening", but not for "aseptic loosening". The amount of new long-term opioid users increased for both indications. Considering this, we cannot conclude that patients revised for "pain without loosening" benefited from surgery, but patients revised for "aseptic loosening" may have had their mechanical problem resolved. Other opioid-requiring diagnoses or procedures within the first postoperative year, CCI $\geq$3, and consumption of NSAID and other analgesics predicted postoperative long-term opioid use.

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Appendix A

Supplementary Table 1
Number of Users of Analgesic Drugs in the 4 Quarters Before and After Revision for the Indications "Pain Without Loosening" and "Aseptic Loosening".

Analgesic	Indication	-Q4	-Q3	-Q2	-Q1	Q1	Q2	Q3	Q4	*P*-Value (X^2: Difference −Q4 and Q4)
N										
Pain without loosening		1,037	1,037	1,037	1,037	1,033	1,031	1,029	1,025	
Aseptic loosening		2,317	2,317	2,317	2,317	2,308	2,298	2,290	2,280	
Opioids	Pain without loosening	380 (37)	401 (39)	375 (36)	376 (36)	817 (79)	391 (38)	359 (35)	330 (32)	.021
	Aseptic loosening	655 (29)	676 (29)	696 (30)	778 (34)	1,734 (75)	794 (35)	722 (32)	680 (30)	.285
Paracetamol	Pain without loosening	462 (45)	488 (47)	492 (47)	510 (49)	698 (68)	542 (53)	531 (52)	525 (51)	.006
	Aseptic loosening	1,022 (44)	1,052 (45)	1,081 (47)	1,159 (50)	1,590 (69)	1,154 (50)	1,133 (49)	1,115 (49)	.001
NSAID	Pain without loosening	363 (35)	355 (34)	349 (34)	333 (32)	545 (53)	320 (31)	280 (27)	292 (28)	.001
	Aseptic loosening	762 (33)	736 (32)	767 (33)	742 (32)	1,093 (47)	664 (29)	632 (27)	577 (25)	<.001
Anticonvulsants	Pain without loosening	71 (7)	83 (8)	78 (8)	69 (7)	126 (12)	90 (9)	91 (9)	93 (9)	.073
	Aseptic loosening	162 (7)	171 (7)	154 (7)	159 (7)	267 (12)	189 (8)	189 (8)	184 (8)	.219
Antidepressants	Pain without loosening	138 (13)	136 (13)	129 (12)	138 (13)	144 (14)	140 (14)	151 (15)	145 (14)	.654
	Aseptic loosening	321 (14)	317 (14)	327 (14)	313 (14)	329 (14)	314 (14)	337 (15)	339 (15)	.449
Other	Pain without loosening	121 (12)	118 (11)	121 (12)	115 (11)	148 (14)	107 (10)	110 (11)	95 (9)	.062
	Aseptic loosening	212 (9)	231 (10)	240 (10)	251 (11)	301 (13)	187 (8)	194 (8)	199 (9)	.502

NSAID, non-steroidal anti-inflammatory drug.

Supplementary Table 2
Number of Opioid Users in the 4 Quarters Before and After Revision by Surgical Subgroup for the Indications "Pain Without Loosening" and "Aseptic Loosening".

Subgroup	Indication	n	-Q4	-Q3	-Q2	-Q1	Q1	Q2	Q3	Q4	*P*-Value (X^2: Difference −Q4 and Q4)
Total	Pain without loosening	1,037	380 (37)	401 (39)	375 (36)	376 (36)	817 (79)	391 (38)	359 (35)	330 (32)	.021
	Aseptic loosening	2,317	655 (29)	709 (29)	731 (30)	810 (33)	1,809 (74)	830 (34)	761 (31)	680 (29)	.627
1: TKA-TKA	Pain without loosening	341	128 (38)	148 (43)	132 (39)	129 (38)	282 (83)	143 (42)	123 (36)	123 (36)	.691
	Aseptic loosening	1,507	410 (27)	429 (28)	448 (30)	521 (35)	1124 (75)	525 (35)	474 (31)	441 (29)	.210
2: Partial revision	Pain without loosening	117	51 (44)	56 (48)	48 (41)	48 (41)	87 (74)	48 (41)	43 (37)	41 (35)	.181
	Aseptic loosening	441	158 (36)	155 (35)	145 (33)	154 (35)	314 (71)	155 (35)	148 (34)	142 (32)	.255
4: UKA-TKA	Pain without loosening	445	150 (34)	149 (33)	153 (34)	152 (34)	365 (82)	161 (36)	152 (34)	128 (29)	.112
	Aseptic loosening	369	97 (26)	92 (25)	103 (28)	103 (28)	296 (80)	114 (31)	100 (27)	97 (26)	1.000
5: Secondary patellabutton	Pain without loosening	134	51 (38)	48 (36)	42 (31)	47 (35)	83 (62)	39 (29)	41 (31)	38 (28)	.092
	Aseptic loosening	-	-	-	-	-	-	-	-	-	-

UKA, unicompartmental knee arthroplasty; TKA, total knee arthroplasty.

Supplementary Table 3
Analgesic Drugs Included in This Study With ATC Codes.

Category	Medicine and ATC-Codes
Opioids	Fentanyl (N01AH01); Morphin (N02AA01); Hydromorphone (N02AA03); Nicomorphin (N02AA04); Oxycodon (N02AA05); Oxycodon and Naloxon (N02AA55); Ketobemidon (N02AB01); Pethidin (N02AB02); Fentanyl(N02AB03); Dextropropoxyphene (N02AC04); Pentazocin (N02AD01); Buprenorphin (N02AE01); Tramadol (N02AX02); Tapentadol (N02AX06)
Paracetamol	Paracetamol (N02BE01)
NSAID	Phenylbutazone (M01AA01); Sulindac (M01AB02); Diclofenac (M01AB05); Etodolac (M01AB08); Aceclofenac (M01AB16); Diclofenac (M01AB55); Piroxicam (M01AC01); Tenoxicam (M01AC02); Lornoxicam (M01AC05); Meloxicam (M01AC06); Ibuprofen (M01AE01); Naproxen (M01AE02); Ketoprofen (M01AE03); Fenoprofen (M01AE04); Flurbiprofen (M01AE09); Tiaprofensyre (M01AE11); Dexibuprofen (M01AE14); Dexketoprofen (M01AE17); Naproxen og Esomeprazol (M01AE52); Tolfenamsyre (M01AG02); Celecoxib (M01AH01); Rofecoxib (M01AH02); Etoricoxib (M01AH05); Nabumeton (M01AX01); Acetylsalicylsyre (N02BA01); Diflunisal (N02BA11); Acetylsalicylsyre, comb. excl. psycholeptica (N02BA51); Salicylamid, combinations with psycholeptics (N02BA75); Phenazone, combinations excl. psycholeptics (N02BB51)
Anticonvulsants	Phenobarbital (N03AA02); Primidone (N03AA03); Phenytoin (N03AB02); Clonazepam (N03AE01); Carbamazepin (N03AF01); Oxcarbamazepin (N03AF02); Valproinsyre (N03AG01); Vigabatrin (N03AG04); Lamotrigin (N03AX09); Topiramat (N03AX11); Gabapentin (N03AX12); Levetiracetam (N03AX14); Zonisamid (N03AX15); Pregabalin (N03AX16)
Antidepressants	Imipramin (N06AA02); Clomipramin (N06AA04); Trimipramin (N06AA06); Amitriptylin (N06AA09); Nortriptylin (N06AA10); Doxepin (N06AA12); Dosulepin (N06AA16); Amoxapin (N06AA17); Maprotilin (N06AA21); Fluoxetin (N06AB03); Citalopram (N06AB04); Paroxetin (N06AB05); Sertralin (N06AB06); Fluvoxamin (N06AB08); Escitalopram (N06AB10); Isocarboxazid (N06AF01); Moclobemide (N06AG02); Mianserin (N06AX03); Mirtazapin (N06AX11); Bupropion (N06AX12); Venlafaxin (N06AX16); Reboxetin (N06AX18); Duloxetin (N06AX21) Agomelatin (N06AX22); Vortioxetin (N06AX26)
Other drugs	Indometacin (M01AB01); Glucosamin (M01AX01); Cannabidiol (N03AX24); Methadon (N07BC02); Codein (R05DA04); Ketobemidon og antispasmodica (N02AG02); Codein og paracetamol (N02AJ06); Codein and acetylsalicylsyre (N02AJ07)

Supplementary Table 4
Charlson Comorbidity Index Diagnosis With International Classification of Diseases, 8th and 10th Edition, and Charlson Weight.

Charlson Comorbidity	International Classification of Diseases, 8th Edition	International Classification of Diseases, 10th Edition	Charlson Weight
Myocardial infarction	410	DI121–22, DI252	0
Congestive heart failure	42709–10, 42719, 42899, 78249	DI099–110, DI130, DI132, DI255, DI420, DI425–29, DI43, DI50, DP290	2
Peripheral vascular disease	440-45	DI70–71. DI731, DI738-39, DI771, DI790, DI792, DK551, DK558–59, DZ958-59	0
Cerebrovascular disease	430-38	DG45–46, DH340, DI60-69	0
Dementia	2900–1, 29309	DF00-3, DF051, DG30, DG311	2
Chronic pulmonary disease	490-93, 515-18	DI278–79, DJ40-47, DJ60–67, DJ684, DJ701, DJ703	1
Rheumatologic disease	712, 716, 734, 446, 13599	DM05-6, DM315, DM32-34, DM351, DM353, DM360	1
Peptic ulcer disease	53091, 53098, 531-34	DK25–28	0
Mild liver disease	571, 57301, 57304	DB18, DK700–3, DK709, DK713-15, DK717, DK73–74, DK760, DK762–64, DK768, DZ944	2
Diabetes without chronic complications	24900, 24906–7, 24909, 25000, 25006–7, 25009	DE100-1, DE106, DE108-111, DE116, DE118-21, DE126, DE128-31, DE136, DE138–41, DE146, DE148, DE149	0
Diabetes with chronic complications	24901–5, 24908, 25001-5, 25008	DE102-5, DE107, DE112–15, DE117, DE122-25, DE127, DE132-35, DE137, DE142–45, DE147	1
Hemiplegia or paraplegia	344	DG041, DG114, DG801-2, DG81-82, DG830-34, DG839	2
Renal disease	403-4, 580-84, 59009, 59319, 7531, 792	DI120, DI131, DN032-37, DN052-57, DN18–19, DN250, DZ490-92, DZ940, DZ992	1
Any malignancy, including leukemia and lymphoma	140-72, 174-94, 200-7, 27559	DC00-26, DC30-34, DC37-41, DC43, DC45-58, DC60-76, DC81-85, DC88, DC90-97	2
Moderate or severe liver disease	7000, 7002, 7004, 7006, 57300, 4560	DI850, DI859, DI864, DI982, DK704, DK711, DK721, DK729, DK765–67	4
Metastatic solid tumor	195-99	DC77-80	6
AIDS/HIV	7983	DB20-22, DB24	4

Supplementary Table 5
Concurring analgesic-Requiring Diagnoses/Procedures with International Classification of Diseases, 8th and 10th edition, and Procedure Codes.

Diagnosis/Procedure	ICD-8/ICD-10 Code or Procedure Code
Fibromyalgia	DM797
Cancer	14009-21000/ 22000-23999/DC000-DC991
Back pain/disorder	72500-72709/72839-72899/DM500-DM549
Neck pain/disorder	DS134, DS134A-G
Peripheral neuropathy	24903/25003/DG600-DG638
Arthroplasty	KNBB0, KNBB01-2, KNBB09, KNBB11-12, KNBB19, KNBB20, KNBB30, KNBB40, KNBB59, KNBB80-82, KNBB89, KNBB99, KNBC01-2, KNBC09, KNBC11-12, KNBC19, KNBC20-22, KNBC29, KNBC30-32, KNBC39, KNBC40-42, KNBC49, KNBC59, KNBC80-82, KNBC89, KNBC99, KNCB0, KNCB01-4, KNCB09, KNCB1, KNCB11-14, KNCB19, KNCB20, KNCB30, KNCB40, KNCB59, KNCB69, KNCB99, KNCC01-4, KNCC09, KNCC11-14, KNCC19, KNCC20-24, KNCC29, KNCC30-34, KNCC39, KNCC40-44, KNCC49, KNCC59, KNCC99, KNDB0, KNDB01-3, KNDB09, KNDB1, KNDB11-13, KNDB19, KNDB2, KNDB20-23, KNDB29, KNDB3, KNDB30-33, KNDB39, KNDB4, KNDB40-43, KNDB49, KNDB5, KNDB50, KNDB59, KNDB8, KNDB80, KNDB80A-B, KNDB81, KNDB81A-B, KNDB82, KNDB82A-B, KNDB83, KNDB83A-B, KNDB89, KNDB89A-B, KNDB99, KNDB0, KNDC01-3, KNDC09, KNDC1, KNDC11-13, KNDC19, KNDB2, KNDB20-23, KNDB29, KNDC3, KNDC30-33, KNDC39, KNDC4, KNDC40-43, KNDC49, KNDC5, KNDC50-53, KNDC59, KNDC8, KNDC80, KNDC80A-B, KNDC81, KNDC81A-B, KNDC82, KNDC82A-B, KNDC83, KNDC83A-B, KNDC89, KNDC89A-B, KNDC99, KNFB0, KNFB01-3, KNFB09, KNFB1, KNFB11-13, KNFB19, KNFB20, KNFB30, KNFB40, KNFB59, KNFB99, KNFC0, KNFC01-3, KNFC09, KNFC1, KNFC11-13, KNFC19, KNFC2, KNFC20-23, KNFC29, KNFC3, KNFC30-33, KNFC39, KNFC4, KNFC40-43, KNFC49, KNFC59, KNFC99, KNGB0, KNGB01-4, KNFB09, KNGB1, KNFB11-14, KNFB19, KNGB20, KNGB30, KNGB40, KNGB59, KNGB99, KNGB99A, KNGC0, KNGC01-2, KNGC02A, KNGC03-4, KNCG09, KNGC1, KNGC11-12, KNGC12A, KNGC13-14, KNGC19, KNGC2, KNGC20-22, KNGC22A, KNGC23-24, KNGC29, KNGC3, KNGC30-32, KNGC32A, KNGC33-34, KNGC39, KNGC4, KNGC40-42, KNGC42A, KNGC43-44, KNGC49, KNGC59, KNGC59A, KNGC99, KNGC99A, KNHB0, KNHB01-3, KNHB09, KNHB1, KNHB11-13, KNHB19, KNHB20, KNHB30, KNHB40, KNHB59, KNHC0, KNHC01-2, KNHC09, KNHC1, KNHC11-12, KNHC19, KNHC2, KNHC20-23, KNHC29, KNHC3, KNHC30-33, KNHC39, KNHC4, KNHC40-43, KNHC49, KNHC59

ICD-8, International Classification of Diseases, 8th edition; ICD-10, International Classification of Diseases, 10th edition.

Supplementary Table 6
Development in Long-Term Opioid Users 1 y After Revision for the Indications "Pain Without Loosening" and "Aseptic Loosening" Sensitivity Analysis of Yearly and Late Revisions for "Aseptic Loosening".

Subgroup	Indication	n	Preoperative Chronic User (-Q4, -Q3, -Q2, -Q1)	Postoperative Chronic User (Q4, Q3, Q2, Q1)	New Chronic Users	Change in Chronic Users
Total	Pain without loosening	1,037	191 (18%)	231 (22%)	94 (9%)	40↑ (4%)
	Aseptic loosening	2,317	407 (18%)	486 (21%)	178 (8%)	79↑ (3%)
Time from primary surgery to TKA <2 y for aseptic loosening	Aseptic loosening	665	139 (21%)	159 (24%)	58 (8%)	20↑ (3%)
Time from primary surgery to TKA >2 y for aseptic loosening	Aseptic loosening	1,652	268 (16%)	327 (20%)	120 (7%)	59↑ (4%)

Paper IV

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Patient-Reported Outcomes and Satisfaction 1 to 3 Years After Revisions of Total Knee Arthroplasties for Unexplained Pain Versus Aseptic Loosening

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ABSTRACT

Background: It is unknown if patients are relieved of pain after knee arthroplasty revision for unexplained pain. The aim of this cross-sectional case-control study was to compare patient-reported outcome measures (PROMs) and satisfaction 1 to 3 years after revision of total knee arthroplasties (TKAs) for the indications of unexplained pain versus aseptic loosening.

Methods: We included 384 patients undergoing TKA revision for the indications of unexplained pain and aseptic loosening from January 1, 2018 to December 31, 2020 from the Danish Knee Arthroplasty Register. A total of 81 patients were revised for unexplained pain and 303 for aseptic loosening. Questionnaires including PROMs (Oxford Knee Score, EQ-5D-5L, and Forgotten Joint Score) and satisfaction with the surgery on a 0-100 scale (100 = not satisfied; 0 = very satisfied) were sent to digitally secured mailboxes. Time from revision to data collection was a median 3.1 years (range, 1.4-4.4 years).

Results: Median Oxford Knee Score was 25 (interquartile range [IQR] 15) versus 31 (IQR 18) 1-3 years after revisions for unexplained pain versus aseptic loosening, $P = .009$. Median EQ-5D-5L was 0.6 (IQR 0.4) versus 0.8 (IQR 0.3) for unexplained pain versus aseptic loosening, $P = .009$. Median Forgotten Joint Score was 50 (IQR 7) versus 50 (IQR 16) for unexplained pain versus aseptic loosening, $P = .905$. Satisfaction was 75 (IQR 38) for unexplained pain and 50 (IQR 73) for aseptic loosening, $P < .001$.

Conclusion: Patients undergoing TKA revision for the indication of unexplained pain had worse results on PROMs than those revised for aseptic loosening. Likewise, patients revised for unexplained pain were less satisfied compared to patients revised for aseptic loosening. This information is valuable to both surgeons and patients when candidates for revision surgery are selected, to obtain the best possible outcomes.

The number of knee arthroplasty revisions performed annually is increasing [1]. It is well known that about 20% of patients undergoing primary knee arthroplasty experience persistent pain afterward but the proportion after revision might be even higher [2,3]. Some patients are revised because of unexplained pain without any other obvious knee pathology present, but it is unknown if these patients are relieved of pain after surgery. The indication of unexplained pain is controversial and generally not

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recommended but still widely used [4,5]. Although revision knee surgery for aseptic reasons may be as safe as primary surgery, patients are less satisfied after revision [6–8]. The use of opioids and other analgesics does not seem to decrease considerably after revision because of pain, suggesting a lack of effect on pain relief [9]. This also applied to patients revised for aseptic loosening. However, they might have had a mechanical problem, which was solved by revision.

Investigations of patient's perspectives are essential when it comes to estimations of pain and life quality. Data on patient-reported outcomes (PROs) after revision knee arthroplasty are limited [10,11]. It is unknown if the patients revised because of unexplained pain are as satisfied with the results as patients revised for the more well-established indication of aseptic loosening. Further knowledge of revisions performed because of unexplained pain is warranted to improve the selection of candidates for revision surgery.

Therefore, the aim of this study was to compare patient-reported outcome measures (PROMs) and satisfaction 1 to 3 years after revision of total knee arthroplasties (TKAs) for the indications of unexplained pain versus aseptic loosening.

Methods

Study Design

This cross-sectional nationwide case-control study was conducted in accordance with the consensus-based standards for the selection of health measurement instruments reporting guidelines for PROM studies [12].

Participants and Data Sources

Data on all knee arthroplasty revisions registered for the indication of unexplained pain or aseptic loosening exclusively in the period January 1, 2018 to December 31, 2020 were collected from the Danish Knee Arthroplasty Register (DKR). The DKR is a nationwide clinical database collecting data on primary and revision knee arthroplasties in Denmark since 1997 [13]. All orthopaedic departments, including private hospitals, report preoperative and intraoperative data to the database. The completeness of the register was 97% for primary knee arthroplasties and 92% for revision knee arthroplasties in 2020 [1]. We retrieved demographic data on age, gender, and body mass index from the DKR. A total of 384 patients were included in the study (Fig. 1). There were 81 patients revised for the indication of unexplained pain and 303 for the indication of aseptic loosening. The overall response rate was 68%. The demographic characteristics were overall alike for responders revised for unexplained pain versus aseptic loosening (Table 1).

We selected the study period 2018-2020, so that time from revision would not exceed 4 years. PROs from patients revised before this time period might be memory-biased and thus not relevant for this study. We included all revisions registered in the DKR for the two indications of investigation and therefore no sample size calculation was performed. We divided the revisions into surgical subgroups defined by the types of prostheses removed and inserted at surgery. We included surgical subgroup 1 (total revision of both femoral and tibial component in a TKA to new TKA) and surgical subgroup 2 (partial revision of either femoral or tibial component in a TKA). The excluded surgical subgroups were not relevant for the study and the number of revisions in most of the excluded groups was too low to perform a meaningful analysis (Fig. 1).

Outcomes

Data Collection

All included patients received an e-mail with a link to an electronic questionnaire in a secured digital mailbox, which linked to the patient's Danish personal registration number. If the questionnaires were not answered within 2 weeks, two reminder

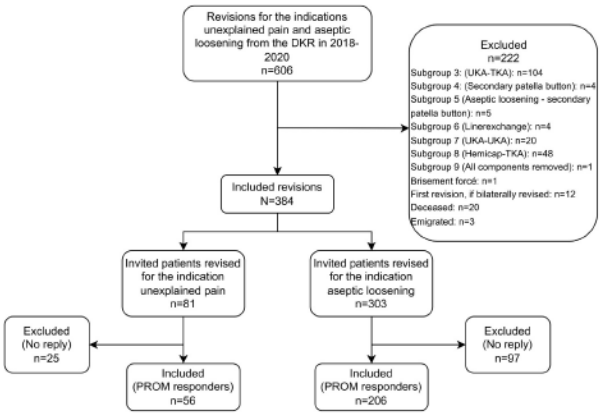

Fig. 1. Flowchart of patients included/excluded in this study. DKR, Danish knee arthroplasty register; UKA, unicompartmental knee arthroplasty; TKA, total knee arthroplasty; PROM, patient-reported outcome measure.

Table 1
Demographic Characteristics of Included Patients for Responders and Nonresponders of Patient-Reported Outcomes.

Characteristic	Responders		*P* Value	Nonresponders		*P* Value
	Pain	Aseptic Loosening		Pain	Aseptic Loosening	
	n = 56 (69%)	n = 206 (68%)		n = 25 (31%)	n = 97 (32%)	
Mean age in years (range)	65 (29-82)	69 (47-91)	.003	65 (44-80)	69 (43-92)	.039
Women (%)	31 (55%)	123 (60%)	.557	17 (68%)	56 (58%)	.350
BMI (Median [IQR]) (3 missing values)	24 (IQR 13)	22 (IQR 12)	.032	21 (IQR 10)	22 (IQR 12)	.649
Surgical subgroup			.572			.137
1. TKA-TKA	49 (88%)	174 (84%)		16 (64%)	76 (78%)	
2. Partial revision	7 (12%)	32 (16%)		9 (36%)	21 (22%)	
Time from primary surgery to revision (Mean [SD])	4.7 (SD 3.9)	6.4 (SD 5.5)	.313	3.9 (SD 3.5)	7.3 (SD 5.8)	.530
Follow-up (Years from revision to data collection) (Median [range])	3.4 (1.5-4.4)	3 (1.4-4.4)	.009	3 (1.6-4.4)	2.9 (1.4-4.4)	.222

PROM, Patient-Reported Outcome Measure; SD, standard deviation; BMI, body mass index; IQR, interquartile range; TKA, total knee arthroplasty; UKA, unicompartmental knee arthroplasty.

e-mails were sent with a 2-week interval. Patients who were not registered to the digital mailbox received a paper version of the questionnaire by postal mail. Paper versions were also sent on request. Study data were collected and managed using REDCap electronic data capture tools hosted at Odense Explorative Patient data Network (OPEN), Odense, Denmark [14,15].

Questionnaires

We included the standardized questionnaires Oxford Knee Score (OKS), EQ-5D-5L, Forgotten Joint Score (FJS), and Copenhagen Knee range of motion (ROM) Scale, and we further asked questions about pain, satisfaction, and reason for revision.

Oxford Knee Score

OKS was calculated from the validated joint specific 12-item questionnaire developed in 1998 to measure outcomes after TKA and it was translated into Danish in 2009 [16,17]. A score of 0 to 48 was calculated, with 48 being the best possible score. Calculation of the OKS followed recommendations from the developers [18].

EQ-5D-5L

EQ-5D-5L consists of a 5-item questionnaire and the EQ visual analogue scale (EQ VAS) designed to measure health state. The Danish edition was validated in 2021 [19]. The EQ Index was calculated from the United Kingdom value set, which was developed from a population sample from 6 countries including Denmark [20].

Forgotten Joint Score

FJS was calculated from the 12-item questionnaire developed in 2012 and translated and validated in Danish in 2016 [21,22]. A total score of 0-100 was obtained. A high score indicated a high degree of "forgetting" the artificial joint. The FJS is an efficient tool for evaluation of small differences in knee performance after surgery. The FJS score was calculated following the instructions by the developers [21].

Copenhagen Knee Range of Motion

We used the Copenhagen Knee ROM Scale to estimate the ROM of the revised knees [23]. The patients reported ROM from the 2-item scale with 11 illustrations of knee motion.

Pain

We asked the patients about their level of pain. The answers were reported on a VAS.

"What was your average pain level the last month on a 0 to 100 scale" (0 = no pain; 100 = worst pain imaginable)

Satisfaction

We asked questions about the satisfaction after surgery.

"How satisfied are you with the result of the surgery on a 0 to 100 scale" (0 = very satisfied; 100 = not satisfied)

Improvement. "How are your knee problems now compared to prior to the operation?"

Data Analyses

Data were presented with means and standard deviations (SDs) for normally distributed continuous variables and median and interquartile range (IQR) for non-normally distributed continuous variables. Distributions were inspected for normality via quantile-quantile plots. Frequency counts and percentages were provided for categorical variables. Pearson's Chi-squared tests were used to test for statistical differences between categorical measures. Wilcoxon Rank-Sum tests were used to test non-normally distributed continuous variables for statistical differences.

Missing data of the respective PROMs were handled as recommended by the developers [18,21,24].

Table 2
Patient-Reported Outcomes of Patients Revised for the Indication of Unexplained Pain Versus Aseptic Loosening.

PROM	Unexplained Pain	Aseptic Loosening	*P* Value
	N = 56	N = 206	
Oxford Knee Score[a]	25 (IQR 15)	31 (IQR 18)	.009[b]
EQ-5D-5L Index[a]	0.6 (IQR 0.4)	0.8 (IQR 0.3)	.009[b]
EQ VAS[a]	61 (IQR 37)	60 (IQR 40)	.276[b]
FJS[a]	50 (IQR 7)	50 (IQR 16)	.905[b]
Copenhagen Knee ROM			
Flexion[a]	5 (IQR 1)	5 (2)	.035[b]
Flexion deficit (0-4)	23 (41%)	54 (26%)	.035
Extension[a]	4 (IQR 1)	4 (IQR 2)	.083[b]
Extension deficit (0-3)	21 (42%)	61 (29%)	.258

If no statistical test is mentioned for *P* values, Chi-squared test was used.
PROM, Patient-reported outcome measure; IQR, interquartile range; EQ-5D-5L Index, a value of 1 indicates the best quality of life and 0 indicate the worst; EQ VAS, EuroQol Visual Analogue Scale: 100 = best health imaginable and 0 = worst health imaginable; Copenhagen Knee ROM = Copenhagen Knee Range of Motion.
[a] Median (IQR).
[b] Wilcoxon Rank-Sum test.

Table 3
Questions on Pain and Satisfaction.

Question	Unexplained Pain n = 56	Aseptic Loosening n = 206	*P* Value
Pain			
What was your average pain level the last month on a 0-100 scale; 0 = no pain; 100 = worst pain imaginable[a]	62 (IQR 41)	45 (IQR 56)	.008[b]
Satisfaction			
How satisfied are you with the result of the surgery on a 0-100 scale; 0 = very satisfied; 100 = not satisfied[a]	75 (IQR 38)	50 (IQR 73)	< .001[b]
Improvement. How are your knee problems now compared to prior to the operation?			.356
Importantly improved	25 (69%)	116 (77%)	
Not importantly improved	11 (31%)	35 (23%)	
Do you find your present situation acceptable considering your daily level of function?			.005
Yes	19 (35%)	109 (57%)	
No	35 (65%)	83 (43%)	
The question was only asked to patients replying no to the above: Do you think the treatment has failed?			.790
Yes	21 (64%)	53 (66%)	
No	12 (36%)	27 (34%)	
Would you go through the surgery again?			.263
Yes	19 (35%)	91 (47%)	
Maybe	21 (39%)	67 (35%)	
No	14 (26%)	36 (18%)	

If no statistical test is mentioned for *P* values, Chi-squared test was used.
IQR, interquartile range.
[a] Median (IQR).
[b] Wilcoxon Rank-Sum test.

Statistical significance was set at the 5% level. For all analyses, we used Stata Statistical Software: Release 17. College Station, Texas: StataCorp LLC.

Ethics and Funding

Permission from the Danish Data Protection Agency was achieved (Journal no. 19/14,416). We achieved accept to contact the patients in our study from the Head of Departments of all included departments performing the revisions.

The authors had no conflicts of interest to declare.

Results

Patient-Reported Outcome Measures

Median OKS was 25 (IQR 15) for unexplained pain versus 31 (IQR 18) for aseptic loosening 1-3 years after revision, $P = .009$ (Table 2 and Fig. 2). Median EQ-5D-5L was 0.6 (IQR 0.4) for unexplained pain and 0.8 (IQR 0.3) for aseptic loosening 1-3 years after revision, $P = .009$ (Table 2 and Fig. 3). There were no differences in these scores within indication groups comparing revisions after 1-2 years versus > 2 to 3 years (Supplementary Table 1).

There were no differences in EQ VAS and FJS between indication groups. The flexion ability estimated by the Copenhagen Knee ROM was slightly better for revisions for aseptic loosening than for unexplained pain (Table 2). PROMs at a surgical subgroup level showed similar results (Supplementary Table 2).

Pain

The average pain score was significantly worse for unexplained pain than aseptic loosening, $P = .008$ (Table 3 and Fig. 4).

Satisfaction

The average satisfaction score was significantly worse for unexplained pain than aseptic loosening, $P < .001$ (Table 3 and Fig. 5). Patients revised for unexplained pain were also less likely to find their knee problem importantly improved or their daily level of function acceptable (Table 3). Scores for pain and satisfaction at a surgical subgroup level showed similar results (Supplementary Table 3).

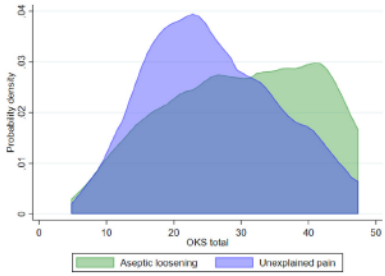

Fig. 2. OKS for the indications of revision unexplained pain and aseptic loosening presented as kernel curves. OKS, oxford knee score.

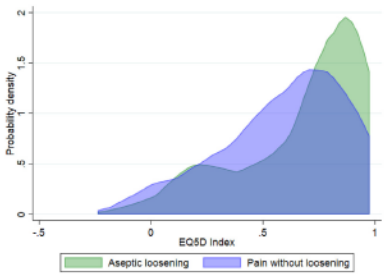

Fig. 3. EQ-5D Index for the indications of revision unexplained pain and aseptic loosening presented as kernel curves.

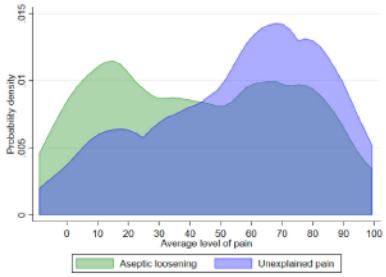

Fig. 4. Average level of pain (0 = no pain; 100 = worst pain imaginable) presented as kernel curves for the indications of revision unexplained pain and aseptic loosening.

Discussion

This was a nationwide study of PROM and satisfaction data from 384 patients collected 1 to 3 years after knee arthroplasty revision for the indications of unexplained pain versus aseptic loosening. We found significantly lower OKS and EQ-5D-5L Index scores for patients revised for unexplained pain. Patients revised for unexplained pain were less satisfied with the result of the surgery. There were 69% revised for pain versus 77% revised for aseptic loosening who considered the result of the surgery an important improvement. The author group has previously conducted a survival study including the same indications as in this study: unexplained pain and aseptic loosening. We found similar rerevision rates between groups [25].

Patient-Reported Outcome Measures

Baker et al investigated PROMs of a cohort of 996 revision patients recorded by the National Joint Registry for England and Wales from 2008 to 2010 [11]. Mean postrevision OKS was 26.4 (95% CI 23.5 to 29.3) for unexplained pain and 27.8 (95% CI 26.6 to 28.9) for aseptic loosening/lysis. Sabah et al investigated a cohort of 10,727 revision patients recruited from the UK National Health Service PROMs dataset from 2013 to 2019. They reported postrevision OKS of 29.0 without a specification of indications [10]. These scores are concordant with those of our study for both indication groups, although we did find a statistical significant difference between groups.

EQ-5D Index values of 0.5–0.7 after revision have been reported [10,11,26]. We reported higher values in our study. Index values differ among populations and the average EQ-5D Index of the Danish population is 0.9; thus, the revised patients had a worse quality of life than expected of Danish citizens [19].

A larger proportion of patients revised for unexplained pain (41%) had a flexion deficit than patients revised for aseptic loosening (26%) estimated by the Copenhagen Knee ROM. A study investigating a cohort of patients revised for unexplained pain also found a large proportion of pain patients with a decreased ROM [27]. The study found poor results of revisions for unexplained pain, especially for those with normal ROM. We did not detect differences in PROMs 1-2 years versus > 2-3 years after revision in both indication groups. This was expected because PROMs after revision have been shown to peak and stabilize after 1 year for most patients [28]. The PROMs were similar among the surgical subgroups. This could indicate a stronger influence of the indication for revision on the outcomes than the influence of the surgical subgroups.

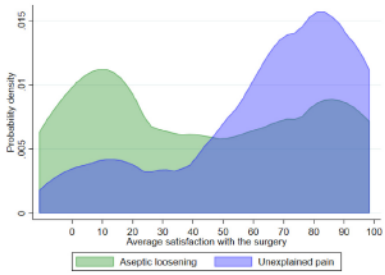

Fig. 5. Average level of satisfaction with the surgery (0 = very satisfied; 100 = not satisfied) presented as kernel curves for the indications of revision unexplained pain and aseptic loosening.

Satisfaction

Satisfaction rates of 72%-88% after aseptic revisions have been reported [10,29]. Baker et al reported satisfaction rates after revision of 58% versus 72% of patients revised for unexplained pain versus aseptic loosening [11]. Sabah et al concluded that two-thirds of the patients achieved a clinically meaningful improvement in joint function [10]. These results correspond to those of our study and it seems that patients revised because of pain are generally less satisfied.

Strengths and Limitations

This was a nationwide study contributing with important information on PROs after knee arthroplasty revisions. Our study provides valuable data on what can be achieved after revision for unexplained pain and aseptic loosening.

We did not have prerevision PROs available for this study, as these are not captured in the DKR; thus, the delta change in PROs may actually not be different between groups, which is a major limitation. In addition, it is unknown if the indication groups differed at baseline or improved/worsened equally. The additional questions asked in this study do bring some information of the patient self-reported improvements or worsening, although memory bias might influence the answers.

The response rate of 68% may be acceptable in a nationwide study; however, results were less certain when responses were not complete. There are missing data in this study, as all patients did not complete or answer every item of each questionnaire. We accounted for this in the data analyses but it could potentially skew the results.

Conclusion

Patients undergoing TKA revision for the indication of unexplained pain had worse results on PROMs than those revised for aseptic loosening. Likewise, patients revised for unexplained pain were less satisfied compared to patients revised for aseptic loosening. This information is valuable to both surgeons and patients when candidates for revision surgery are selected, to obtain the best possible outcomes.

Acknowledgments

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Appendix

Supplementary Table 1
Patient-Reported Outcome Measures Presented as Total Scores for Unexplained Pain and Aseptic Loosening and as Scores in Two Time Periods Defined as Time From Revision to Data Collection (1-2 Y Versus 3 to < 4 Y) for Each Indication.

PROM Outcome Measure	Unexplained Pain			P (1-2Y Versus > 2-3)	Aseptic Loosening			P (1-2Y Versus > 2-3Y)	P (Pain Versus AL)
	Total n (%) n = 56	1-2 Y n (%)	>2-3 Y n (%)		Total n (%)	1-2 Y n (%)	>2-3 Y n (%)		
		n = 23	n = 33		n = 206	n = 104	n = 102		
Oxford Knee Score[a]	25 (15)	26 (16)	24 (12)	0.667[b]	31 (18)	31 (19)	31 (17)	0.338[b]	0.009[b]
EQ-5D-5L Index[a]	0.6 (0.4)	0.7 (0.3)	0.6 (0.4)	0.311[b]	0.8 (0.3)	0.8 (0.4)	0.8 (0.3)	0.176[b]	0.009[b]
EQ VAS[c]; 100 best health imaginable-0 worst health imaginable	61 (37)	65 (32)	50 (41)	0.306[b]	60 (40)	62 (32)	53 (40)	0.257[b]	0.276[b]
FJS[a]	50 (7)	50 (9)	48 (10)	0.112[b]	50 (16)	50 (13)	48 (16)	0.61[b]	0.905[b]
Copenhagen Knee ROM									
Flexion[a]	5 (1)	4 (2)	5 (2)	0.122[b]	5 (2)	5 (1)	5 (2)	0.706[b]	0.035[b]
Flexion deficit (0-4)	23 (41%)	12 (52%)	11 (33%)	0.242	54 (26%)	24 (23%)	30 (29%)	0.354	0.035
Extension[a]	4 (1)	4 (1)	4 (1)	0.998[b]	4 (2)	4 (1)	4 (2)	0.647[b]	0.083[b]
Extension deficit (0-3)	21 (42%)	8 (47%)	13 (38%)	0.675	61 (29%)	31 (29%)	30 (28%)	0.909	0.258
Additional questions									
What do you think was the reason for reoperation of your knee?									
Pain	23 (43%)	12 (52%)	11 (35%)		51 (27%)	29 (30%)	22 (23%)		
Loosening of the components	7 (13%)	2 (9%)	5 (16%)		83 (43%)	42 (43%)	41 (43%)		
Instability	8 (15%)	3 (13%)	5 (16%)		21 (11%)	6 (6%)	15 (16%)		
Decreased range of motion	13 (24%)	6 (26%)	7 (23%)		16 (8%)	9 (9%)	7 (7%)		
Other	3 (5%)	0 (0%)	3 (10%)		22 (11%)	12 (12%)	10 (11%)		
What was your average pain level the last month on a 0-100 scale; 0 = no pain; 100 = worst pain imaginable[a]	62 (41)	50 (38)	72 (31)	0.061[b]	45 (56)	50 (59)	35 (55)	0.228[b]	0.008[b]
How satisfied are you with the result of the surgery on a 0-100 scale; 0 = very satisfied; 100 = not satisfied[a]	75 (38)	73 (30)	81 (42)	0.343[b]	50 (73)	50 (82)	35 (69)	0.141[b]	< 0.001[b]
How are your knee problems now compared to prior to the operation?									0.042
Better, an important improvement	13 (25%)	5 (23%)	8 (26%)		87 (45%)	42 (43%)	45 (48%)		
Somewhat better, but enough to be an important improvement	12 (23%)	8 (36%)	4 (13%)		29 (15%)	15 (16%)	14 (15%)		
Very small change, not enough to be an important improvement	4 (8%)	1 (4%)	3 (10%)		14 (7%)	9 (9%)	5 (5%)		
About the same	5 (9%)	0 (0%)	5 (16%)		23 (12%)	9 (9%)	14 (15%)		
Very small change, not enough to be an important improvement	3 (6%)	1 (5%)	2 (6%)		7 (4%)	4 (4%)	3 (3%)		
Somewhat worse, but enough to be an important deterioration	9 (17%)	5 (23%)	4 (13%)		11 (6%)	4 (4%)	7 (7%)		
Worse, an important deterioration	7 (13%)	2 (9%)	5 (16%)		21 (11%)	14 (15%)	7 (7%)		
Improvement				0.169				0.085	0.356
Importantly improved	25 (69%)	13 (81%)	12 (60%)		116 (77%)	57 (71%)	59 (83%)		
Not importantly improved	11 (31%)	3 (19%)	8 (40%)		35 (23)	23 (29%)	12 (17%)		

(continued on next page)

Supplementary Table 1 (*continued*)

PROM Outcome Measure	Unexplained Pain			P (1–2Y Versus > 2–3)	Aseptic Loosening			P (1-2Y Versus > 2-3Y)	P (Pain Versus AL)
	Total n (%) n = 56	1-2 Y n (%)	>2-3 Y n (%)		Total n (%)	1–2 Y n (%)	>2–3 Y n (%)		
		n = 23	n = 33		n = 206	n = 104	n = 102		
Do you find your present situation acceptable considering your daily level of function?				0.272				0.915	0.005
Yes	19 (35%)	10 (43%)	9 (29%)		109 (57%)	56 (57%)	53 (56%)		
No	35 (65%)	13 (57%)	22 (71%)		83 (43%)	42 (43%)	41 (44%)		
The question was only asked to patients replying no to the above: Do you think the treatment has failed?				0.632				0.813	0.790
Yes	21 (64%)	7 (58%)	14 (67%)		53 (66%)	27 (67%)	26 (65%)		
No	12 (36%)	5 (42%)	7 (33%)		27 (34%)	13 (33%)	14 (35%)		
Would you go through the surgery again?				0.220				0.125	0.263
Yes	19 (35%)	6 (26%)	13 (42%)		91 (47%)	51 (52%)	40 (42%)		
Maybe	21 (39%)	12 (52%)	9 (29%)		67 (35%)	35 (35%)	32 (34%)		
No	14 (26%)	5 (22%)	9 (29%)		36 (18%)	13 (13%)	23 (24%)		

If no statistical test is mentioned for *P* values, Chi-squared test was used.
PROM, Patient-reported outcome measure; IQR, interquartile range; EQ VAS, EuroQol Visual Analogue Scale where 100 = best health imaginable and 0 = worst health imaginable; Copenhagen Knee ROM, Copenhagen Knee Range of Motion.
[a] Median (IQR).
[b] Wilcoxon Rank-Sum test.

Supplementary Table 2
Patient-Reported Outcomes From Patients Revised for the Indication Unexplained Pain Versus Aseptic Loosening by Surgical Subgroups 1 and 2.

PROM	Unexplained Pain		Aseptic Loosening	
	N = 56		N = 206	
Surgical Subgroup	1. TKA-TKA	2. Partial Revision	1. TKA-TKA	2. Partial Revision
	n = 49	n = 7	n = 174	n = 32
OKS (median [IQR])	26 (13)	19 (9)	31 (16)	24.5 (23)
EQ-5D-5L Index (median [IQR])	0.7 (0.4)	0.5 (0.5)	0.8 (0.4)	0.7 (0.5)
EQ VAS (median [IQR])	62 (37)	40 (50)	60 (31)	40 (39.5)
FJS (median [IQR])	50 (8)	46 (13)	50 (17)	48 (13)
Copenhagen Knee ROM				
Flexion (median [IQR])	5 (2)	5 (1)	5 (1)	5 (2)
Flexion deficit (0-4)	20 (41%)	3 (43%)	40 (23%)	14 (44%)
Extension (median [IQR])	4 (1)	3 (1)	4 (2)	4 (1)
Extension deficit (0-3)	17 (35%)	4 (57%)	49 (28%)	12 (38%)

PROM, Patient-reported outcome measure; OKS, Oxford Knee Score; IQR, interquartile range; EQ-5D-5L, a value of 1 indicates the best quality of life and 0 indicate the worst; EQ VAS, EuroQol Visual Analogue Scale where 100 = best health imaginable and 0 = worst health imaginable; Copenhagen Knee ROM, Copenhagen Knee Range of Motion.

Supplementary Table 3
Questions on Pain and Satisfaction for Patients Revised for the Indication Unexplained Pain Versus Aseptic Loosening by Surgical Subgroups 1 and 2.

Questions	Unexplained Pain n = 56		Aseptic Loosening n = 206	
Surgical Subgroup	1. TKA-TKA n = 49	2. Partial Revision n = 7	1. TKA-TKA n = 174	2. Partial Revision n = 32
Pain				
What was your average pain level the last month on a 0-100 scale; 0 = no pain; 100 = worst pain imaginable (median [IQR])	56 (48)	70 (20)	35 (57)	38 (35)
Satisfaction				
How satisfied are you with the result of the surgery on a 0-100 scale; 0 = very satisfied; 100 = not satisfied (median [IQR])	73 (37)	80 (32)	33 (70)	73 (64)
Improvement. How are your knee problems now compared to prior to the operation?				
Importantly improved	22 (71%)	3 (69%)	104 (81%)	12 (55%)
Not importantly improved	9 (29%)	2 (40%)	25 (19%)	10 (45%)
Do you find your present situation acceptable considering your daily level of function?				
Yes	17 (36%)	2 (29%)	97 (60%)	12 (40%)
No	30 (64%)	5 (71%)	65 (40%)	18 (60%)
The question was only asked to patients replying no to the above: Do you think the treatment has failed?				
Yes	18 (62%)	3 (75%)	36 (58%)	17 (94%)
No	11 (38%)	1 (25%)	26 (42%)	1 (6%)
Would you go through the surgery again?				
Yes	18 (38%)	1 (14%)	77 (47%)	14 (47%)
Maybe	17 (36%)	4 (57%)	57 (35%)	10 (33%)
No	12 (26%)	2 (29%)	30 (18%)	6 (20%)

Appendix I.

Tables with results of study 4

Table 3: Demographic characteristics of included patients for responders and non-responders of PROMs.

Characteristic	Responders		p value	Non-responders		p value
	Pain n=90 (66%)	Aseptic loosening n=249 (70%)		Pain n=47 (34%)	Aseptic loosening n=106 (30%)	
Age (Mean (SD))	65.4 (SD 10.5)	68.3 (SD 9.1)	0.427	64.8 (SD 10.7)	68.9 (SD 10.3)	0.172
Sex (Female)	53 (59%)	147 (59%)	0.981	35 (74%)	62 (58%)	0.058
BMI (Median (IQR)) *(4 missing values)*	25 (IQR 12)	23 (IQR 12)	0.039	24 (IQR 14)	22 (IQR 13)	0.408
Surgical subgroup			<0.001			<0.001
1. TKA-TKA	49 (45%)	174 (61%)		16 (29%)	76 (64%)	
2. Partial revision	7 (6%)	32 (11%)		9 (16%)	21 (18%)	
3. UKA-TKA	33 (30%)	43 (15%)		19 (34%)	9 (8%)	
4. Secondary patella button	1 (1%)	-		3 (5%)	-	
Time from primary surgery to revision (Mean (SD))	4.7 (SD 3.9)	6.4 (SD 5.5)	0.313	3.9 (SD 3.5)	7.3 (SD 5.8)	0.530
Follow-up (Years from revision to datacollection) (Median (range))	2.9 (1.5-4.4)	2.9 (1.4-4.4)	0.604	3.2 (1.5-4.4)	2.9 (1.4-4.4)	0.466

PROM=Patient-Reported Outcome Measure; SD=standard deviation; BMI=body mass index; IQR=interquartile range; TKA=total knee arthroplasty; UKA=unicompartmental knee arthroplasty.

Table 4. Patient-reported outcomes of patients revised for the indication unexplained pain vs aseptic loosening.

PROM	Unexplained pain N=90	Aseptic loosening N=249	p-value
Oxford Knee Score[a]	26 (IQR 17)	31 (IQR 16)	0.001[b]
EQ-5D-5L Index[a]	0.7 (IQR 0.4)	0.8 (IQR 0.3)	<0.001[b]
EQ VAS[a]	50 (IQR 41)	62 (IQR 33)	0.042[b]
FJS[a]	48 (IQR 9)	50 (IQR 15)	0.406[b]
Copenhagen Knee ROM			
Flexion[a]	5 (IQR 2)	5 (2)	0.018[b]
Flexion deficit (0-4)	35 (39%)	64 (26%)	0.062
Extension[a]	4 (IQR 1)	4 (IQR 2)	0.01[b]
Extension deficit (0-3)	38 (42%)	71 (29%)	0.064

PROM=Patient-reported outcome measure; If no statistical test is mentioned for p-values, Chi-square test was used; [a]Median (IQR); [b]Wilcoxon Rank Sum test; IQR=interquartile range; EQ-5D-5L Index - a value of 1 indicates the best quality of life and 0 indicate the worst; EQ VAS=EuroQol Visual Analogue Scale - 100=best health imaginable and 0=worst health imaginable; Copenhagen Knee ROM=Copenhagen Knee Range of Motion.

Table 5. Questions on pain and satisfaction.

Question	Unexplained pain n=90	Aseptic loosening n=249	p-value
Pain			
What was your average pain level the last month on a 0-100 scale; 0= no pain; 100= worst pain imaginable[a]	62 (IQR 48)	40 (IQR 55)	0.001[b]
Satisfaction			
How satisfied are you with the result of the surgery on a 0-100 scale; 0= very satisfied; 100= not satisfied[a]	72 (IQR 39)	50 (IQR 73)	<0.001[b]
Improvement. How are your knee problems now compared to prior to the operation?			0.042
- Importantly improved	39 (65%)	146 (78%)	
- Not importantly improved	21 (35%)	41 (22%)	
Do you find your present situation acceptable considering your daily level of function?			0.003
- Yes	34 (39%)	133 (58%)	
- No	53 (61%)	98 (42%)	
The question was only asked to patients replying no to the above: Do you think the treatment has failed?			0.929
- Yes	33 (66%)	62 (65%)	
- No	17 (34%)	33 (35%)	
Would you go through the surgery again?			0.138
- Yes	31 (36%)	112 (48%)	
- Maybe	35 (40%)	76 (33%)	
- No	21 (24%)	45 (19%)	

If no statistical test is mentioned for p-values, Chi-square test was used; IQR=interquartile range; [a]Median (IQR); [b]Wilcoxon Rank Sum test.

Appendix II.

Indications in registers

Table 6. Indications in registers

Australia	Denmark	Finland	Netherlands	Norway	Sweden	UK
Instability	Instability	Instability	Instability	Instability	Instability	Instability
Infection	Infection	Infection	Infection	Infection	Infection	Infection
Aseptic loosening	Aseptic Loosening	Aseptic Loosening	Patellar pain	Loose distal component	Wear	Aseptic Loosening
Pain	Pain	Pain	Loosening tibia	Loose proximal component	Fracture	Wear
Patellofemoral Pain	Secondary patella button	Wear	Malalignment	Pain	Patella	Pain
Other	Polyethylene failure	Other	Loosening femur	Dislocation of patella	Loosening	Lysis
	2. part of 2. stage revision		Progression of osteoarthritis	Defect polyethylene	Progression	Stiffness
	Exchange of patella button		Insert wear	Malalignment	Other	Malalignment
	Progression of osteoarthritis		Revision after removal of components	Fracture		Fracture
	Other		Arthrofibrosis	Dislocation – not patella		Dislocation
			Patellar dislocation	Progression of osteoarthritis		Implant fracture
			Fracture	Loosening patella		Component dissociation
			Loosening patella	Other		Other
			Other			

Appendix III.

Australian diagnosis hierarchy of revision knee replacement

Table 7. Australian diagnosis hierarchy of revision knee replacement

Rank	Diagnosis	Category
1	Tumour	Dominant diagnosis independent of prosthesis/surgery
2	Infection	
3	Incorrect Side	Surgical procedure
4	Incorrect Sizing	
5	Malalignment	
6	Metal Sensitivity	Reaction to prosthesis
7	Loosening/Lysis	
8	Wear Tibial/Insert	Wear and implant breakage
9	Wear Femoral	
10	Wear Patella	
11	Implant Breakage Femoral	
12	Implant Breakage Tibial	
13	Implant Breakage Patella	
14	Bearing Dislocation	
15	Dislocation	Stability of prosthesis
16	Instability	
17	Patellar Maltracking	
18	Fracture (Femur/Tibia/Patella/Periprosthetic)	Fracture of bone
19	Progression of Disease	Progression of disease on non-operated part of joint
20	Patellar Erosion	
21	Synovitis	New diseases occurring in association with joint replacement
22	Arthrofibrosis	
23	Avascular Necrosis	
24	Heterotopic Bone	
25	Patello-femoral Pain	Pain
26	Pain	
27	Other	Remaining diagnoses

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