Validation and outcome studies from the Danish Knee Ligament Reconstruction Registry

A study in operatively treated anterior cruciate ligament injuries

PhD dissertation

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Preface

This PhD thesis is based on studies carried out during my employment at the Department of Orthopaedic Surgery and Department of Clinical Epidemiology, Aarhus University Hospital, Denmark, in the period from September 2011 to February 2014.

I would like to express my sincere gratitude to all those who made this work possible. First, I would like to thank Professor Martin Lind for his skilful guidance and mentorship and his never-ending flow of ideas and, of course, for introducing me to orthopaedic research. Also, my profound gratitude and thanks go to Alma Pedersen for her guidance through the field of epidemiology, for productive discussions, for her always-cheerful nature and many laughs and for being available when things got tough. Finally, warm and grateful thanks to Theis Thillemann for his never-ending patience and excellent guidance and introduction to the world of research and for always being available for productive discussions.

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Lene Rahr Wagner, June 2014

This thesis is based on the following papers:

I. Rahr-Wagner L, Thillemann TM, Lind MC, Pedersen AB. Validation of 14,500 operated knees registered in the Danish Knee Ligament Reconstruction Registry: Registration completeness and validity of key variables. Clin Epidemiol. 2013 Jul 22;5:219-28.

II. Rahr-Wagner L, Thillemann TM, Mehnert F, Pedersen AB, Lind MC. Is the use of oral contraceptives associated with operatively treated anterior cruciate ligament injury? A case-control study from the Danish Registry of Knee Ligament Reconstruction. *August 2014, accepted for print at Am J of Sports Med.*

III. Rahr-Wagner L, Thillemann TM, Pedersen AB, Lind MC. Increased risk of revision after anteromedial compared with transtibial drilling of the femoral tunnel during primary anterior cruciate ligament reconstruction: results from the Danish Knee Ligament Reconstruction Register. Arthroscopy. 2013 Jan;29(1):98-105.

List of abbreviations:

ACL: Anterior cruciate ligament

ADL: Activity of daily living

AM: Anteromedial

ATC codes: Anatomical Therapeutic Chemical Classification code

CI: Confidence interval

CRS: Civil Registration System

DKRR: The Danish Knee Ligament Reconstruction Register

DNRP: The Danish National Registry of Patients

NDPD: The National Danish Prescription Database

HR: Hazard ratio

HT graft: Hamstring graft

ICD-10: The International Classification of Diseases, 10th revision.

IDA: The integrated Database for Labor Market Research

IQR: Interquartile range

IKDC: The International Knee Documentation Committee

KOOS: Knee injury and Osteoarthritis Outcome Score

NDPD: National Danish Prescription Database

NOMESCO: The Nordic Medical Statistic Committee

NSAID: Non-steroid anti-inflammatory drugs

OC: Oral contraceptives

PROM: Patient-reported outcome measures

PT autograft: Patellar tendon autograft

QoL: Quality of life

PPV: Positive predictive value

RCT: Randomized clinical trial

RR: Relative risk

TT: Transtibial

Contents

1. Introduction

The anterior cruciate ligament (ACL) acts as an important stabiliser of the knee for rotational and anterior-posterior stability.[1] Injury to the ACL is a common and serious knee injury in the young and physically active population.[2] The median age for sustaining ACL injury in Scandinavia is 23-27 years,[3] and the annual incidences of primary ACL reconstruction in Denmark and Norway are 38 and 34 out of 100,000, respectively.[3]

Many individuals with a torn ACL develop meniscal damage and osteoarthritis of the knee, irrespective of treatment.[4-6] In addition, ACL injury may lead to unsatisfactory knee function, decreased activity and a poor knee-related quality of life (QoL), thus requiring surgery. Nevertheless, there is a lack of knowledge regarding how to reduce the likelihood of ACL injury and how to improve the short- and long-term prognosis after ACL reconstruction and hence how to reduce the likelihood of subsequent osteoarthritis in this young population.

In recent years, advances in information technology have facilitated access to large clinical databases such as the Danish Knee Ligament Reconstruction Registry (DKRR). This has given clinicians and healthcare planers the opportunity to study risk and prognosis on a large scale and hence to answer research questions that were previously beyond our reach.

An enhanced understanding of these complex questions regarding the likelihood of sustaining ACL injury and how to improve the prognosis after primary ACL reconstruction would have pronounced clinical implications for the individual patient, a major public health impact as well as socioeconomic benefits. Using the newly established DKKR, we therefore found it important to evaluate selected questions on the likelihood of sustaining operatively treated ACL injury and on the prognosis after ACL reconstruction.

In the future, a better understanding of these risk factors and prognostic factors in ACL-reconstructed patients will hopefully prove instrumental in improving their QoL and in limiting the long(term consequences for this large group of young patients.

2. Aims of thesis

The overall objective of this study was to validate the DKRR and to perform the first outcome studies based on data from the registry.

The specific aims were:

I. To establish a basis for testing of the hypotheses of Studies II and III, we aimed to validate the DKRR data. Specifically, we set out to: (a) assess the completeness of the registration of the ACL reconstruction procedures; (b) validate the data quality of key variables in the DKRR; and (c) test the hypothesis of no difference in the outcome measures between responders and non-responders recorded in the DKRR.

II. To examine the association between use of oral contraceptives (OC) and the likelihood of sustaining operatively treated ACL injury in a large nationwide population-based case-control study.

III. To examine the association between surgical techniques employed and failures recorded after primary ACL reconstruction. This was done using the anteromedial (AM) or the transtibial (TT) technique for femoral drill hole placement during primary ACL reconstruction as exposure variables and by using ACL revision, objective and subjective measures as outcome measures.

3. Background

To provide the reader of this thesis with an understanding of the various and complex opportunities in ACL reconstruction, a brief introduction to the anatomy of the ACL and ACL injuries is provided along with a historical review and a presentation of some technical aspects of ACL reconstruction. This is followed by background information on the study of risk and prognosis in ACL reconstruction. Furthermore, literature search and background information relating to the three studies will conclude this section.

3.1 Anterior cruciate ligament (ACL)

The ACL (Figure 3.1.1) is an important ligament of the knee. It acts as a stabiliser of the knee and controls the anterior movement of the tibia, tibial rotation, and it also has a proprioceptive function owing to the presence of numerous sensory endings.[1,7]

The ACL is primarily composed of collagen fibres but also consists of fibroblasts and elastin. Recently, it has been demonstrated that the ACL is composed of two functional bundles, the anteromedial bundle and the posterolateral bundle.[8] The component ACL bundles are named based on their tibial insertion sites. In several cadaveric studies, the overall width of the ACL has been shown to range from 7 to 17 mm, with the average being 11 mm.[1,9] Forces transmitted through ACL bundles vary with knee-joint position. Greater forces are transmitted through the anteromedial bundle at 60 and 90 degrees of flexion, and the posterolateral bundle receives the greatest force at full extension.[10] Because most injuries to the ACL occur when the knee is at full extension, the posterolateral bundle is considered more important for overall biomechanical stability.[1,10]

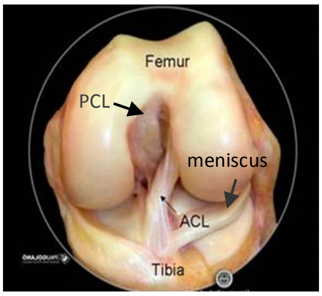


Figure 3.1.1: Anatomy of the knee; ACL = anterior cruciate ligament; PCL = posterior cruciate ligament. (with kind permission of Freddy Fu)

As outlined in the introduction, injury to the ACL is common in the younger population. Most ACL injuries are acquired during sports activities, especially contact and pivoting sports. Differences in sports activity are seen between countries reflecting the cultural habits of the individual countries.[3,11,12,12,13] Several studies have attempted to identify risk-factors predisposing ACL injury and have found an association between intercondylar notch stenosis and the risk of ACL injury.[14,15] Also, female sex has been associated with a higher risk of ACL injury and, hence, an association with menstrual cycle and female sex-hormone has been proposed.

3.2 Anterior cruciate ligament reconstruction

3.2.1 Historical view

ACL reconstructions have evolved rapidly over the past three decades, from an open technique (Figure 3.2.1) to a minimally invasive arthroscopic technique (Figure 3.2.2). In the beginning of the 20th century, ACL repair was done by open surgery and involved suturing of the injured ACL, and hence, initially, replacement of the ACL was not performed. The first successful open suture of an injured ACL was performed in 1895,[16] but it was only in the 1960s that the concept of open ACL reconstruction truly began (Figure 3.2.1). Open ACL reconstruction continued until the mid-1980s, and David Dandy was the first to perform an arthroscopically assisted ACL reconstruction at Newmarket General Hospital in England in April of 1980.[16]

Since suture of the ACL was done with a minimum of success, the idea evolved of completely removing the torn ACL and replacing it with an autograft. Such surgery was first performed in 1917 using fascia lata. During the following 50 years, the idea of ACL reconstruction was debated, but it was not until the 1970s that the concept of replacing the torn ACL with an autograft gained acceptance.[16] Also, femoral tunnel placement has evolved over the past three decades. Reaming through a medial parapatellar tunnel, in 1995 O'Donnell was the first to describe an alternative to the traditional transtibial (TT) approach for femoral tunnel placement.[17] This was followed by Bottoni in 1998, who inserted the femoral guide through the anteromedial (AM) portal for better femoral tunnel placement.[18] Over the past two decades, this has led to an increased use of the AM portal technique. Furthermore, as the ACL consists of two bundles, theoretical speculations arose in the 1980s[19] on how to reconstruct both bundles in order to reach a more anatomically correct reconstruction and thereby increase rotational stability. Hence, the interest in double-bundle ACL reconstruction was introduced.

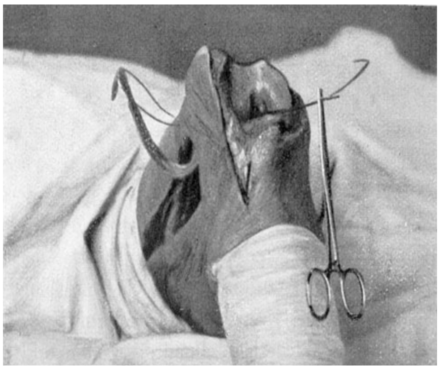


Figure 3.2.1: Intra-operative open ACL reconstruction performed in 1955 using facia lata. (With kind permission of Walter De Gruyter).[16]

In a historical perspective, ACL reconstruction has travelled far over the past three centuries, but the concept of arthroscopic ACL reconstruction has evolved only during the past three decades.

Figure 3.2.2: Modern arthroscopic ACL reconstruction (with kind permission of Professor Martin Lind).

3.2.2 Overview of surgical techniques

As mentioned above, today, ACL reconstructions are done arthroscopically. Many different techniques, graft choices and implant choices are available during ACL reconstruction.

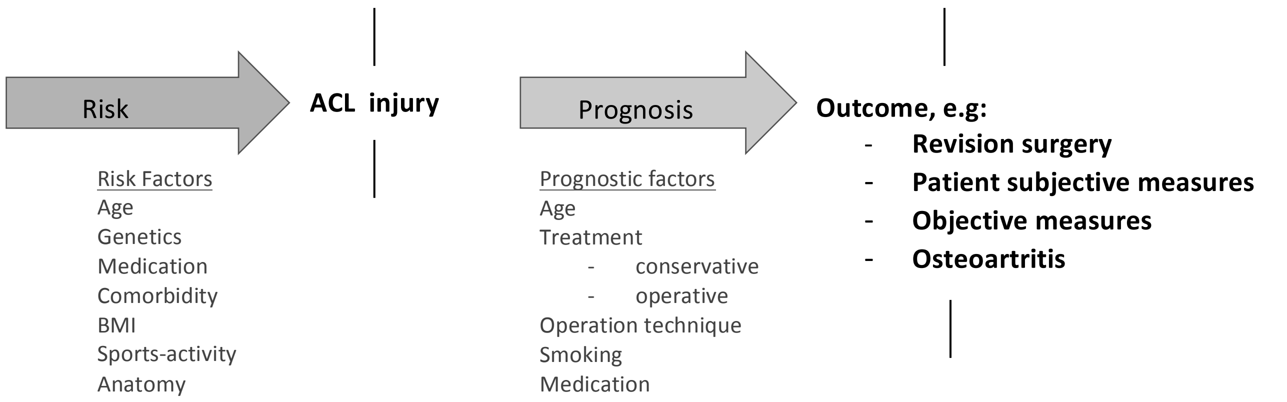
Single-bundle ACL reconstruction is currently the gold standard and the most commonly used operative technique for ACL reconstruction. Because interest in anatomical ACL reconstruction has increased and the ACL consists of two bundles, the idea of double-bundle ACL reconstruction has gained increased interest. This has led several researchers to compare single-bundle to double-bundle techniques. Presently, however, current literature does not support better results for re-establishment of rotational stability after ACL injury when the double-bundle technique is used. This is probably because, surgically, the double-bundle technique is more complex. Hence, the single-bundle ACL reconstruction remains the gold standard.[20] Furthermore, various operation techniques and grafts for ACL reconstruction exist. Surgeons still discuss if drilling the femoral tunnel should be done transtibially (figure 3.6.1) using a designated guide, outside-in, or using the new and potentially more anatomically correct AM technique (figure 3.6.1).[21] The most frequently used grafts for ACL reconstruction are hamstring (HT) and patellar tendon (PT) autografts, although great inter-country variation is seen. In Scandinavia, the HT graft has been used in about 84% of cases in recent years.[3] In the United States (US), the most widely used graft types are HT (44%) and PT (42%) autografts, and US surgeons are less reluctant to use allograft (13%) than Scandinavian surgeons (0.2%).[3,12] There are advantages and disadvantages of all graft choices, and the choice of graft usually depends on the surgeon's personal preferences and an assessment that takes patient characteristics into consideration. An optimal graft is fast healing, strong, and restores knee joint stability with low morbidity. Animal studies suggest that PT grafts heal more rapidly because bone-to-bone healing is more rapid than bone-to-tendon healing.[12,22] Rapid healing is essential in ACL reconstruction as it allows for earlier and more accelerated rehabilitation. Therefore, PT grafts have been suggested for more active patients who are younger than 20 years of age, since failure rates seem to be higher in this age group.[23,24] However, many studies have shown that ACL reconstruction using PT autograft is associated with donor-site morbidity such as anterior knee pain, pain on kneeling and patello-femoral osteoarthritis.[25, 28] In recent years, use of HT grafts has therefore become more popular owing to its lower rate of donor site morbidity.[25] Moreover, different types of fixation of the graft exist. Suspensory fixation (e.g. EndoButton), fixation with interference screws and transfemoral fixation with cross-pins are the three major principles for femoral fixation of grafts in ACL reconstruction. Numerous clinical studies have evaluated and compared these fixation techniques and found no differences in clinical outcome parameters.[29,33] Suspensory fixation has been a reliable and simple fixation for ACL reconstruction for many years. However, studies have shown that graft-tunnel motion can be 2 to 3 mm during physiologic loads using EndoButton fixation.[34] This intra-tunnel motion has been associated with tunnel widening and it has hence been associated with a possible poor outcome after ACL reconstruction.[35,36] It is still unknown which operation technique, graft type and fixation technique provide the best clinical outcome, and the impact of these different surgical procedures on the long- and short-term outcome are debated. At present, the most commonly used technique for ACL reconstruction in Denmark is the single-bundle technique with an HT graft and the AM technique for femoral tunnel drilling.[37,38]

3.3 Studying risk and prognosis

3.3.1 Studying risk of sustaining operatively treated ACL injury

In medicine, risk is the likelihood that an individual will develop a certain disease.[39] Hence, studies in risk usually deal with healthy people and their likelihood of developing a disease of interest. Factors that are associated with an increased likelihood of causing a disease in question are referred to as risk factors (Figure 3.3.1).[40] Risk factors can often be modified in order to change the likelihood of a disease. In Study II, the association between OCs and the likelihood of sustaining operatively treated ACL injury is studied.

Figure 3.3.1 Conceptualisation of the likelihood of sustaining operatively treated anterior cruciate ligament (ACL) injury and prognosis after treatment (e.g., ACL reconstruction). Modified from Fletcher[40]



3.3.2 Studying prognosis after ACL injury

A prognosis predicts the course of a disease and can be described with respect to different outcomes.[40] Outcomes often refer to a specific clinical event such as death, complications, or the patients' quantity of discomfort, e.g. measured as QoL.[39] Prognostic factors are associated with the outcome of interest for a specific disease and should not be confused with risk factors, although some, such as age, may affect both risk and prognosis (Figure 3.3.1).[40] In Study III, we study the operation technique as a prognostic factor after ACL injury. Identifying prognostic factors has a major clinical impact on the prognosis, because, once known, their influence can be eliminated or reduced.

Since the burden associated with ACL injuries and hence later development of osteoarthritis is a significant personal and socioeconomic problem in healthcare, we decided to evaluate these questions in the following three studies: a validation study, a study on risk and a study on prognosis.

3.4 Background, Study I

3.4.1 Literature search, Study I

The primary aim of this study was to identify validation studies on ACL reconstruction databases in Denmark. Therefore, we conducted a Medline search using the following query (last search September 1, 2013):

("Comparative Study" [Publication Type]) OR "Validation Studies" [Publication Type]) AND ("Anterior Cruciate Ligament"[Mesh]) OR (“Anterior Cruciate Ligament Reconstruction"[Mesh]) OR ("Anterior Cruciate Ligament") OR (“Anterior Cruciate Ligament Reconstruction") AND "Registries/standards”[Mesh] OR “ACL registries” OR "Registries"[Mesh] AND Denmark

This query did not return any hits. Therefore we extended the literature search to also include validation studies from other countries using the following query:

("Comparative Study" [Publication Type]) OR "Validation Studies" [Publication Type]) AND ("Anterior Cruciate Ligament"[Mesh]) OR (“Anterior Cruciate Ligament Reconstruction"[Mesh]) OR ("Anterior Cruciate Ligament") OR (“Anterior Cruciate Ligament Reconstruction") AND "Registries/standards”[Mesh] OR “ACL registries” OR "Registries"[Mesh]

This query returned seven hits. The following inclusion criteria were applied in this study: (1) validation studies; (2) ligament reconstruction registers. By evaluating the titles and abstracts, we found two studies that were relevant for the present study. A review of the reference lists of these papers revealed one more study that was relevant for this thesis. Since we had identified only three relevant studies, we extended the search further to include registries on joint replacement since these have existed for several decades in Scandinavia, have been validated and are deemed highly reliable.

("Validation Studies" [Publication Type]) AND (" Arthroplasty "[Mesh]) AND ("Registries"[Mesh])

This query returned ten hits. Again, by evaluating the titles and abstracts, we identified another three studies that were relevant for the present thesis. A review of the reference lists of these papers yielded one additional study suitable for this thesis. Appendix 1 outlines the findings of the literature search.

3.4.2 Clinical epidemiology and validation studies

In etiological studies there are two alternatives when studying the association between exposure and outcome: 1) experimental studies, i.e. randomised clinical trials (RCTs), or 2) non-experimental (observational) studies, i.e., cohort studies, case-control studies and cross-sectional studies.[39] The RCT is commonly considered the gold standard in clinical research as opposed to non-randomised trials.[39] Well-designed RCTs with an adequate power are time-consuming and usually very costly to perform, and many RCTs therefore end up being too small and therefore have insufficient power.[41] Consequently, not all research questions can be answered in RCTs and the RCT design is often not suitable for the study of associations between rare exposures and outcome.

Recent years have seen advances in information technology that have facilitated access to large clinical databases. This gives researchers the possibility to assess disease exposures and outcomes at a large scale. Clinical databases are an attractive source of data for observational studies for a host of reasons: data are readily available, costs can be reduced considerably, and working with large-scale data allows researchers to study rare outcomes and improve the precision of their estimates.[42-44] Furthermore, since data in existing databases are collected prospectively and independently of the research objective, the risk of information and selection bias may be reduced. In addition, the use of clinical databases for research furthers timely and early dissemination of information on specific clinical issues. Previous studies from the Norwegian Knee Ligament Registry have demonstrated the importance of national clinical orthopaedic databases in medical research.[45-47] Reviews comparing the results from RCTs and observational/database studies have shown that the results obtained from observational studies correlate with the results of RCTs on the same exposures and outcomes.[48,49]

Databases may have some limitations that pertain to the completeness of the data, the quality of data collection and unmeasured confounding which may have strong implications for the range of conclusions that can be drawn from observational studies.[41] Thus, it is important to be aware of and to evaluate these issues before using the databases for clinical research, and it is of crucial importance to evaluate the completeness of registration and to validate the data quality of key variables in the databases to ensure that valid and reliable conclusions may be drawn from their data.

The literature review revealed that validation studies of other Scandinavian registries have reported a very high completeness, which makes them reliable for future research (86-99%).[50-52] No validation of the DKRR has been performed prior to this thesis. Hence, in this study we validated the DKRR to test its value for future research. Our review of the literature underlines the importance of reporting completeness estimates, but also the need for a thorough description of the calculation method used to ensure that results are comparable across countries. Hence in Study I of this thesis, the methods described by Sorensen et al. were used to calculate the completeness of data.[53]

3.5 Background, Study II

3.5.1 Literature search, Study II

The primary aim of this literature search was to identify studies elucidating the impact of OC use on the likelihood of sustaining operatively treated ACL injury. We therefore conducted a Medline search using the following query (last search 1 January 2014):

(“Contraceptives, Oral, Hormonal” [Mesh]) OR (“Contraceptives, Oral” [Mesh]) OR ("oral contraceptive" [All Fields]) OR ("oral contraceptives" [All Fields]) OR (“estrogen” [Mesh]) AND (“Anterior Cruciate Ligament reconstruction” [Mesh]) OR (“Anterior Cruciate Ligament” [Mesh]) OR (“Anterior cruciate ligament injury"[All Fields]) OR (ACL[All Fields]) OR (“Anterior Cruciate Ligament Reconstruction” [All Fields])

This query returned 47 hits after restricting the search to studies in English and Danish. The following inclusion criteria were chosen: (1) studies using estrogen or OC as exposure; (2) ACL, ACL injury or ACL reconstruction as outcome measures. By evaluating the titles and abstracts, we identified 12 papers that were relevant for the present study. Review of the reference lists of these studies revealed another three studies of relevance for this thesis. Appendix 2 outlines the findings of the search.

3.5.2 Oral contraceptive (OC) use in women and the likelihood of sustaining operatively treated ACL injury

Women are 2-9 times more likely to sustain ACL injury than men.[54-58] The causes explaining the increased female incidence of ACL injuries are multifactorial and may include: a difference in femoral notch size, valgus of the knee, neuromuscular differences, differences in knee laxity and differences in core stability between the sexes.[54,59-61] Additionally, hormonal effects have been proposed as an aetiological factor explaining the difference in the incidence of ACL injury.

Results from basic science studies show that estrogen receptors are present on the human ACL and that the synthesis of collagen is reduced in the presence of an increased level of estrogen.[62] [63] Furthermore, animal studies have shown that administration of reproductive hormones alter the mechanical properties of the ACL.[56,64] It has therefore been concluded that estrogen is associated with tendon matrix composition. Others have found that fluctuations in serum estrogen levels can cause alterations in the ACL fibroblast metabolism, which may, in turn, result in structural and compositional changes of the ACL and hence contribute to an increased vulnerability of the female ACL.[65,66] Others have investigated the difference in muscle stiffness in OC users and non-OC users and found no difference.[67] Also, results indicate that women have a higher incidence of ACL injury and a greater knee laxity in the pre-ovulatory phase than they do during other phases of the menstrual cycle and further an increased knee laxity when using OCs.[7,68-73 74] These findings suggest that cyclic hormonal changes may be one explanation for the increased female likelihood of ACL injury. Furthermore, the findings indicate that the menstrual cycle and OC use may affect the ACL.[65,69,75] In contrast to the above studies other have found no influence of OC on biological, clinical or mechanical properties of the ACL.[76-79]

The menstrual cycle, which is controlled by the pituitary gland, causes a monthly estrogen fluctuation. OCs, which are used by 50–89% of women in Western countries at some point of their life, stabilise the hormone level during the menstrual cycle, which prevents the estrogen surge.[80,81]

This literature search revealed conflicting results regarding the evaluation of the clinical association of OC with the likelihood of ACL injury and ACL reconstruction. To date, we have found one clinical study suggesting a protective association between OC use and the likelihood of sustaining sports injuries.[82] The authors prospectively studied 108 women soccer players from the first through third Swedish football league and followed them for 12 months. They found a lower rate of traumatic injuries, especially to the knee and ankle, in the group using OCs compared with the group not using OCs.[82] In contrast, a case-control study including 93 cases and 93 controls by Ruedl et al. showed no difference in the incidence of OC use between ACL-injured and non-ACL-injured female recreational skiers.[60] Further, in a large prospective study, Agel et al found no association between OC use and the risk of non-contact ACL injury[78]

Any confirmed association between the use of OC and the likelihood of ACL injury in this young population could have a major clinical and public health impact as well as socioeconomic consequences. To address the limitations and counter-conclusiveness of the extant literature, we conducted Study II - a large nationwide population-based pharmaco-epidemiological case-control study evaluating the association of OC use with the likelihood of sustaining operatively treated ACL injury.

3.6 Background, Study III

3.6.1 Literature search, Study III

The primary aim of this literature search was to identify studies on the impact of femoral tunnel placement and the likelihood of ACL revision surgery and other outcome measures after primary ACL reconstruction. We conducted a Medline search using the following query in Medline (Last search September 1, 2013):

("Anterior Cruciate Ligament Reconstruction/methods"[Mesh] OR "Anterior Cruciate Ligament/ therapy"[Mesh] OR "Anterior Cruciate Ligament Reconstruction"[Mesh] OR "Anterior Cruciate Ligament Reconstruction" [All Fields]) AND (anteromedial [All Fields] OR transtibial [All Fields]) NOT (double-bundle [All Fields])

This query returned 283 hits after restricting it to studies in English and Danish. The following inclusion criteria were chosen: (1) studies comparing AM with TT technique for femoral tunnel drilling as exposure; (2) ACL-reconstructed patients; (3) revision surgery, clinical failure, Tegner scores or patient-reported outcome measures (PROMs) as outcome measures as well as biomechanical outcome measures and cadaveric studies. By evaluating the titles and abstracts, we found 26 papers of relevance for the present study. Review of the reference lists of these papers revealed two more studies that were suitable for this thesis. Appendix 3 outlines the findings of this literature search.

3.6.2 Femoral tunnel placement as predictors of good outcome after ACL reconstruction

Different predictors are of importance for a good prognosis after primary ACL reconstruction. In biomechanical studies, graft strength has been shown to increase with increasing graft diameter.[83,84] This has been confirmed in clinical studies which demonstrate that decreased autograft size is a predictor of early graft revision.[24] Furthermore, it has been demonstrated that a low patient age (younger than 20–25 years) is associated with a higher failure rate than is observed in older patients.[23,24,84] Finally, it has been shown that femoral tunnel placement during ACL reconstruction is of critical importance for a good clinical result, and incorrect tunnel placement is cited as the most common cause of clinical failure.[85-87]

Two alternatives for femoral tunnel placement are generally used: the TT and the AM technique.

The traditional TT approach for femoral tunnel placement is limited by its trans-tibial drilling (Figure 3.6.1). Hence, angulation of the tibial tunnel restricts the placement of the femoral tunnel and places the femoral tunnel higher in the intercondylar notch (Figure 3.6.1) which results in decreased sagittal obliquity compared with the AM technique.[19,88-90,90-95] Also, cadaveric studies show a better rotational stability with AM placement of the femoral tunnel than with TT placement.[96-98] The TT placement of the femoral tunnel has also been shown to be unable to capture the centre of the native femoral footprint,[21,85,88,89,93,97,99,100] whereas the AM portal leaves the surgeon with more options for placement of the femoral tunnel.[101-103] Hence, to overcome the limitations created by the tibial tunnel and to give the single bundle ACL reconstruction more rotational stability, the AM surgical approach to the femoral tunnel has been introduced (Figure 3.6.1). When applying the AM technique, the surgeon is able to visualize and position the femoral tunnel independently of the tibial tunnel. Although cadaveric studies have shown that the AM technique is superior to the TT technique, this technique is not without its limitations. The AM technique involves a substantially increased risk of critically short tunnels, nerve damage, and a risk of posterior wall blowout.[90,93,104,105] Although the AM drilling technique is more challenging due to lack of "easy to use" guides for femoral drill hole placement and the need for hyperflexion during drilling, this method has become more popular in recent years owing to a trend towards anatomical ACL reconstruction.

The literature directly comparing the AM with the TT technique is sparse, and most knowledge on this subject stems from cadaveric/laboratory studies. Also, clinical results from studies on the use of either the AM or TT technique reveal mixed results, with some studies finding superior

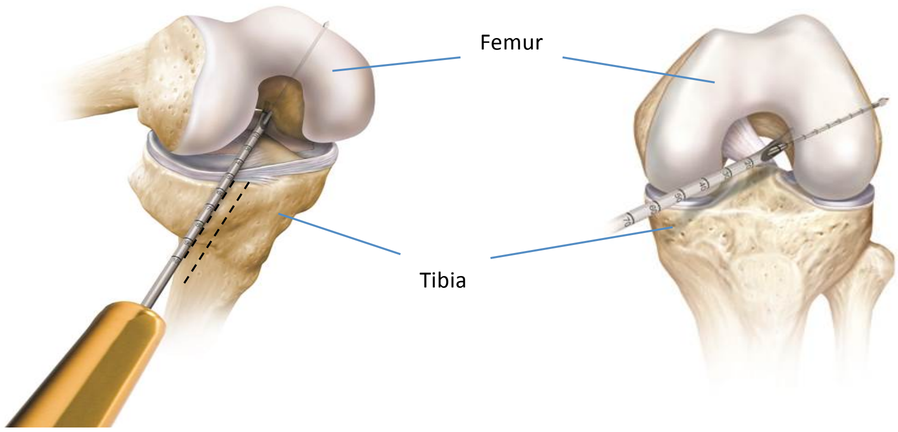


Figure 3.6.1: L*eft*: the transtibial drilling of the femoral tunnel. The drill will pass through the tibia continuing onward to the femur. Hence, the tibial tunnel restricts the placement of the femoral tunnel. *Right*: Illustrates the anteromedial drilling technique. The drill will pass through the medial portal, making the angle of the femoral tunnel independent of the tibial tunnel. (With kind permission from Søren Schou, the Arthex Library).

results in the AM group, whereas other studies found no differences.[106-113] Our literature search identified only one well-designed RCT using femoral tunnel placement as exposure and magnetic resonance imaging, subjective and objective measures as outcome.[114] Furthermore, one meta-analysis from 2010 was identified by our literature search. Although this meta-analysis compared the AM with the TT technique for femoral tunnel drilling, the authors were unable to identify any studies directly comparing the clinical outcome of AM with that of TT.[99] Hence, the meta-analysis was only an indirect comparison of the two techniques. No previous study has directly compared the two methods in relation to the risk of undergoing revision ACL reconstruction. Therefore, clinical studies comparing the two methods are warranted. An RCT requires a large patient material and a long follow-up time if revision surgery is used as outcome, and this does not seem feasible. Hence, in Study III, the impact of the two surgical techniques was evaluated in a large cohort study based on DKRR data.

3.6.3 Outcome measures in studies on ACL reconstruction

Different ways to measure success after ACL reconstruction exist. These include the risk of revision ACL reconstruction, objective knee stability tests, functional and activity level tests and patient-reported outcome measures (PROMs). The optimal outcome measure would be one that addresses the specific problems in regard to the disease. In the absence of a single outcome measure that investigates all relevant aspects of ACL function, investigators often use a broad range of outcome measures to evaluate the outcome: knee laxity (KT-1000 measurement, Lachman test, pivot-shift test), return to activity (pre- and post-injury employment and Tegner), and functionality (Lysholm, International Knee Documentation Committee (IKDC), and Knee Injury and Osteoarthritis Outcome Score (KOOS)). The use of so many different outcomes can be costly and time-consuming. Also, the lack of consensus on a specific outcome measure makes it difficult to compare different studies.

3.6.3.1 Revision ACL reconstruction

Revision ACL reconstruction is defined as having a second ACL reconstruction procedure performed in the same knee as the primary ACL reconstruction. During ACL revision surgery, the previous ACL graft is removed, previous screws are removed if necessary, bone defects are filled with bone-graft if required, and a new autograft or allograft is used to replace the previous ACL graft.[1,23] ACL revision is a hard failure endpoint for ACL reconstruction.

3.6.3.2 Objective knee stability tests

Objective knee stability can be quantified by using the pivot-shift test and instrumented sagittal knee stability testing that are objective measures of the outcome after ACL reconstruction.

These measures are very dependent on the clinician doing the observations. The pivot-shift test is a dynamic test of the knee, which measures the anterior subluxation and the rotational stability of the ACL. The pivot-shift test consists of grading on a four-point scale from normal (0), glide (1), and clunk (2), to gross (3).[115] In the sagittal stability test, a Rolimeter, KT1000, or KT2000 is used to measure the difference in sagittal stability between the operated knee and the healthy knee.

3.6.3.3 Patient-reported outcome measures (PROM)

In recent years, the interest in PROMs as an outcome for the success of ACL reconstruction has gained growing interest and PROMs are identified as important outcome measures after ACL reconstruction.[116,117] PROMs are collected via standardised questionnaires designed to measure underlying items that are not directly measurable, such as pain or daily activities. PROMs assess the patient's own opinion of function and treatment effect.[118] PROMs can be divided into generic, anatomical-specific and condition-specific. The generic-specific PROMs, e.g. Short Form (SF-36), have been developed to assess the overall health status irrespective of any underlying pathology and diagnosis. The anatomic-specific PROMs, such as the KOOS and the IKDC, were created for patients with pathologies related to a specific anatomical region such as the knee and hip regardless of type of pathology. Finally, the condition-specific PROMs address a specific pathology in a specific anatomical region and may be the best instrument because these are more detailed with regard to the specific disease and more sensitive to disease-specific and treatment-specific effects.[118,119] A wide range of PROMs has been used in ACL research.[50,120-122] When initiating the Scandinavian registries, the KOOS was chosen as the PROM of choice.[13]

The KOOS, an anatomic-specific PROM, was developed as an instrument to evaluate the short- and long-term consequences of knee injury in patients with knee injuries and osteoarthritis, and it has been adapted for use in several countries.[6,123-126] The KOOS ranges from 0 to 100, with higher scores representing better results. The KOOS consists of five sub-scores: Sport & Recreation, Pain, QoL, Activity of Daily Living (ADL), and Symptoms (Appendix 4).[124] The five sub-scores should be evaluated separately. $KOOS_4$ is a patient-reported outcome, computed from the four most responsive KOOS sub-scores, omitting ADL.[6] Although, the $KOOS_4$ has been used in previous studies to evaluate the mean score of these four sub-scores[6,127,128] no previous studies have validated this combined $KOOS_4$ measure using standardized validation methods. In several studies, the Sport & Recreation and QoL sub-scores have been shown to be the most responsive of the sub-scores.[13,116,121,129-131] The post-operative KOOSs 1 to 2 years after ACL reconstruction ranged from 50 to 88, depending on the sub-score, with QoL scoring lowest and ADL scoring highest.[6,23,37,38,116] The KOOS has limitations when studying the outcome after ACL reconstruction as it lacks a domain that evaluates instability, including specific symptoms such as “giving away”.[121]

3.6.3.4 Other outcome measures

Other important outcome measures exist. Single-legged hop tests are functional tests used to assess the combination of muscle strength, neuromuscular control and the ability to tolerate loads in relation to sport activities. These tests are widely used, reliable, based on objective measurements and have the ability to discriminate between those who return to previous activity before ACL injury and those who do not.[132]

The Tegner score was first published in 1985 and is a sports-specific activity level score, which quantifies activity on a scale from 0 to 10, with higher scores representing a higher level of activity (Appendix 5).[133,134] Individuals competing in sports at an elite level have a Tegner score of 10, individuals participating in sports at a recreational level have a Tegner score of 6, and individuals on a disability pension due to knee problems have a score of 0.[134] The average Tegner activity level in the normal healthy population is 5.7.[135] Some problems are associated with this score because it relates activity to specific sports rather than specific functions and diseases, and it has not been validated.[120] Tegner scores after an ACL reconstruction range from 4.5 to 5.0. [37,38]

3.6.3.5 Outcome measures applied in this thesis

In Study III, various outcome measures were used in order to meet the drawbacks of each individual outcome measure. Revision ACL reconstruction was used as a hard endpoint after primary ACL reconstruction, to show the reconstructed failures. Since patients with primary ACL may have problems without being revised, this is only a proxy for the real number of failures and hence does not necessarily reflect the result after ACL reconstruction in general. Therefore, we also decided to evaluate objective measures (pivot shift test and sagittal instability measures) as well as the KOOS, the $KOOS_4$ and the Tegner scores as outcomes. This was done to facilitate assessment of patients who do not undergo revision surgery but, nevertheless, have an unsatisfactory result.

4. Material and methods

4.1 Settings and data sources

We based the three studies performed as part of this thesis on the DKRR, which at present contains more than 20,000 ACL procedures.

Denmark has a population of 5.6 million people. The National Health Service provides tax-financed healthcare to all Danish residents, including free access to hospital care at medical, surgical, and psychiatric departments as well as general practitioner visits. Patients with acute medical conditions are admitted to specialist treatment at public hospitals. Private hospitals are also accessible in Denmark, and they have reimbursement agreements with the Danish State but also provide services for privately insured patients.

Danish citizens are registered in various administrative and medical registries with a unique personal identification number assigned to all citizens at the date of birth.[136] We obtained data from the existing national population-based registers and databases. Since the unique Danish personal identification number is consistently used throughout all Danish registries, it is possible to obtain precise individual-level data through data-linkage between the Danish registries (Figure 4.1.1).

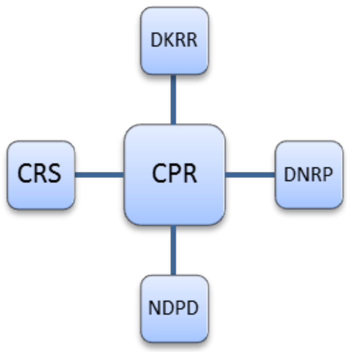


Figure 4.1.1 : Linkage of nationwide registers using the unique Danish personal identification number. Abbreviations: CPR: unique personal identification number; DKRR: Danish Knee Ligament Reconstrution Registry; CRS: Civil Registration System; DNRP: Danish National Registry of Patients; NDPD: The National Danish Prescription Database

4.1.1 Danish Knee Ligament Reconstruction Registry (DKRR)

Over the past two decades, Scandinavian national arthroplasty registers have generated important knowledge and served as an important source for research as well as quality and control tools.[137] In 2004, Norway started the world's first national knee ligament registry, an initiative which was soon followed by Denmark and Sweden.[46] These registers serve as national surveillance systems designed to monitor the outcome of knee ligament surgery. The DKRR is such a nationwide clinical database, which was established on 1 July 2005. The purpose of the DKRR was to improve the monitoring and quality of both primary and revision knee ligament surgery in Denmark.[13] Registration is compulsory according to Declaration no. 459 of 15 June 2006, and all public and private hospitals report to the registry.[138] Using a standardised form and a secure internet portal, detailed preoperative, intraoperative and one-year follow-up data are recorded by the operating surgeon.[13] Furthermore, patients report outcome scores on the function of their knee using the KOOS[124] and the Tegner functional scores are reported.[134] These data are recorded online by the patient before surgery and one year after surgery.

4.1.2 The Danish Civil Registration System (CRS)

The CRS provides all Danish citizens with a unique ten-digit personal identification number at birth. Since 1968, information on changes in the vital status of all Danish citizens including changes in address, date of emigration, and the date of death have been recorded in the CRS.[136] Precise individual-level linkage between public Danish registers is possible owing to the personal identification number. In our studies, the CRS was used to link various databases and to ensure complete follow-up on all patients.

4.1.3 The Danish National Registry of Patients (DNRP)

The DNRP holds data on 99.4% of all discharges from Danish non-psychiatric hospitals since 1977 and outpatient visits since 1995.[139] Data in the DNRP include the personal identification number, admission and discharge dates, discharge diagnoses and operations, etc.[140] In Denmark, hospital discharge codes are registered in accordance with the International Classification of Diseases (ICD), 10th revision (ICD-10) of 1994;[141] and operation codes are registered according to the Nordic Medico-Statistical Committee (NOMESCO), which was established in 1966.[142] The attending physicians record these discharge and operation codes, and financial reimbursement from the Danish state to the hospitals depends on this registration.

4.1.4 The National Danish Prescription Database (NDPD)

The NDPD contains records from 1994 onwards on date of redemption, type of drug, quantity dispensed, strength of drug and other data.[143] Each time a prescription is redeemed at a pharmacy, a record of the patient's personal identification number, the date, and the type and quantity of the drug prescribed is recorded in the prescription database. These individual-level data on all prescription drugs sold in Danish community pharmacies are recorded in the Register of Medicinal Products Statistics operated by Statens Serum Institut. The NDPD is reimbursement-driven and keeps records using automated bar-code data entry and hence provides data of a high quality and facilitates linkage with many other nationwide individual-level databases. Hence, the NDPD is a very powerful epidemiological tool. In this thesis, the NDPD was used to identify OC use in the five-year period leading up to the index date.

4.1.5 The Integrated Database for Labour Market Research (IDA)

The IDA was established in 1980 and contains data on employment and income among other social variables. The IDA is described in detail elsewhere.[144]

4.1.6 Medical records

For the validation of key variables in Study I, we reviewed medical records from a random sample of approximately 5% of all primary ACL reconstruction surgeries registered in the DKRR from 1 January 2008 to 31 December 2009 (n = 240). A computer-generated random sample was obtained from six hospitals, both private and public, from all over Denmark. A 5% random sample was chosen to ensure a reasonable statistical precision of the estimated positive predictive values (PPVs). The medical records were reviewed systematically, and we retrieved information on possible confounding factors for future research from the DKRR. Specifically, the following factors were reviewed: cartilage injury, meniscal injury treatment, activity leading to ACL rupture, diagnosis registered as ACL rupture, choice of graft, choice of femoral tunnel placement (AM or TT technique), number of femoral tunnels, date of operation, and choice of femoral and tibial fixation. The medical record review was performed by a single independent researcher (LR-W) who was not involved in the treatment and who used a standardised form and EpiData (EpiData Association, Denmark) software. This software facilitates secure data entry owing to its error detection features. To optimise security in data entry in this study, pre-installed "checks" were made in EpiData, which makes it impossible to enter invalid numbers not previously defined by the reviewer. Furthermore, data entry and review were done twice.

4.2 Specific study design and methods, Study I

4.2.1 Study design

In order to test the hypotheses of Studies II and III, we conducted a validity assessment in Study I in which we evaluated the completeness and validity of the data registered in the DKRR. Study I consists of three sub-studies: (1) a study on the registration completeness of the ACL reconstruction procedures in the DKRR, (2) a study on the registration quality of key variables, and (3) a study on the differences in KOOS and Tegner scores in responders versus non-responders recorded one year after surgery.

4.2.2 Study population and study period

4.2.2.1 Completeness of the ACL reconstruction procedures in the DKRR

The completeness of the registration of the primary ACL reconstruction procedure was defined as a measure of sensitivity, as recommended by Sorensen and colleagues, i.e. the number of patients registered as having had an ACL reconstruction in both the DKKR and the DNRP, divided by the number of patients registered in the DNRP as having had an ACL reconstruction in the same period.[53] All operation codes for primary ACL reconstructions performed between 1 July 2005 and 31 December 2011 were identified in the DNRP and the DKRR. The DNRP was used to identify patients with ACL reconstruction using the following NOMESCO codes: NGE45 and NGE55C. The DNRP was used as the gold standard. Registration in the DNRP and the DKRR were compared to compute the registration completeness of the ACL reconstruction surgeries in the DKRR. We identified 14,943 primary ACL procedures in 14,721 patients from the DKRR. Similarly, we identified 17,276 primary ACL procedures in 16,734 patients from the DNRP. Linking between the DKRR and the DNRP was performed at the individual level via the unique personal identification number. Records of which leg had undergone operation were not available in 33% of the ACL reconstructions registered in the DNRP. It was therefore decided to include only the first operation for all patients in the registry. This implied exclusion of 222 operated knees from the DKRR and 542 operated knees from the DNRP. For 221 knees, the year of operation registered was not the same in the DNRP and the DKRR. These knees were therefore excluded. This left us with 14,500 operated knees registered in the DKRR and 16,513 operated knees registered in the DNRP.

In accordance with Ytterstad et al., we defined large-volume hospitals as those performing more than 30 operations a year and small-volume hospitals as those performing 30 or less operations per year.[52] Hence, completeness was stratified according to hospital volume, sex and age.[23,24]

4.2.2.2 Data quality of key variables

In the second analysis in Study I, we validated the quality of key variables calculating the positive predictive value (PPV) using medical records as the gold standard. We randomly selected the medical records of 240 patients registered in the DKRR as having had primary ACL reconstruction surgery from 1 January 2008 to 31 December 2009. These dates were chosen to ensure that we would be studying a period in which the database had been operational for some time to ensure that the surgeons were familiar with the registration task. We validated the data quality of key variables including cartilage damage, meniscal treatment, activity leading to ACL rupture, diagnosis registered as ACL rupture, choice of graft, choice of femoral tunnel placement (AM or TT technique), number of femoral tunnels, date of operation and choice of femoral and tibial fixation.

4.2.2.3 Data quality of patient-reported outcome measures

In the third analysis of Study I, we assessed the data quality of the recorded outcome measures (KOOS and Tegner scores). The assessment was performed by comparing the KOOS and the Tegner scores from patients who gave their subjective scores one year after the operation (responders) with those of patients who did not give their subjective scores one year after the operation (non-responders). The aim was to evaluate whether there were any differences in registered KOOS and Tegner scores in the DKRR between the two groups.

In order to achieve 95% statistical power and a 5% probability that the null hypothesis was false, we made power calculations. Our power calculation indicated a needed sample size of 52 in each group in order to demonstrate a difference in KOOS scores of 10. Since we were aware of the risk of people not responding to the questionnaires, we decided to randomly select 100 patients for each group.

We therefore conducted a study in which new KOOS and Tegner questionnaires were sent to 100 responders and 100 non-responders. A total of 62 (62%) of the responders and 39 (39%) of the non-responders answered the questionnaire, and an estimate of their mean scores was calculated (Table 5.1.3).

4.3 Specific study design and methods, Study II

In study II, we evaluated a possible association between the use of OC and the likelihood of sustaining operatively treated ACL injury.

4.3.1 Study design

Study II was a nested case-control study based on prospectively collected data from the DKRR and other national registries (Figure 4.1.1*)*. A case-control study is an observational study in which a designated group of people with a particular outcome are matched up with a control group without that outcome.[145] The levels of exposure variables in the two groups are then compared to see if the exposures are associated with the outcome. A nested case-control design compares the incident cases nested in a cohort study with controls drawn at random from the rest of the cohort, in this case the Danish female population.[39] Usually, matching is done on age and gender, but also ethnicity, smoking, etc., could be used for matching.[39] In our study, we restricted the cohort to women in the DKRR and matching was done on age only.

4.3.2 Study population and study period

4.3.2.1 ACL-reconstructed cases

In Study II, the DKRR was used to identify all incident primary ACL-reconstructed women in Denmark from 1 July 2005 to 31 December 2011, i.e. the case population. This definition of ACL injury was chosen to facilitate identification of a cohort of patients with a high likelihood of having a validated injury to the ACL. The date of ACL injury was considered the index date. Since only the month and year of injury were registered in the DKRR, the 15th of every month was chosen as the day of injury for all cases. In total, we identified 5,431 primary ACL-reconstructed women in 5,391 female patients. A total of 81 patients were excluded from the analysis due to use of middle- or high-dose OC. This was done to make the participants comparable. We included only the first operation if more than one ACL reconstruction had been performed in a patient. Hence, we excluded 40 knees because an operation had been performed on the contralateral knee. Since Danish Prescription Registry data were available only as from 1994, we excluded all patients (n = 264) with an index-day before the year 2000. This ensured a reasonable follow-up time. Furthermore, 549 patients were excluded due to incorrect or missing registration of their date of injury (n =218) and incorrect registration of redeemed OC (n = 331) defined as more that 66 months of redeemed prescriptions over a five-year period (Figure 4.3.1). This left us with 4,497 primary ACL procedures, which we included as cases in our analysis.

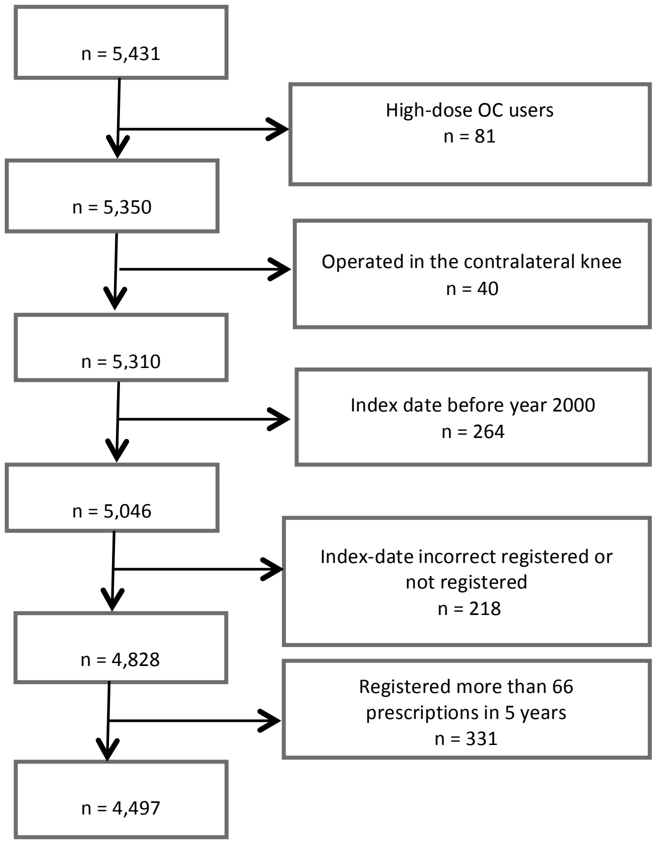


Figure 4.3.1: Flow chart showing patients (cases) included in this study. Inclusion criteria were women registered in the DKRR with an ACL reconstruction (n = 5,431) and two age matched controls. This figure shows the exclusion criteria. When excluding a case using the criteria listed above we excluded the whole strata, hence excluding the 2 matched controls, in order not to destroy the matching. We ended up including 4,497 cases in our cohort. The controls were also excluded if they were using middle- or high- dose OC and with incorrect registration of OC as in the case group. We ended up including 8,858 controls in our cohort. For some cases it was only possible to match one control. In total we had 13,355 people in our cohort

4.3.2.2 Population controls

We used the CRS to identify and match two female controls to each case registered in the DKRR. The cases and controls were matched by age on the year of ACL reconstruction of the case group. The controls were assigned index data identical to those of their corresponding cases. Controls were sampled using risk-set sampling; i.e. only individuals who were alive and for whom no prior history of ACL injury had been registered in the DNRP (i.e. not being registered with one of the following ICD-10 diagnose-codes: DM236, DS835, DS835A-F) were eligible for selection.[146] Whenever a case was excluded due to the above criteria, the whole strata were excluded. Hence, each time a case was excluded, the two matched controls were also excluded to ensure that the matching remained intact. Controls were also excluded if they were using middle- or high- dose OCs and if registration of their OC was incorrect, like in the case group. In total, we included 8,858 controls for analysis. For 136 of the cases included in our analysis, it was possible to match only one control.

4.3.3 Exposure

4.3.3.1 Oral contraception use

OCs contains estrogen and progesterone, and product refinement has decreased the daily dose of estrogen to ≤ 35 μg of estrogen in low-dose OCs. Middle- and high-dose OCs are classified as those containing between 35 and 50 μg of estrogen and more than 50 μg, respectively.

In Study II, we used the NDPD to prospectively identify all OC prescriptions redeemed by the cases and controls before the index date. Next, we linked the data from the DKRR and the DNRP with information on redeemed prescriptions from the NDPD (see Figure 4.1.1). OC exposure was identified using the Anatomical Therapeutic Chemical Classification code (ATC codes) of G03AA and G03AB, which are primarily low-dose OCs. We only included low-dose OC. High- and middle-dose OCs are no longer recommended due to their side effects and are therefore rarely used and these OCs were therefore excluded to ensure that the populations were comparable. We categorised exposure according to the number of prescriptions redeemed by each individual in the five years leading up to the index date, with one redeemed prescription corresponding to three months of OC use. We defined the reference group ("never users") as individuals who had redeemed 0 prescriptions in the entire study period. In contrast, "ever users" redeemed one or more prescription during the whole study period. We further sub-divided ever users into two strata (Figure 4.3.2). In the first stratum, we defined "current users" of OCs as patients who

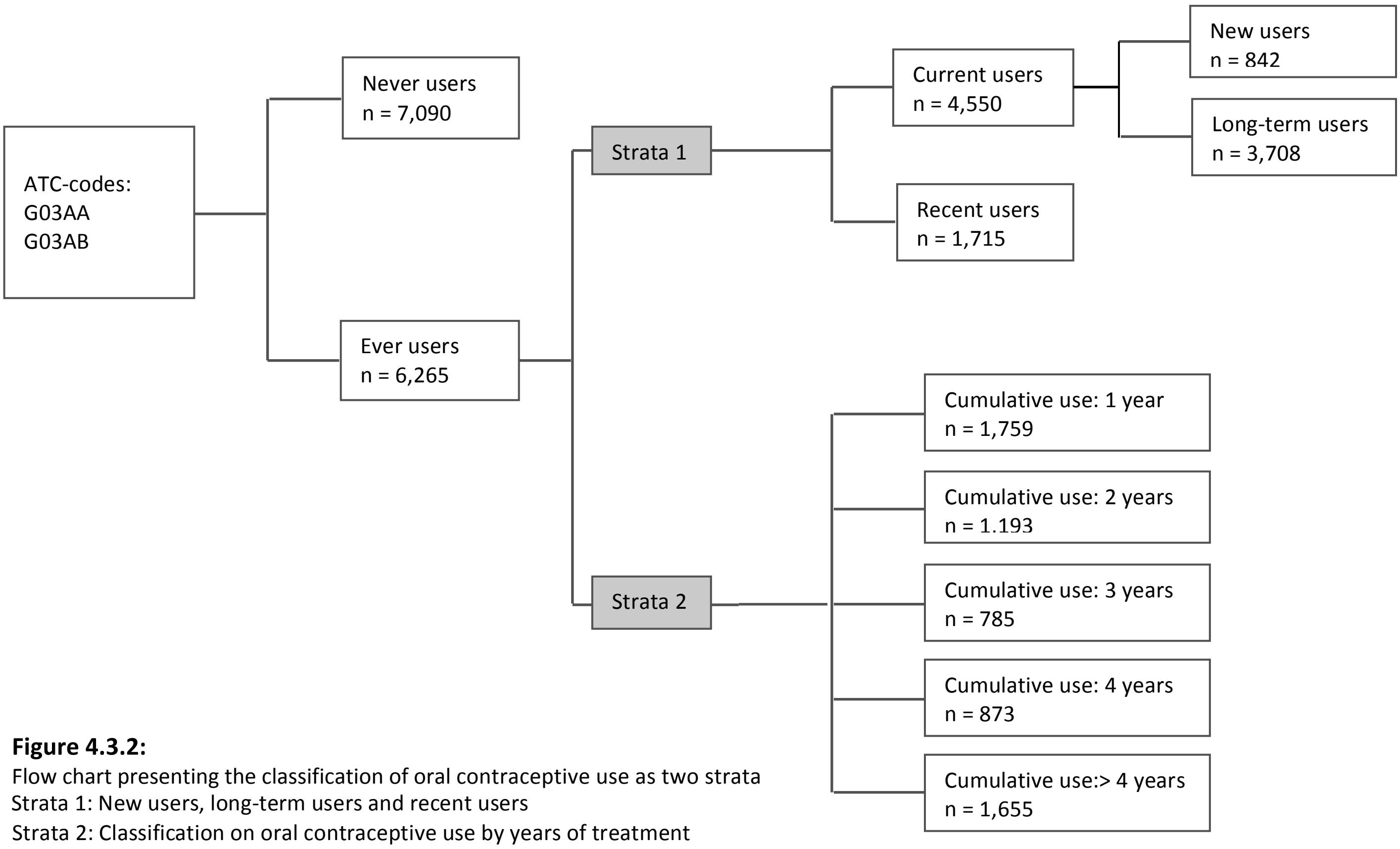


Figure 4.3.2:
Flow chart presenting the classification of oral contraceptive use as two strata
Strata 1: New users, long-term users and recent users
Strata 2: Classification on oral contraceptive use by years of treatment

redeemed their most recent prescription within one year of the index date. In order to evaluate whether the use of OCs had any long-term association with ligament laxity, we further sub-categorised two groups of current users as described in other studies[147]: “new users” were defined as those who had redeemed their first prescription within the first year before the index date, and “long-term users” were defined as those who had redeemed additional prescriptions one to five years before the index date. We defined those who redeemed their most recent prescription more than one year before the index-date as “recent users”. In order to facilitate investigation of a potential cumulative association of OC use, in strata 2 we further sub-classified ever OC users into groups with one, two, three, four, and more than four years of OC use in the entire study period (Figure 4.3.2).

4.3.4 Outcome

The outcome in Study II on OC use is the likelihood of sustaining operatively treated ACL injury, which is defined as being registered in the DKKR as having had a primary ACL reconstruction performed. This definition of ACL injury was chosen to allow us to identify a cohort of patients with a high likelihood of having a validated injury of their ACLs.

4.3.5 Covariates

We included a number of covariates in the analysis in Study II because of their potential association with the exposure and the outcome of interest not on the causal pathway between the exposure and the outcomes.[148] Data on these potentially confounding factors were obtained from several registries including the CRS (age and immigration), the DNRP (obesity and pregnancy/birth), the NDPD (medication use) and IDA (information on gross income). In order to capture patients who may be physically inactive, we used obesity as a proxy for physical inactivity. We identified patients with obesity (ICD-10: E65.8 and E66) in the five years leading up to the index date (yes versus no) and used this as a confounder in our analysis. Since use of non-steroidal anti-inflammatory (NSAIDs) drugs may be associated with physical activity, we chose to include NSAID use as a confounder in our analysis. NSAID drug use (ATC-code: M01A) was recorded if two prescriptions or more had been redeemed in the five years leading up to the index date. Since immigration status and income could be associated with OC use and attending pivoting sports, and hence with a risk of sustaining an ACL injury, we also included these two variables in our final model. Information on gross income was calculated as an average of the three years before the index date. To address other means of hormonal changes in the female, pregnancy and birth we also used as confounders in our analysis. Specifically, we identified pregnancy and giving birth (ICD-10: DO00-DO99) within five years prior to the index date (yes versus no).

4.4 Specific study design and methods, Study III

In Study III, we examined the impact of different surgical techniques on the prognosis after ACL reconstruction.

4.4.1 Study design

We conducted a nationwide population-based cohort study. A cohort study is an observational study of a designated group of people (DKRR) with a common characteristic who are followed over a period of time.[39] In a cohort study, various exposures are evaluated with respect to specific outcomes. In our open cohort study, we evaluated the placement of the femoral tunnel, with revision surgery as the primary outcome. In an open cohort, also referred to as a dynamic cohort, the cohort will take new members in as time passes, which in our study was whenever patients were ACL reconstructed. In this setting, it is problematic to measure risk estimates since new people are added continuously. To counter this challenge, the time at risk has to be measured whereby the amount of time each person spent in the cohort will be taken into account. Some people may be hard to follow up; either because they move away or cannot be tracked. We dealt with these issues in our cohort study through individual-level linkage with the CRS which made it possible to account for any *loss to follow-up*.

4.4.2 Study population and study period

In this study, we identified 9,239 primary ACL procedures in 9,202 patients from the DKRR between 1 January 2007 and 31 December 2010. This study period was chosen because registration of femoral drill hole placement was initiated in 2007. A total of 85 patients emigrated during the study period. In 20 operated knees, the patients resided in Greenland; and in 37 operated knees, the patients were of non-Danish nationality; these two groups were lost to follow-up. Finally, 806 (8.7% of total) knees were excluded due to missing information on femoral drill hole placement. Additionally, one patient had revision surgery registered before primary surgery and was therefore excluded. In total, we included 8,375 primary ACL procedures for further analysis.

4.4.3 Exposure

In Study III, we investigated the impact of using either the AM or the TT technique for femoral drill hole placement on our outcome measures. Information on the use of the AM or TT technique was retrieved from the DKRR.

4.4.4 Outcomes

The primary outcome in Study III was revision ACL surgery. Patients who are diagnosed with a lesion in their primarily operated ACL, but do not undergo revision ACL surgery, are not registered in the DKRR as a failure and hence are not included as a revision outcome. All primary ACL procedures in the two groups were followed up from the day of primary ACL surgery and to the date of revision of primary ACL if revision occurred, to their date of death, or to the status date, i.e. the end of the study period (31 December 2010), whichever came first.

The secondary outcomes were parameters of objective knee stability, i.e. instrumented sagittal knee stability testing (e.g. Rolimeter or KT1000) and pivot-shift scores.

Finally, we used the KOOS and the Tegner scores one year after surgery, if reported. Both preoperatively and postoperatively, these data were linked to the femoral drill hole placement data. Preoperative and postoperative KOOS and Tegner scores were available for 3,059 patients (37%) and 2,563 patients (31%), respectively.

4.4.5 Covariates

We included a number of covariates in the analysis in Study III because of their potential association with the exposure and the outcome of interest not on the causal pathway between the exposure and the outcomes.[148] To identify relevant confounders, we studied the literature and evaluated our data.[23,24,99,129,149,150] In the present study, the analysis was based mainly on the DKRR without linkage to the DNRP; and covariates were hence limited to the information retrieved from the DKRR, which in this study was appropriate in accordance with the exposure and outcome. Hence, we retrieved data at the time of surgery from the DKRR on gender, age (≤20 and >20 years of age), cartilage damage >1cm^2 present (no/yes or missing), operated meniscal damage (yes/no or missing), choice of graft, prior surgery to the knee (yes and no) and activity leading to primary ACL rupture. We regarded the fixation methods as part of the casual pathway and hence did not use this factor as a confounder in our analysis, although a sensitivity analysis was made including fixation method in the statistical model.

4.5 Statistical analysis

In this thesis, statistical analysis was computed using Stata, version 12 (Stata release 12, College Station, Texas, USA). P values of less than 0.05 were considered statistically significant. Normality was tested using Q-Q plots and histograms. The studies in this thesis were all approved by The Danish National Board of Health and the Danish Data Protection Agency.

4.5.1 Patient characteristics

In Study II, we tabulated cases and controls in accordance with their OC use, patient demographics and covariates. Further, in Study III, we tabulated the patients using either the AM or the TT method for femoral tunnel drilling by patient demographics and various covariates.

4.5.2 Completeness of data, Study I

4.5.2.1 Completeness of patient registration

The DNRP was used as a gold standard to calculate the registration completeness of the ACL reconstructions in the DKRR as a measure of sensitivity.[53] Registration completeness was defined as the number of patients registered in both the DKKR and the DNRP as having had ACL reconstruction, divided by the number of patients registered in the DNRP as having had ACL reconstruction in the same period. Analyses were stratified according to age, gender and hospital volume to assess whether there was any association between these variables and the completeness of data registration.

$$\textit{Sensitivity/completeness} = \frac{\textit{Number of patients registered in the DKRR and in DNRP}}{\textit{Total number patients registered in the DNRP}}$$

4.5.2.2 Data quality of key variables

In order to validate the data quality of selected key variables, we assessed the PPV using medical records as the gold standard. For each of the selected variables, we defined the PPV as the number of patients with a given variable registered in both the DKRR and the medical record, divided by the total number of patients with a given variable registered in the DKRR.

$$PPV = \frac{\textit{Number of patients with a given variable registered in the DKRR and in medical records}}{\textit{Total number patients with a given variable registered in the DKRR}}$$

4.5.2.3 Data quality of patient-reported outcome measures

The percentage of registered KOOS and Tegner scores was calculated as the number of registered KOOS and Tegner scores divided by the total number of operations registered in the DKRR pre- and post-operatively. To evaluate whether there was any difference in KOOS and Tegner scores between the responders and non-responders in the one-year postoperative evaluation questionnaire, we calculated the mean score for each group, and any data differences were tested using Student's t-test and the Wilcoxon rank sum test.

4.5.3 Conditional logistic regression, Study II

In Study II (case-control study), the patients were restricted to females and they were matched on age. We used conditional logistic regression to compute the crude and adjusted odds ratio with 95% confidence intervals (CI) assorting OC use and the likelihood of operatively treated ACL injury. Given the risk set sampling design and the fact that operatively treated ACL injury is a rare outcome, the odds ratio can be interpreted as relative risk (RR).[145,146] We fitted the model controlling for the following confounders: age, immigration, obesity, pregnancy/birth, use of NSAID, and gross income.

4.5.4 Cox proportional hazard regression model, Study III

Using the Kaplan-Meier method, we estimated the failure probability at different follow-up times in the AM and TT groups. We used Cox regression analyses to compare the revision risk following primary ACL reconstruction among patients in whom the AM and TT techniques were used. We computed the hazard ratios as a measure of RR, with 95% confidence interval (95% CI) for patients treated with the AM compared with the TT technique, both crudely and adjusted for potentially confounding factors. In the final model, we included the following covariates: sex, age, cartilage damage >1cm^2 present, operated meniscal damage, choice of graft, prior surgery to the knee and activity leading to primary ACL rupture. The assumption of the Cox regression model was assessed with use of log-log plots and Schoenfeld residuals, and it was found to be suitable. Furthermore, using Cox regression analysis, we calculated the adjusted RR of having a positive pivot-shift test or more than 2 mm sagittal instability to the operated knee compared with the healthy knee in the AM group compared with the TT group. The mean values of the

KOOS and Tegner scores before surgery and a year after surgery for the patients operated with the AM and TT techniques were compared using Student's t-test or the Wilcoxon rank-sum test.

4.5.5 Sensitivity analyses, Studies II and III

To examine the robustness of our results, we conducted four sensitivity analyses in Study II and four sensitivity analyses in Study III.

In Study II, we conducted a sensitivity analysis to examine the potential of any compliance problems associated with the use of OC to rule out the risk of information bias. We changed the cut point for being a never user of OC. This was done by performing an analysis that defined never users as those redeeming one or less than one prescription during the entire study period and ever users as those with two or more redemptions during the study period. This was deemed necessary since redeeming only one prescription may indicate that other means of anti-conception had been initiated, and, hence, if only one prescription was redeemed, it may not have been used. Also, two sensitivity analyses were made defining new users as those who had redeemed their first prescription within the first three or six months before the index date, and long-term users as those who had redeemed additional prescriptions from three or six months to five years before the index date. In this sensitivity analysis, we defined people who redeemed their most recent prescription more than three or six months before the index date as recent users. This analysis was performed to evaluate if the cases and controls were actually on an OC at the time of their injury or not. Further, in Study II we performed a sensitivity analysis including the excluded patients with incorrect registration of OC use and compared the results with the main results. Finally, in Study II, we conducted a sensitivity analysis to examine the potential influence of any missing values in the covariates by comparing results on RR estimates with and without multiple imputations (see section 4.5.5.1).

In Study III, we conducted a sensitivity analysis on the missing values in the exposure variable for femoral tunnel placement in order to further rule out the risk of selection bias. This allowed us to compare the results in the sensitivity analysis with the main results. Further, due to many missing values in objective measures and the KOOS and the Tegner scores one year after surgery, we evaluated the difference in covariates for responders and non-responders to the objective measures and the KOOS and the Tegner scores. Furthermore, we made a sensitivity analysis evaluating the association of graft-fixation method as a potential confounder. Finally, we conducted a sensitivity analysis to examine the potential influence of missing values in the covariates on the RR estimates. This was done by comparing results on RR estimates with and without multiple imputations (see section 4.5.5.1).

4.5.5.1 Missing data and multiple imputation, Studies II and III

Missing data are a frequent problem in observational studies. The concept of missing data refers to data containing various codes lacking a response.[151] Over the years, several methods have been introduced in the literature to deal with missing data.[152-155] Most methods can lead to inefficient analysis and biased estimates. The use of more sophisticated methods such as multiple imputations is therefore warranted. The technique of multiple imputation, which originated in the early 1970s,[156] has gained increasing popularity in recent years.[157-160] With this technique, various estimates are used, which reflects the uncertainty of the missing variables.[161] An imputation represents one set of plausible values for missing data. Hence, using multiple imputations replace missing values with a set of plausible values, and in this way this approach deals with missing values.

In Studies II and III, we used multiple imputations to examine the potential influence of missing values, generating 20 imputed datasets. The RRs were calculated as the average RRs of the 20 datasets, corrected for between- and within-imputation variation. The imputation models included all the described covariates in each study and were used as the adjusted measures in Study II.

4.5.6 Stratified analyses, Study III

In Study III, we stratified data on the following covariates: sex, age, cartilage damage >1cm^2 present, operated meniscal damage, choice of graft and activity leading to primary ACL rupture. We carried out these analyses because the association of the exposure may differ between these subgroups of ACL-reconstructed patients, i.e., there may be an *effect measure modification*.

5. Results

5.1 Study I

In total, 18,050 patients were identified in the DKRR and the DNRP from July 2005 to December 2011. A total of 12,963 (71.8%) patients were registered in both registries, 3,550 (19.7%) were registered only in the DNRP, and 1,537 (8.5%) were registered only in the DKRR. Patient demographics for these three groups are shown in Table 1 of Paper I in this thesis.

5.1.1 Completeness of patient registration

The overall registration completeness of the ACL reconstruction in the DKRR was 78.5% (95% CI: 77.9% to 79.1%) from 2005 to 2011 (Table 5.1.1). The completeness rose from 60.3% (95% CI: 57.4% to 63.1%) in 2005 to 86.3% (95% CI: 84.9% to 87.7%) in 2011 (Figure 5.1.1). There was no difference in completeness when data were stratified according to gender and age. However, a considerable difference was seen when data were stratified according to hospital volume; large-volume hospitals enjoyed a higher degree of registration completeness than low-volume hospitals (81.6% (95% CI: 80.9% to 82.2%) versus (64.5% (95% CI: 62.3% to 66.5%)) (Figure and Table 5.1.1).

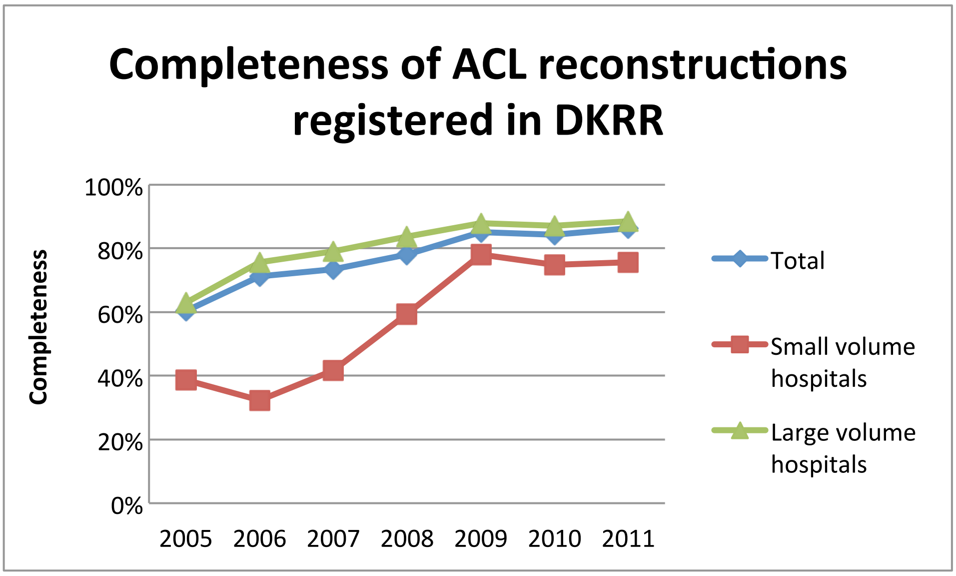


Figure 5.1.1: Completeness of registration stratified on hospital volume. Small-volume hospitals: less or equal to 30 annual operations; Large-volume hospitals: more that 30 annual operations.

5.1.2 Accuracy of key variables

In general, the data quality of the key variables was good. The PPV ranged from 85% to 100% (Table 5.1.2). The PPV was 96% for the use of TT technique for femoral tunnel drilling, 100% for "choice of graft", 85% for "cartilage damage" and 96% for "treatment of meniscus damage".

Table 5.1.1: Completeness* of registration for ACL reconstruction surgery in the DKRR compared with the DNRP stratified according to sex, age, small-volume versus large-volume hospitals, and year of registration

		Patients registered in				Degree of completeness
		Both [n (%)]	Only DNRP [n (%)]	Only DKRR [n (%)]	**Total (n)**	**[% (95% CI)]**
2005-2011		**12,963 (71.8)**	**3,550 (19.7)**	**1,537 (8.5)**	**18,050**	**78.5 (77.9-79.1)**
2005-2011	**≤20 years**	3,449 (76.3)	773 (17.0)	299 (6.6)	4,521	81.8 (80.6-82.9)
	>20 years	9,514 (70.3)	2,777 (20.5)	1,238 (9.2)	13,529	77.4 (76.7-78.1)
2005-2011	**Male**	7,783 (71.3)	2,208 (20.2)	937 (8.6)	10,928	77.9 (77.1-78.7)
	Female	5,180 (72.7)	1,342 (18.8)	600 (8.5)	7,122	79.4 (78.4-80.4)
2005-2011	**Small volume****	1,317 (56.0)	726 (30.8)	311 (13.2)	2,354	64.5 (62.3-66.5)
	Large volume**	11,646(75.1)	2,628 (17.0)	1,226 (7.9)	15,500	81.6 (80.9-82.2)
2005		690 (52.2)	455 (34.5)	176 (13.3)	1,321	60.3 (57.4-63.1)
2006		1,870 (65.6)	758 (26.6)	224 (7.8)	2,852	71.2 (69.4-72.9)
2007		1,828 (67.5)	660 (24.4)	219 (8.1)	2,707	73.5 (71.7-75.2)
2008		1,737 (70.7)	480 (19.9)	231 (9.4)	2,458	78.0 (76.2-79.7)
2009		2,335 (77.3)	407 (13.5)	278 (9.2)	3,020	85.2 (83.8-86.5)
2010		2,323 (77.6)	433 (14.5)	238 (7.9)	2,994	84.3 (82.9-85.7)
2011		2,180 (80.8)	347 (12.9)	171 (6.3)	2,698	86.3 (84.9-87.7)

**196 ACL-reconstructed knees could not be placed in either the small- or the large-volume group

*Registration completeness was defined as a measure of the sensitivity as recommend by Sorensen et al.: the number of patients registered as having had ACL reconstruction in both the DKKR and the DNRP, divided by the number of patients registered as having had ACL reconstruction in the DNRP during the same period.

5.1.3 Data quality of patient-reported outcome measures

Subjective outcome scores for both the KOOS and the Tegner scores were available for 4,799 out of 14,500 operations (33.1%) preoperatively; one year after surgery, these outcome scores were available for 3,852 out of 14,500 patients (26.6%). No difference was found in either of the five KOOS sub-scores or in the Tegner scores between responders and non-responders in the one-year postoperative questionnaire (Table 5.1.3). The patient characteristics of responders and non-responders are outlined in Table 5 in Paper I of this thesis and are comparable for the two groups.

Table 5.1.2: Validity of key variables registered in the Danish Knee Reconstruction Registry using medical records as gold standard. 240 medical records used.

	DKRR	Medical record		Missing Medical record	PPV % (95 % CI)
		Yes	No		
Cartilage damage	Yes	29	5	0	29/34 = **85** (69-95)
	No	27	127	12	
	Missing DKRR	13	26	1	
Treated meniscal damage	Yes	103	4	0	103/107 = **96** (90-99)
	No	26	107	0	
Sport as activity reason for the ACL rupture	Yes	172	29	1	172/201 = **86** (80-90)
	No	4	33	0	
	Missing DKRR	0	1	0	
Diagnosis of ACL lesion	Yes	240	0		240/240 = **100**
	No	0	0		
Hamstring as graft choice	Yes	208	0	2	208/208 = **100**
	No	0	24	0	
	Missing DKRR	4	1	1	
Transtibial placement of femoral canal	Yes	136	6	60	136/142 = **96** (91-98)
	No	3	18	16	
	Missing DKRR	1	0	0	
One femoral canal (versus two)	Yes	237	0	2	237/237 = **100**
	No	0	0	0	
	Missing DKRR	1	0	0	
OP date	Identical	238	0	1	238/239 = **99** (93-100)
	No identical	0	1		
Method for fixation of graft in femur	Identical	217		7	217/233 = **93** (89-96)‡
Method for fixation of graft in tibia	Identical	220		6	220/234 = **94** (90-97)‡

Abbreviations: DKRR: Danish Knee Ligament Reconstruction Registry; CI: Confidence interval; PPV: Positive predictive value; Identical: Indicates that the registration in the DKRR is identical to the registration in the medical records. ‡ Approximately 20 different modes of fixation are available. Therefore, calculation was made by placing the variables with identical registration in the DKRR and the medical records into the numerator, and dividing them by the total number of cases registered.

Table 5.1.3: Results from questionnaires on the KOOS and the Tegner scores. Mean value of the KOOS and the Tegner scores in the group of patients who previously recorded subjective scores (responders) compared with the group of patients for whom such scores had not previously been recorded (non-responders).

Previously answered subjective measures	**n**	**Pain** mean (SD)	**Symptom** mean (SD)	**ADL** mean (SD)	**Sport** mean (SD)	**Qol** mean (SD)	**Tegner** mean (SD)
Yes (responders)	62	83.1(15.0)	60.4 (13.8)	88.0 (15.7)	64.5 (26.9)	64.5 (25.4)	4.87 (2.0)
No (non-responders)	39	78.5 (19.2)	59.8 (12.1)	83.7 (19.7)	56.9 (26.8)	59.3 (24.5)	4.56 (1.9)
P value		0.09	0.38	0.12	0.97	0.82	0.72

Abbreviations: ADL = Activity of daily Living; QoL= Quality of Life

5.2 Study II

5.2.1 Patient characteristics

Descriptive data are presented in Table 5.2.1 for the whole study population counting 4,497 cases and 8,858 controls. On the index date, the median age of the cases was 24.0 years (interquartile range (IQR): 17.1 to 37.9 years), the majority being between 15 and 20 years of age. NSAID use was more common in the case than in the control group, and cases also had a higher gross income than controls. Obesity, being pregnant and immigrant status were more common among controls.

Table 5.2.1: Patient characteristics in study II

	Cases (n = 4,497)	**Control (n = 8,858)**
Age, median (index date)	24.0 (IQR = 17.1–37.9)	23.7 (IQR = 17.0–37.7)
	n (%)	**n (%)**
Age ≤ 15 years (n = 1,285)	415 (9.2)	870 (9.8)
Age > 15 and ≤ 20 years (n = 4,233)	1,429 (31.8)	2,804 (31.7)
Age > 20 and ≤ 30 years (n = 2,515)	849 (18.9)	1,666 (18.8)
Age > 30 and ≤ 40 years (n = 2,685)	915 (20.4)	1,769 (20.0)
Age > 40 years (n = 2,638)	889 (19.8)	1,749 (19.7)
Obese	70 (1.6)	236 (2.7)
Pregnancy/birth	631 (14.0)	1,667 (18.9)
NSAID use within five years, yes	1,009 (22.4)	1,719 (19.4)
Immigrants and descendants, yes	109 (2.4)	608 (6.9)
Gross income < 26,800 Euro/year	2,326 (51.7)	4,935 (55.7)
Exposure variables	**n (%)**	**n (%)**
Never users (reference) (n = 7,090)	2,450 (54.5)	4,640 (52.4)
Recent users (n = 1,715)	538 (12.0)	1,177 (13.3)
New users (n = 842)	283 (6.3)	559 (6.3)
Long-term users (n = 3,708)	1,226 (27.3)	2,482 (28.0)
Cumulative OC use	**n (%)**	**n (%)**
Total use: 1 year (n = 1,759)	554 (12.3)	1,205 (13.6)
Total use: 2 year (n = 1,193)	361 (8.0)	832 (9.4)
Total use: 3 year (n = 785)	241 (5.4)	544 (6.1)
Total use: 4 year (n = 873)	284 (6.3)	589 (6.7)
Total use: > 4 year (n = 1,655)	607 (13.5)	1,048 (11.8)

Abbreviations: IQR: inter quartile range

5.2.2 Likelihood of operatively treated ACL injury

We used the DKRR to find all incident ACL-injured patients treated with ACL-reconstruction. In the case group (patients who had operatively treated ACL injury), 2,047 (45.5%) had used OCs at some point over a five-year period compared with 4,218 (47.5%) in the control group (people with no ACL injury). Compared with never users, ever users of OCs had a lower likelihood of sustaining operatively treated ACL injury: adjusted RR = 0.82 (95% CI: 0.75 to 0.89). Long-term and recent OC users also had a lower likelihood of operatively treated ACL injury according to adjusted RRs of 0.82 (95% CI: 0.75 to 0.90) and 0.81 (95% CI: 0.72 to 0.89), respectively. No association between new users and likelihood of operatively treated ACL injury was found (Table 5.2.2).

There was a trend towards a dose-response association, with a RR of 0.83 (95% CI: 0.74 to 0.94), 0.78 (95% CI: 0.68 to 0.90) and 0.75 (95% CI: 0.64 to 0.90) of sustaining an operatively treated ACL injury if using OCs for 1, 2, and 3 years within a five-year period, respectively. Using OC for more than four years did not seem to alter the likelihood of sustaining operatively treated ACL injury, RR = 0.88 (95% CI: 0.77 to 1.01) (Table 5.2.3).

The results of the sensitivity analysis did not change the results. Hence, no changes were seen when the other definition of OC use was employed; nor when three or six months were used as the cut-off for the new user group or when never users were defined as those redeeming one or less than one prescription during the entire study period and ever users as those who redeemed two or more redemptions during the study period. Similarly, the sensitivity analysis on multiple imputations did not alter the result. Finally, no changes in the results were seen when the calculations included the excluded patients with incorrect registration of OC.

Table 5.2.2: Relative risk of sustaining operatively treated ACL injury when using oral contraceptives or not

	Crude RR	**Adjusted RR***
Never users†, (n = 7,090)	1.0 (ref)	1.0 (ref)
Ever users‡, (n = 6,266)	0.89 (0.81-0.96)	0.82 (0.75-0.90)
New users§, (n = 842)	0.96 (0.82-1.12)	0.89 (0.76-1.05)
Long-term users£, (n = 3,708)	0.90 (0.81-0.99)	0.80 (0.74-0.91)
Recent users**, (n = 1,715)	0.83 (0.73-0.93)	0.81 (0.72-0.89)

Abbreviations: ACL = anterior cruciate ligament; RR = relative risk
*Using multiple imputation adjusted for: age, obesity, pregnancy/birth, income, ethnicity, NSAID
†Never users = users, who redeemed 0 prescriptions in the five-year period before ACL injury
‡Ever users = users, who redeemed ≥ one prescription in the five-year period before ACL injury
§New user = current user, first prescription redeemed within one year before index date
£Long-term user = current user, first prescription redeemed more than one year before index date
**Recent user = used their most recent prescription more than one years before the index date

Table 5.2.3: Dose-response analysis association between duration of oral contraceptive use and the relative risk of sustaining operatively treated ACL injury

Number of years using OC	Crude RR	Adjusted RR*
Never users†, (n = 7,090)	1.0 (ref)	1.0 (ref)
Cumulative OC use		
Total use: 1 year (n = 1,759)	0.85 (0.76-0.96)	0.83 (0.74-0.94)
Total use: 2 years (n = 1,193)	0.80 (0.70-0.92)	0.78 (0.68-0.90)
Total use: 3 years (n = 785)	0.81 (0.69-0.96)	0.75 (0.64-0.90)
Total use: 4 years (n = 873)	0.89 (0.76-1.05)	0.81 (0.69-0.96)
Total use: more than 4 years (n = 1,656)	1.08 (0.95-1.23)	0.88 (0.77-1.01)

Abbreviations: ACL = anterior cruciate ligament; RR = relative risk; OC = Oral contraceptives
*Using multiple imputation adjusted for: age, obesity, pregnancy/birth, income, ethnicity, NSAID
†Never users = users who redeemed 0 prescriptions in the entire study period

5.3 Study III

5.3.1 Characteristics

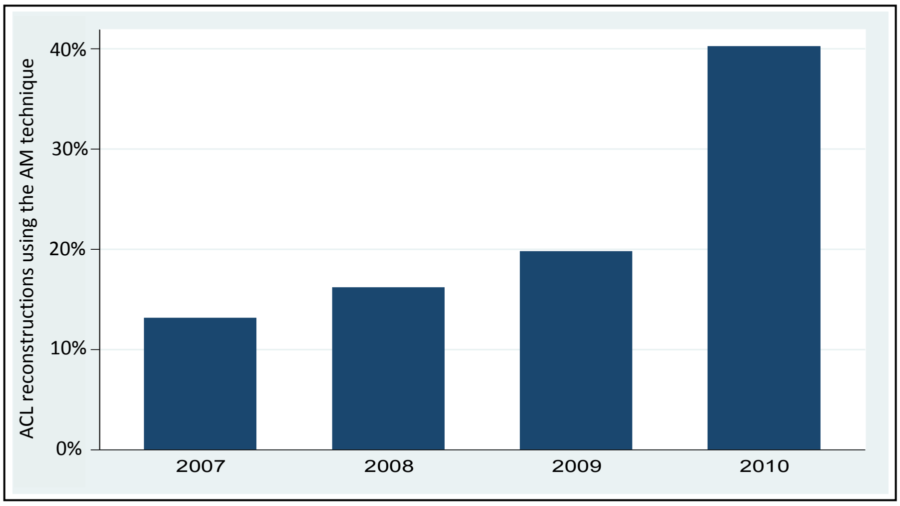
Patient characteristics are outlined in Table 1 of Paper III, and causes of revision-surgery are shown in Table 5.3.1. No difference in reason for revision was found between the two groups. Over a four-year period, the use of the AM technique increased from 13% of all operations in 2007 to 40% in 2010 (Figure 5.3.1). In the AM group, 39 of 1,945 knees were revised, and in the TT group 102 of 6,430 knees were revised over the four-year observation period. The average follow-up period was 22.2 months (95% CI: 21.8 to 22.4), and 16.2 (95% CI: 15.6 to 16.8) and 24.0 (95% CI: 23.6 to 24.3) months for AM and TT, respectively.

Table 5.3.1: Causes of revision surgery after primary ACL reconstruction in the anteromedial and transtibial group (in %).

Cause of revision surgery	*Femoral tunnel placement technique*	
	Anteromedial, n (%)	***Transtibial, n (%)***
New trauma	16 (42.1)	39 (38.2)
Tunnel-widening	1 (2.6)	3 (2.9)
Suboptimal placement of the graft in tibia	3 (7.9)	8 (7.8)
Suboptimal placement of the graft in femur	3 (7.9)	13 (12.7)
Infection	5 (13.2)	5 (4.9)
Unknown reason for instability	7 (18.4)	23 (22.6)
Other ligament failure	1 (2.6)	6 (5.9)
Other	2 (5.3)	5 (4.9)
Total	**38 (100%)***	**102 (100%)**

* For one patient no cause of revision was recorded

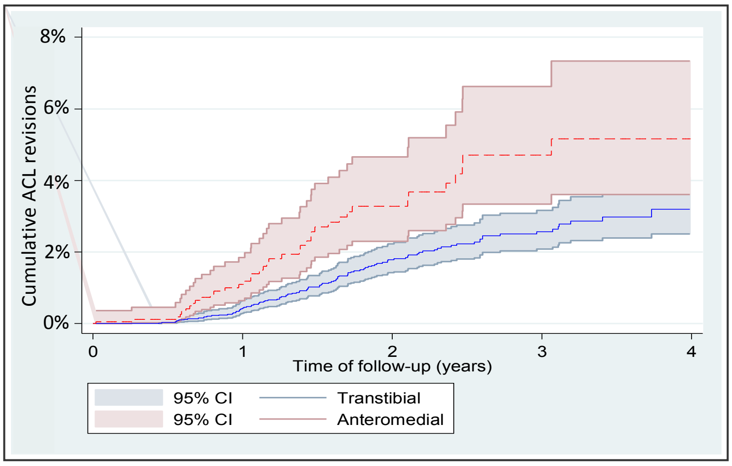
Figure 5.3.1: Use of AM technique for femoral tunnel drilling from 2007–2010 (%)



5.3.2 Risk of revision

The Kaplan-Meier four-year cumulative failure rate was 5.16% (95% CI: 3.61% to 7.34%) in the AM group and 3.20% (95% CI: 2.51% to 4.08%) in the TT group (Figure 5.3.2). The failure rates were 1.09% (95% CI: 0.65% to 1.85%), 3.28% (95% CI: 2.30% to 4.66%), and 4.71% (95% CI: 3.34% to 6.63%) among patients treated with the AM technique after 1, 2, and 3 years, respectively. In comparison, the failure rate was 0.44% (95% CI: 0.29% to 0.65%), 1.78% (95% CI: 1.42% to 2.23%), and 2.57% (95% CI: 2.09% to 3.16%) among patients treated with the TT technique, after 1, 2, and 3 years, respectively.

Figure 5.3.2: Kaplan-Meier failure curves of primary ACL reconstructions using either the AM or TT approaches for femoral drill hole placement. Outcome is revision ACL reconstruction



The crude overall RR for revision surgery in the AM group compared with the TT group was 2.01 (CI: 1.39 to 2.92). The overall RR for revision adjusted for the mentioned confounders was 2.04 (CI: 1.39 to 2.99). Furthermore, the adjusted RR of having revision after one and two year was 2.32 (CI: 1.17 to 4.57) and 2.04 (CI: 1.33 to 3.14), respectively.

The sensitivity analysis on the missing exposure variables did not alter these results. Furthermore, using multiple imputations in the adjusted measures did not change the results. Finally, the use of different fixation methods is shown in Table 5.3.2. The sensitivity analysis using suspensory fixation compared with other fixation methods as a confounder revealed a RR of revision surgery in the AM group of 2.10 (1.42-3.10) compared with the TT group.

Table 5.3.2: Table showing the use of fixation method in the femur in the AM and the TT group

	Femoral tunnel placement technique	
	Transtibial	*Anteromedial*
	n (%)	*n (%)*
Suspensory fixation	**1,612 (25%)**	**909 (50%)**
Screw fixation	**1,131 (18%)**	**379 (21 %)**
Transfix with cross pins	**3,584 (57%)**	**531 (29%)**

229 patients could not be placed in any of the groups

5.3.2.1 Stratified analyses

The subgroup analysis revealed no major changes in RR of revision between the AM and the TT technique irrespectively of gender, age, cartilage damage and meniscal damage. However, it was noted that the risk estimates tended to be higher among patients with an HT graft than among patients with a PT graft (RR = 2.20 (95% CI: 1.48 to 3.27) and RR = 0.55 (95% CI: 0.07 to 4.21), respectively).

5.3.3 Risk of objective instability

The AM technique for drill hole placement was associated with an increased risk of a positive pivot-shift test for rotational instability compared with the TT technique, with an adjusted RR = 2.86 (95% CI: 2.40 to 3.41) (Table 5.3.3). Furthermore, we observed that the patients with AM technique for drill hole placement had an increased risk of having a difference in sagittal instability between the operated and the healthy knee above 2 mm compared with the TT group, with an adjusted RR = 3.70 (95% CI: 3.09 to 4.43) (Table 5.3.3). The use of multiple imputation in the adjusted measure did not alter the results.

Pivot-shift was recorded for 4,138 (49%) of the operations, and the sagittal instability data were recorded for only 3,925 (47%) of the operations. Covariates in the group with objective measures recorded one year after surgery were comparable to those of the group who did not have objective measures recorded one year after surgery (Appendix 6).

Table 5.3.3: Pivot-shift test* for rotational instability and instrumented sagittal knee instability (e.g. Rollimeter or KT 1000) one year postoperatively. Presentation of the incidence and the adjusted RR of having a positive pivot-shift test or a sagittal instability > 2 millimetres on instrumented sagittal instability tests in the AM group compared with the TT group.

Objective tests		*Femoral tunnel placement technique*	
		Transtibial	***Anteromedial***
Pivot-shift test for rotational instability	Positive test; n (%)	401 (13.6%)	206 (19.5%)
	Adjusted RR** (95% CI)	1.0 (reference)	2.86 (2.40-3.41)
Instrumented sagittal instability	> 2 millimetres; n (%)	320 (11.4%)	208 (19.8%)
	Adjusted RR** (95% CI)	1.0 (reference)	3.70 (3.09-4.43)

*Positive pivot shift test includes glide (1), clunk (2), and gross (3) during the pivot-shift test; **RR: Relative risk, adjusted for gender, age (≤20 and >20 years of age), cartilage damage >1cm^2 present, operated meniscal damage, choice of graft, prior surgery to the knee, and activity leading to primary ACL rupture

5.3.4 PROM and activity level score as outcome measure

The preoperative and the one-year postoperative KOOS and the Tegner scores were comparable for the two groups (see Table 4 in Paper III). A total of 37% of patients reported these measures before surgery, and 31% of patients reported these measures one year after surgery. A comparison of covariates in responders versus non-responders of KOOS and Tegnser scores one year after surgery showed no difference (Appendix 7).

6. Discussion

6.1 Methodological considerations

This thesis was based on data from national clinical registries, and it therefore has several strengths and limitations. The fact that the DKRR, the DNRP and the NDPD are large national databases is an obvious strength from a data quality perspective. Also, owing to the unrestricted and free access to healthcare in Denmark, the DKRR provides an unselected study population. Furthermore, the DKRR has the potential for extensive individual-level linkage to other important databases owing to the unique personal identification number given to all Danish citizens. This linkage affords the possibility of individual measurements. Additionally, these nationwide population-based databases provide an excellent data source at a low cost and with a potential low risk of bias.

6.1.1 Selection bias

Selection bias is a systematic error that can occur when the association of interest between exposure and outcome differs between participants and non-participants of a given study.[148] Hence, excluding patients who redeemed middle and high-dose OC (Study II) and patients without registration of the technique used for femoral tunnel drilling (Study III) could introduce selection bias. Since our data were collected prospectively and were not dependent on outcome, there is no indication that the association between the exposure and the outcome differs between participants and non-participants; hence, the risk of selection bias due to the above is low. In addition, we conducted a sensitivity analysis on missing exposure variables in Study III that did not alter the results.

In Study III we need to be aware that when new methods are being introduced, this may result in greater attention to the outcome and, hence, a greater revision rate; and this could also bias our results, although the opposite might as well be the case.

All three studies in this thesis were conducted using high-quantity administrative and medical databases in well-designed populations in the context of a tax-supported healthcare system that guarantees free healthcare to all residents. These features minimise the risk of selection bias. Nevertheless in Study III, the completeness of registration of objective and subjective measures is a recurrent problem. Hence, pivot-shift was recorded for 49% of the operations and the sagittal instability data were recorded for only 47% of the operations. The challenge of achieving a high percentage of patients in the clinical follow-up is substantial when dealing with a national cohort. Still, the risk of selection bias may be limited owing to the prospective collection of data and because covariates in the group who had objective measure recorded one year after surgery that were comparable to the covariates in the group who did not record objective measures one year after surgery. Also, in Study III, we showed no difference in the KOOS and the Tegner scores recorded in the AM and the TT group and, hence, no difference in patient satisfaction after surgery. This may also indicate that the risk of selection bias due to missing objective outcome data is low, since both groups showed the same level of satisfaction and accordingly the same willingness to participate in clinical follow-up. Nevertheless, due to the low registration rate for the subjective and objective data, this finding should be interpreted with caution as it may not necessarily be generalised to the full population of ACL-reconstructed patients.

Also, the registration of the KOOS and the Tegner scores was not acceptable in Study III. Only about 37% of the patients reported these scores before surgery, and only 31% of the patients reported the KOOS and the Tegner scores one year after surgery. In Studies I and III, we evaluated the difference in covariates in responders versus non-responders (Table 5 in Paper I and Appendix 7) and found the two groups to be comparable. In Study I, we showed no difference in responders versus non-responders to the KOOS and the Tegner score questionnaires one year after surgery. However, in Study I, fewer patients than calculated actually answered the questionnaire reducing our sample size and power. Therefore the result of no difference between responders and non-responders in terms of KOOS must accordingly be interpreted with caution due to the risk of type 2 error.

In Study II, we used the DKRR to identify ACL reconstruction as an outcome looking at only one definition of ACL injury. Some patients are not willing to undergo surgery, accepting instead a reduction in their activity level and chronic knee instability. In other cases, surgeons do not find that the patients are suitable for surgery and, finally, elite athletes may be more susceptible to ACL reconstruction than other patients. Our case population in Study II only comprises operatively treated ACL-injured patients and our population may therefore differ from the patients with ACL injury who were not operated, and this would introduce bias. Thus, we may only draw conclusions concerning operatively treated ACL injury patients.

Furthermore, in Study III, we used revision ACL reconstructions as an outcome. Doing this, we did not identify all failures since some patients accept a chronically unstable knee and reduce their activities, and others are unsuitable for re-operations. Thus, the revision surgery rate is a conservative measure of the real number of failures after ACL reconstructions. However, there is no indication that the ACL failure rates and ACL revision rates differed in the AM and the TT groups.

6.1.2 Information bias

To compare two groups, we need information on exposure, and bias may accordingly occur due to measurement errors in the information collected. Information bias arises if the information on exposure is subject to misclassification. Such misclassification can occur if there is a systematic error in the information regarding the exposure (femoral tunnel placement and the use of OCs) or if the information on exposure is not independent of the outcome (risk of revision ACL surgery or likelihood of operatively treated ACL injury).[148] Misclassification can either be differential or non-differential. In differential misclassification, the misclassification of the exposure (i.e. operation technique) is associated with outcome status (i.e. revision ACL reconstruction). Differential misclassification may lead to unpredictable information. In non-differential misclassification, the exposure is misclassified independently of the outcome status and non-differential misclassification will produce bias towards the null in most instances.[148]

An obvious strength of Study II is that the NDPD has a high validity and is virtually complete, and this reduces the risk of information bias. However, the use of redeemed prescriptions as a measure of OC use will always involve a risk of compliance problems.[143] Compliance is difficult to measure, and we do not know if compliance is different between cases and controls. Again, since patients not taking the redeemed prescriptions were independent of the outcome (having operatively treated ACL injury), this potential misclassification is non-differential; and, if biased, this would produce bias toward the null and therefore support the association found in this study. Due to the risk of information bias, we conducted a sensitivity analysis classifying non-users as those who had redeemed one or less than one prescription throughout the entire study period since one prescription may indicate that other means of anti-conception had been initiated, and thus the single prescription redeemed had not been used. This did not alter the results. Also, in Denmark it is not possible to redeem OCs without a prescription, thus it is unlikely that "never users" have obtained and taken OCs, and this is a clear strength.

Recall bias is a common type of information bias that occurs in case-control studies when the information collected relies on retrospective information from questionnaires or interviews. In our case-control study (Study II), this is unlikely to occur since our data on OC use are based on prospectively collected data from a NDPD.

As NSAID is available over the counter, some authors have questioned the information on NSAID use from databases such as the NDPD.[162] It is generally accepted to use NSAID prescriptions to measure associations of NSAIDs since regular users of NSAIDs have an economic incentive to obtain the drugs by prescription due to the reimbursement provided by the Danish State.[147,163] A recent Danish study has quantified the proportion of total sales made on prescription and concluded that the potential for identification of individual-level use of NSAIDs from prescription registries in Denmark is high.[164] Therefore, we assessed that the risk of information bias due to NSAID use is low.

In study III, the operative technique data and data on covariates were based on data from the DKRR. Since the data collection on exposure variables was prospective and independent of registration of any subsequent revision, and as a high PPV was found in Study I, the risk of information bias was very limited and, hence, a potential misclassification would be non-differential and thus bias the results toward the null and therefore support the association.

Finally, using the DNRP as gold standard in Study I, we face a risk of bias since the diagnosis code for ACL reconstruction has not yet been validated in the DNRP and may therefore not be correctly registered. Though the DNRP is not a perfect gold standard, it is a well-accepted and an independent data source we can use to make comparisons, and it has been used previously to measure the completeness of registration of various national clinical databases.[137,165]

6.1.3 Confounding

A confounder is an independent variable and must be (1) an extraneous risk factor for the outcome of interest. Also, (2) it must be associated with the exposure of interest without being an effect of the exposure; viz., (3) it must not be a part of the causal pathway between exposure and outcome (Figure 6.1.1).[39]

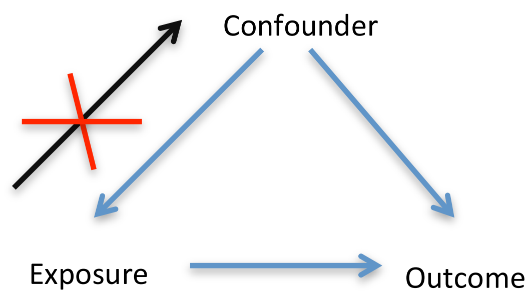


Figure 6.1.1: Confounding triangle

There are several ways to account for confounding. In this thesis, we used restriction, matching, and adjusting using multivariate analysis. In Study II, we restricted our study group to female patients and matched our cohort on age; and we used multivariate regression analysis to adjust for potential confounders. In Study III, we used multiple regression analysis to adjust for confounders. Although we adjusted for a number of potential confounding factors, our study may suffer from residual, unmeasured and unknown confounding, just like other observational studies. Residual confounding results from misclassification of confounders because of incomplete adjustment. Information on different confounders in our study was retrieved from national registries such as the DKRR and the DNRP that have a high precision, and this reduces the risk of residual confounding.[166] A risk of residual confounding may be present in Study II since the coding of obesity in the DNRP is considered to be incomplete as these information only rely on hospital contacts and thus, likely underestimates the true prevalence of obesity in the population.[167]

Unmeasured confounding arises when potential confounders are not available in the registries at hand. In our studies, candidates for confounders include patients' physical activity, smoking, or the quality of rehabilitation, which are not available in the DKRR or the other registers. Although few studies show no association between being an OC user and being an athlete or between the use of OC and the level of physical activity,[168-171] there is no clear evidence to determine if the use of OC differs between athletes and the general population. Hence, we cannot rule out that being an athlete is a potential, unmeasured confounder in Study II. We are unable to adjust for this confounder in our analysis.

Further, our endpoint evaluation in Study II is likelihood of operatively treated ACL injury and we consequently only study the ACL injured patients who are treated operatively. These constitute about half of the ACL-injured patients as the rest are treated conservatively. There may be a difference between patients who undergo surgery and patients who are treated conservatively given that surgeons may be more reluctant to operate non-athletes than athletes. Therefore, in Study II, our conclusions only apply to operatively treated ACL-injured patients.

6.2 Discussion and comparison with extant literature

6.2.1 Study I

6.2.1.1. Completeness of patient registration

The overall registration of ACL reconstruction procedures in the DKRR was good and has improved over time as the surgeons have become familiar with the task of making registration.

Sensitivity and specificity must generally be calculated to estimate the quality of the classification of hospital discharge and operative procedures. In accordance with Sorensen et al., completeness provides an estimate of the sensitivity, which we calculated in this study.[53] The comparison between registries (the DKRR and the DNRP) performed in this study does not give us the opportunity to measure specificity, but we assumed that the specificity was close to one since our background population is large and the ACL reconstruction procedure is rare.[53]

The completeness of other databases has been evaluated in previous studies.[45,51,137,172-174] Studies from the Norwegian Registry of Knee Ligament Reconstruction reported a very high completeness (86-99%) when the Norwegian National Patient Registry was used as a gold standard.[45,51,52] The higher completeness observed in the Norwegian study compared with our study may be explained by several factors. First, the Norwegian study used a different method for calculation of completeness. We defined the completeness as an estimate of the sensitivity (a/a+c) (Table 6.2.1) as recommended by Sorensen et al.[53] Hence, we calculated the number of cases registered in both registries (the DKRR and the DNRP) and divided this number by the number of cases registered in the DNRP within the same period.

Table 6.2.1: 2 X 2 table of the illustrating how completeness was measured.

		Gold Standard, i.e. the DNRP		
		+	-	Total
The database of interest, i.e., the DKRR	+	a	b	a+b
	-	c	d	c+d
	Total	a+c	b+d	

a: Operations registered in the DNRP and the DKRR; b: Operations registered in the DKRR, but not in the DNRP;
c: Operations registered in the DNRP, but not in the DKRR; d: Operations not registered in either the DNRP or the DKRR;
a+b = All operations registered in the DKRR; a+c = All operations registered in the DNRP; Sensitivity = a/a+c

The Norwegian study calculated completeness as the number of operations registered in the Norwegian Registry of Knee Ligament Reconstruction (a+b) divided by the number of cases registered in the Norwegian National Patient Registry (a+c). This will tend to overestimate the results. Our completeness changed from 78.5% to 87.8% when we calculated our completeness from 2005 to 2011 using the same method as that which was used in the Norwegian and other studies. The importance of using the correct formula is underlined by the study by Espehaug et al. in which they found a completeness above 100%, which is only possible when the measure is calculated as (a+b)/(a+c) and not as a measure of sensitivity.[174]

Some of the previous validity studies are based on a selected population, and this could also overestimate the results.[45,51,137] Our results are based on all hospitals in Denmark that perform ACL reconstructions. Some studies exclude patients who undergo surgery at private hospitals. In our study, such hospitals were mostly the small-volume hospitals with low registration completeness, and exclusion of private hospitals would therefore tend to overestimate the results.[137] Also, we calculated the completeness at the individual level, which may not be the case in previous studies, which did not enjoy access to a personal identification number.[172,174]

The differences in the design of these validation studies hampered their comparison. However, the above studies do indicate that there is an overall, high degree of completeness of registration in the Scandinavian registries, which makes them reliable for future research. Our review of the literature highlights the importance of reporting the completeness estimates, but also of a thorough description of the calculation methods used to be able to compare the results across countries.

In our study, registration completeness improved over time. This may be explained by the surgeons becoming more familiar with the registration task.[174,175] Although the authorities ask all surgeons to register surgery, no penalty is invoked by failure to register, and surgeons hence have to become familiar with the registration procedure over time to achieve the overall goal of registration completeness. The goal for completeness in the DKRR is defined as above 90%,[23] which has been reached by other registries in Scandinavia.[45,137] We stratified completeness according to small-volume versus large-volume hospitals and found that large-volume hospitals performed better than small-volume hospitals, which is in accordance with a recent study from the Norwegian Registry of Knee Ligament Reconstruction.[52] In the future, intensive feedback primarily from small-volume departments is necessary to improve completeness.

In the DKRR's annual report, it is noted that several hospitals actually do provide good registration results, but the total registration completeness may suffers due to poor registration at a few private and public hospitals.[138]

We regarded the DNRP as the gold standard in the study of completeness. However, we identified 1,537 procedures in the DKKR that had not been registered in the DNRP, which shows that the DNRP is not a perfect reference. About 79% of these 1,537 missing cases in the DNRP underwent surgery at private hospitals. Private hospitals get no financial reimbursement for registering data in various administrative and clinical databases when treating insurance patients and self-paying patients. Hence, there is no financial incentive to register these procedures in the DNRP, which may explain why so many operations had not been registered. In our study, the private hospitals are small-volume hospitals, which have been found to have low registration completeness.[52,138] Furthermore, the low registration rate in the DNRP may be due to misclassification because primary ACL procedures have been reported using other codes that trigger a higher compensation from the Danish State (i.e. revision ACL reconstructions). This would tend to underestimate our estimates and hence strengthen our association. We found that 85 of the 1,537 missing variables in the DNRP were registered with the code of revision ACL surgery and seven patients were registered with the diagnosis of PCL reconstruction.

6.2.1.2 Data quality of key variables

A high PPV for key variables was shown in Study I. The medical records were randomly picked by a computer, which minimises the risk of bias. In the DKRR, there was a high frequency of missing values concerning "cartilage damage" and "activities leading to ACL rupture". This has prompted an evaluation of the registration system, which found that the registration of cartilage damage was imprecise. The registration of cartilage lesions has therefore now been simplified, which will hopefully improve registration in the future. Also, the medical records showed a high percentage of missing data on the method used for femoral tunnel drilling (TT or AM). The femoral tunnel was previously almost only drilled transtibially.[166] When only one method is available, the surgeon probably does not feel that it is essential to record this action. Improvement in the registration completeness of the method of femoral tunnel drilling will therefore probably not be achieved until the surgeons become fully aware of the existence of other methods and are faced with a choice between relevant alternatives.

6.2.1.3 Data quality of patient-reported outcome measures

As expected, the registrations of subjective outcome scores were low. It was therefore important to evaluate whether there was any significant and clinically important difference between the responders and the non-responders with regard to their KOOS and Tegner scores at the one-year follow-up. No significant difference was noted in the mean estimates of the KOOS and the Tegner scores between responders and non-responders; but since fewer patients than expected answered the questionnaire, our power was lower than estimated and, therefore, a risk of type 2 error does exist, i.e. a risk of concluding that there is no difference between responders and non-responders although a difference may actually exist. Therefore, these results should be interpreted with caution and further improvement and validation of these scores are warranted.

In other Scandinavian countries, a higher response rate is seen, and future studies hence need to look further into the quality of registration of the KOOS and the Tegner scores in the DKRR. Presently, an evaluation on the response rate is being performed which will hopefully improve this registration in the future.

6.2.2 Study II

Study II is the first nationwide pharmaco-epidemiological study to evaluate the association between OC use and the likelihood of sustaining operatively treated ACL injury. The primary finding of this large population-based case-control study was that OC use was associated with a reduced likelihood of sustaining operatively treated ACL injury, with a slight trend towards a dose-dependent association. The decreased RR for sustaining operatively treated ACL injury was 11–19%.

The speculation that OC might have an effect on the ACL was introduced by *in vitro* studies in the 1990s. Liu et al. were the first to demonstrate that human ACL is an estrogen target tissue by identifying estrogen receptors in the ACL specimens from 13 women and four men.[62] In their study, the specimens were obtained from an older population (average age 57 years) and with varying degrees of pathology (tumours, osteoarthritis and ACL tears). This is a major limitation compared with the young ACL-injured group of patients in the present study. Supporting these findings, an i*n vitro* study showed a dose- and time-dependent association between 17β-estradiol and ACL cells, derived from a 32-year-old woman who underwent total knee arthroplasty. In this study, the authors observed a decrease in fibroblast proliferation with increasing 17β-estradiol and suggested that rhythmic variation in estrogen during the menstrual cycle might be associated with ACL fibroblast metabolism.[176] However, an *in vitro* study of 12 male ACL specimens and 14 female ACL specimens from ACL-reconstructed patients by Faryniarz et al. showed that there was no difference in the expression of estrogen receptors between men and women. On the basis of these findings, they concluded that estrogen alone may not play a role in gender differences in ACL injuries.[63] They did not, however, account for the higher serum estrogen level in women than in men, and their finding of an equal number of receptors therefore does not rule out that estrogen levels may influence the female ACL. The study by Faryniarz is supported by an immunohistochemical study by Seneviratne et al. from 2004.[76] In this study, the authors exposed cultured ovine ACL fibroblasts to physiological levels of estrogen and demonstrated no effect on collagen synthesis. They concluded that it is unlikely that a monthly 2-3-day increase in circulating estrogen can result in rapid, clinically significant alterations in the material properties of the ACL *in vivo*.

Supporting our results, an *in vitro* animal study indicated an association between estrogen levels and the mechanical properties of the ACL, as an increased failure load and an increased toughness of the ACL were observed in the estrogen-treated group.[64] Hence, the authors concluded that chronic exogenous steroid treatment in rats - dosed to mimic OC use in humans

- was associated with better mechanical properties in the OC-treated group than in the control group.

To date, only one clinical study has shown that women taking OCs have a lower rate of sports injuries than women not taking OCs.[82] In this prospective study, the authors followed 108 women soccer players from the first through the third Swedish football league for 12 months. The women answered a questionnaire on their menstrual-cycle history, contraceptives and menstrual disorders. All traumatic injuries in the study period were recorded. The authors found a lower rate of traumatic injuries, especially to the knee and ankle, in the group using OCs compared with the group not using OCs. Also supporting the protective association between OC and risk of ACL injury, a study by Martineau et al. showed a higher anterior knee laxity for non-users of OCs than for OC users. Hence, the authors concluded that OC yields a significant decrease in knee laxity.[59]

Some studies have questioned the hypothesis of a protective association between OCs and the risk of ACL injury,[60,77-79] but only a few of these studies have evaluated the association of OCs with the likelihood of sustaining ACL injury directly.[60,78] A case-control study by Ruedl et al. showed no difference in OC use between 93 ACL-injured and 93 non-ACL-injured female recreational skiers.[60] In this study, the external validity was low due to the restricted population of recreational skiers since it is reasonable to assume that recreational skiers may differ from OC users in the general population. Also, no information on recent user status or the duration of OC use was given; and due to the study design, there is a significant risk of information bias. In a large prospective study on OC use, Agel et al. showed no difference in non-contact ACL injuries between users and non-users of OCs.[78] In this study, no information on recent user, new user, or duration of OC use was given. These clinical results are supported by the findings from a recent animal study on 24 monkeys which were either sham-operated or ovariectomised. The authors of the animal study found no difference in the mechanical properties of the ACL in the two groups and therefore concluded that there is no direct association between estrogen and the mechanical and material properties of the ACL.[77]

The complex interplay among hormones and their relationship to ligamentous laxity and ACL injury remains unclear. As mentioned, several studies do show a relationship between the menstrual cycle and OC use and the risk of sustaining ACL injury/increased knee laxity. These are small studies with plenty of limitations. The risk of selection bias due to exclusion criteria is considerable. The risk of information and recall bias is also notable in these studies since some rely on questionnaires.[59,60,78] Furthermore, power analyses were lacking in several studies. The contradictive results, then, are probably due to small sample sizes, and the results could be due to chance. To sum up, previous studies give us no clear answer to the question as to whether there is any protective association between the use of OC and the likelihood of sustaining ACL injury or ACL reconstruction.

Although our study does suggest that an association exists between OC use and a reduced likelihood of sustaining operatively treated ACL injury, our results have to be considered as preliminary. We still need more clinical studies and RCTs to further clarify the biological and causal association between OC use and the likelihood of operatively treated ACL injury.

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6.2.3 Study III

In Study III, we examined the prognosis after ACL injury treated with reconstruction. This is the first nationwide register-based cohort study presenting the results of AM compared with TT femoral drill-hole placement after primary ACL reconstruction. Our study showed that the introduction of the AM technique for femoral tunnel drill hole placement in ACL reconstruction increased the risk of revision ACL reconstruction compared with the traditional TT technique. In addition, AM drill hole placement was associated with more instability in terms of the pivot-shift test and sagittal instability measures. However, we found no differences in KOOS, $KOOS_4$ or the Tegner score. This study emphasises the importance of national clinical databases because they allow us to evaluate the early associations of new treatments.

Our results are in accordance with a meta-analysis by E. Alentorn-Geli et al. that indirectly compared TT with AM portal technique in ACL reconstruction.[99] Studies with a minimum of one year of follow-up were included in this meta-analysis. They found a graft failure rate of 5.7% in the AM group compared with a failure rate of 2.3% in the TT group. However, all studies included were case series, and none of the studies were comparative.

Some studies have indicated that the AM technique outperforms the traditional TT technique in terms of rotational stability.[97,106,107,109,177,178] In a cross-sectional study of a cohort of 47 patients, Alentorn-Geli et al. used the KT1000 and the Lachman test and thereby demonstrated a better knee stability in the AM group than in the TT group.[178] Likewise, cadaveric studies have shown a better knee stability in the AM group than in the TT group using the Lachman and the pivot-shift tests.[97,111] This is in contrast to our study and a recent RCT (2013) of 64 patients which showed no difference in pivot-shift test scores two years after surgery.[114] Furthermore, other studies have shown no difference in knee joint KT1000 measures between the two methods.[110,111,113] Therefore, using objective measurements as outcome, there is no clear evidence of which method is superior.

Several studies of the outcome after ACL reconstruction have evaluated the results in terms of subjective PROMs.[6,108,112,114,129,179] We also evaluated PROM to see whether there was any correlation between this and the choice of technique for femoral drill hole placement. KOOS sub-scores were not significantly different between the two groups in the present cohort study. As in previous publications, $KOOS_4$ was used in our study to evaluate the outcome after ACL reconstruction, and no difference was seen between the two groups. Furthermore, we saw no difference in the Tegner score between the two groups. These observations were in accordance with the results of RCTs reported by Noh et al. and with a cross sectional study by Alentorn-Geli et al. which also found no difference in IKDC and Tegner scores between the TT and the AM groups.[114,178]

Several problems have been associated with the AM technique. In a cadaveric study, Bedi et al. showed a decrease in tunnel length and an increased tendency to compromise the posterior wall, and hence posterior tunnel blow-out, when using the AM technique compared with the TT technique.[93] Inferior exit of pins engaging the peroneal nerve, iatrogenic damage to the cartilage of the medial femoral condyle, and slipping of the aimer on hyperflexion have also been described as problems that must be overcome when the AM technique is being used.[180,181] On the other hand, studies have shown a greater coronal obliquity and less tunnel widening of the femoral tunnel with the AM technique.[90,93,182] Because there are several technical challenges to overcome when the AM technique is used, we propose that a learning curve is part of the explanation for our present findings. The population of ACL surgeons in Denmark is approximately 100, and our study period represents a transition during which nearly half of these surgeons learned the AM technique (Figure 5.3.1). Despite the fact that the transition to the AM technique is an attempt to adopt a more anatomical approach with regard to femoral tunnel placement, we have no data to demonstrate to which extent this was actually accomplished. One can speculate that some of the tunnel placements were poor due to technical problems related to poor visualisation.

Another factor that might explain the finding of a higher revision rate for the AM technique has been suggested by Xu et al., who showed that an anatomically reconstructed anterior-medial bundle is exposed to a significantly higher *in situ* force than a non-anatomical, high placement of the anterior-medial bundle. Hence, a greater load is carried by an anatomically reconstructed graft, which makes it more vulnerable than the non-anatomically placed graft, which, on the other hand, transfers more load to other structures in the knee.[183] This may also be part of the explanation as to why our study shows a greater revision rate in the AM group than in the TT group.

Whether revision rates improve as surgeons gain routine with AM portal techniques needs to be determined in future national registry studies, and an on-going monitoring of the results achieved with the AM approach is therefore necessary and exemplifies the importance of a national registry.

7. Conclusions

7.1 Study I

In conclusion, the validation study showed an acceptable completeness of the registration of the ACL reconstructions in the DKKR, especially within the past three years. Future efforts to improve registration completeness from small-volume hospitals are needed. Also, we found a high PPV for all explored key variables in the DKRR. Although, the KOOS and the Tegner scores at the one-year follow-up were comparable for responders and non-responders the results must be interpreted with caution, since a risk of type 2 error might be introduced due to smaller sample size that a priory estimated. Further improvement in response rate and validation of these scores are warranted.

7.2 Study II

Study II – a national population-based pharmaco-epidemiological study including 13,355 women – indicates an association between OC use and a reduced likelihood of sustaining operatively treated ACL injury. Though, our results have to be considered as preliminary and hence, we still need more clinical studies and RCTs to further clarify the biological and causal association between OC use and the likelihood of operatively treated ACL injury.

7.3 Study III

Study III demonstrated an increased risk of revision ACL reconstruction when the AM technique was used for femoral drill hole placement compared with the TT technique in the crude data as well as in the stratified and adjusted data. We propose that the increased revision rate may be caused by technical failures due to the introduction of a new and more complex procedure.

This study emphasises the importance of clinical databases because they facilitate early evaluation of new treatments.

8. Perspectives

The studies presented in this thesis have improved our knowledge of the likelihood of sustaining operatively treated ACL injury and the impact of using different surgical techniques during ACL reconstruction. They have also demonstrated that the DKRR enjoys an acceptable completeness of registration and a good registration of key variables – although validation on objective measures, the KOOS and the Tegnser scores, needs further improvement and validation in the future. Hopefully, our studies will provide a motivation for additional studies to elucidate further the questions raised in this thesis which, in turn, may improve our knowledge of ACL injury and ACL reconstructions and lead to a better short- and long-term outcome for this group of young patients.

The possible implication of this thesis for patients, researchers, physicians and healthcare planers is primarily that we now have a valuable validated tool for future research that will allow us to evaluate important associations between exposures of interest and outcomes after primary ACL reconstruction. Still, it must be acknowledged that future improvement and validation of the objective and subjective measures are warranted. In addition, the thorough evaluation of the database has triggered changes in the database structure that will further optimise the basis for future research. The study on the use of OC indicates an association between the use of OC and the likelihood of sustaining operatively treated ACL injury, which should be further evaluated in experimental trials. Additionally, the present thesis has increased our knowledge of ACL reconstruction techniques. The results reported on the femoral tunnel drilling technique have triggered international discussions on the potential challenges and implications of initiating a new surgical technique. Also, as a result of our findings, it is being discussed whether action needs to be taken to improve the prognosis for the individual patient after primary ACL reconstruction. Furthermore, our studies have proven that the DKRR can reveal early associations of new treatments.

Study II exemplified that the value of the DKRR may prove to be even greater than previously anticipated owing to the possibility of individual linkage to other important databases such as the NDPD and the DNRP. This linkage gives us valuable information that can be used to investigate the implications of drug use and comorbidity. In future studies, linkage could be extended to include biochemical and microbiological databases which will pave the way for an even broader application of the DKRR in future research. Thus, data linkage may enable us to (1) investigate the association between medication and prognosis after ACL reconstruction, (2) evaluate the comorbidity of ACL-reconstructed patients, (3) study various predictors in ACL reconstruction surgery, and (4) evaluate the association of different exposures with the risk of infections and other clinical outcomes using the NDRP and biochemical databases.

Nevertheless, our study exposed some of the weaknesses of Danish national clinical databases such as the DKRR. One of the main weaknesses is the lack of clinical data and missing data, and the low response rate on one-year follow-up data, which is a major limitation to this study. Presently, an evaluation of the response rate is being conducted and, hopefully, this will help us improve the data collected in the DKRR in future.

Furthermore, we lack data on covariates such as BMI, smoking and alcoholic consumption and physical activity. In future, this information may be made available through a population-based national database of the general population's state of health established under the "Hvordan har du det?"-study (How are you?) or through the National Danish Anaesthetic Database. In addition, it is important to continue to emphasise the importance of the DKRR to the patients and clinicians in order to achieve a better registration rate and to reduce the risk of missing data and hence bias.

This thesis supports future research in the DKRR, although better registration of objective and subjective data is needed. The DKRR already has a number of strong features, but it is important for future research that the DKRR is continuously developed and updated for an even higher data quality.

9. Summary

The burden of ACL injuries and their short- and long-term consequences and hence later development of osteoarthritis is a significant personal and socioeconomic problem in the today's healthcare system. Therefore, understanding the impact of different risk factors on sustaining ACL injury and the prognostic impact of different surgical techniques on the outcome after ACL reconstruction is critical to achieving an improved clinical outcome for the ACL-injured patient.

The primary approach in the literature is to investigate such research questions through RCTs. Well-designed RCTs are time-consuming and usually very costly, and this challenges their feasibility. The use of two different surgical techniques for femoral tunnel drilling during ACL reconstruction has been a much debated research question over the past decade. Nevertheless, no RCTs or clinical studies have been conducted that direct compare these two methods in an effort to determine the risk of undergoing revision ACL reconstruction, which may be due to the limited feasibility of performing an RCT investigating this question. Comparative studies using existing data from clinical databases therefore represent a welcome alternative to RCTs because these databases are readily available, provide access to large-scale data and therefore allow us to study rare outcomes. The DKRR, on which this PhD thesis is based, is such a database.

In order to do reliable research on clinical databases, these databases need to be validated. In Study I, we aimed to validate the data of the DKRR. We validated the operation code of ACL reconstruction and the key variables registered in the DKRR. The validity study established an acceptable completeness of registration of the operation code and a high PPV of key variables.

In Study II, a case-control study, we investigated a possible association between the use of OC and the likelihood of sustaining operatively treated ACL injury. This association has been asserted for many years, but previous studies are few and based on small cohorts with a low external reproducibility and a high risk of bias. We demonstrated a protective association between OC use and the likelihood of sustaining operatively treated ACL injury. This observed association may be owed to the pharmacological effects of OCs, but we cannot rule out that unmeasured confounding may have influenced our results.

In Study III, we investigated the prognosis after ACL injury and evaluated the association between the use of the AM and the TT technique for femoral tunnel drilling during primary ACL reconstruction in a cohort study. We demonstrated a higher revision rate and reduced knee stability in the AM group compared with the TT group. Hence, this new AM method is associated with a poorer clinical outcome than the traditional TT method. This result illustrates

the importance of database studies to evaluate any early associations of new treatments and hence improve the outcome for the individual patient.

In conclusion, the studies in this thesis have demonstrated that observational studies on ACL-reconstructed patients can be conducted properly using clinical databases such as the DKRR. Furthermore, our study also exposed some of the weaknesses of Danish national clinical databases, such as the DKRR, including a lack of clinical data and missing data, which have to be taken into consideration when doing research on clinical databases.

This thesis may help us establish valid associations between exposure to various factors and the outcome, thereby allowing us to better understand the factors determining the likelihood of operatively treated ACL injury and the clinical implications of ACL reconstruction. The study may thus be beneficial to the ACL-injured patient in both the short and the long term by reducing the risk of meniscal and cartilage damage and later development of osteoarthritis.

10. Danish summary

En bedre forståelse af forhold, der har betydning for korsbåndsskader og korsbåndsoperationer er vigtig. Da korsbåndsskader primært rammer yngre mennesker mellem 15 og 30 år, har et godt behandlingsresultat ikke blot store individuelle, men også samfundsmæssige langtidskonsekvenser. Den primære tilgang til sådanne forskningsspørgsmål i litteraturen er at foretage randomiserede kliniske studier. For at lave et godt randomiseret forsøg kræves et stort patient-materiale, og denne type forsøg er derfor ofte meget bekostelige og tidskrævende, hvilket i sidste ende kan umuliggøre opsætning af forsøgene. Et eksempel på dette er sammenligning mellem to metoder ved placering af femurkanalen under korsbåndsoperationer. Dette har været et forskningsspørgsmål, man har debateret gennem de seneste 10-år, men på trods af dette foreligger der stadig ingen randomiserede forsøg, der undersøger risikoen for revisionsoperationer som endepunkt. Det kan i sådanne tilfælde være en fordel at lave studier baseret på eksisterende data i form af databasestudier, som har den store fordel, at data er tilgængelige og at patientmaterialet er stort, hvorfor det er muligt også at lave studier på sjældne eksponeringer og udfald.

Dette ph.d.-projekt har belyst patient- samt operationsrelaterede forhold, som har betydning for udviklingen af operationskrævende korsbåndsskader og resultaterne efter korsbånds-operation, hvilket potentielt kan forbedre behandlingen af en stigende gruppe af yngre patienter.

Valideringsstudiet har vist en overordnet god registreringsgrad af korsbåndsoperationer i korsbåndsregistret (DKRR) og en udmærket registrering af variabler i DKRR. Valideringsstudiet har derved styrket DKRR som en fremtidig forskningsressource. Yderligere validerede vi patienternes subjektive scorer, hvilket ikke viste nogen forskel mellem respondenterne og ikke-respondenterne. Dette resultat kræver dog yderligere forbedring og validering pga. en meget lav svarprocent.

Hormonstudiet bidrager med vigtig viden omkring risikoen for operativt behandlede korsbåndsskader hos kvinder. Dette emne har kun tidligere været undersøgt i små studier med høj risiko for bias. Vi viste en forebyggende sammenhæng mellem brugen af p-piller og risikoen for korsbåndsskader. Dette kan være forårsaget af den farmakologiske effekt af p-pillerne, men vi kan ikke udelukke ikke-målbar confounding.

I studie III viste vi, at anvendelse af en ny operationsmetode til placering af femurkanalen er forbundet med en højere revisionsrate end en gammel, traditionel operationsmetode. Studiet illustrerer vigtigheden af databasestudier og den hermed forbundne mulighed for at undersøge sjældne outcome, da det ikke tidligere har været muligt at belyse dette spørgsmål gennem eksperimentelle studier.

Samlet har de studier, der indgår i denne afhandling vist, at observationelle studier baseret på eksisterende registermateriale kan bidrage med ny viden om risikoen for korsbåndsskader og prognosen efter operation til gavn for den enkelte patient samt desuden have samfundsøkonomiske fordele. Derudover har koblingen til andre databaser gjort det muligt at se effekten af forskellige medikamenter og disses betydning for outcome. Databasestudier kræver dog, at der tages stilling til fejlkilder som bias og confounding, og at disse behandles og diskuteres korrekt.

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PAPER I

Clinical Epidemiology

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ORIGINAL RESEARCH

Validation of 14,500 operated knees registered in the Danish Knee Ligament Reconstruction Register: registration completeness and validity of key variables

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Introduction: The aim of this study was to validate the registration in the Danish Knee Ligament Reconstruction Register (DKRR) by assessing the registration completeness of the anterior cruciate ligament (ACL) reconstruction code and detecting the validity of important key variables. Furthermore, we assessed data quality of patient-related outcome scores.

Material and methods: All operation codes for ACL reconstruction from 2005–2011 were identified in the Danish National Registry of Patients and were compared with the cases registered in the DKRR to compute the completeness of registration. We also assessed the validity of key variables in the DKRR using medical records as a reference standard to compute the positive predictive value. Finally, we assessed potential differences between responders and nonresponders to subjective patient-related outcome scores (Knee Injury and Osteoarthritis Outcome Score [KOOS] and Tegner scores) 1 year after surgery.

Results: The completeness of the registration of patients in the DKRR increased from 60% (2005) to 86% (2011). Large-volume hospitals had a higher completeness than small-volume hospitals. With a positive predictive value between 85%–100%, the validity of key variables was good. KOOS scores versus Tegner scores for responders and nonresponders were comparable.

Conclusion: The results show a good registration of ACL reconstruction procedures in the DKRR, but there is room for improvement mainly at small-volume hospitals. Overall, the validity of the key variables in the DKRR was good and no difference was found in KOOS and Tegner scores for responders versus nonresponders. Therefore, we conclude that the DKRR is a valid source for future research.

Keywords: ACL, anterior cruciate ligament registry, predictive value

Introduction

Anterior cruciate ligament (ACL) injury is a common and serious injury seen in the young and active population. It is important to evaluate which operation method ensures the optimal result for the individual patient. The surgeon and the patient are faced with the difficult task of deciding in favor of either conservative rehabilitation or surgery to achieve the best outcome and, if the choice falls on surgery, which kind of surgery is best for the patient. In a recent descriptive epidemiological study, Nordenvall et al[1] described the incidence of 78 ACL injuries per 100,000 inhabitants in Sweden. A total of 38% of these patients underwent ACL reconstruction. On the basis of this Swedish ACL registry, they found that patients who underwent surgery were younger than

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those who were offered initial rehabilitation.[1] The study by Nordenvall et al[1] shows the importance of reporting baseline epidemiological data to facilitate validation and assessment of the generalizability of the results from registers and clinical studies.

Detailed knowledge on ACL lesions and treatment modalities is of critical importance for the study of postreconstruction graft survival and its long-term clinical outcome. Clinical studies on the basis of primary data collection have been performed to evaluate the outcome after ACL reconstruction. However, these studies are often small and are based on single-center data because data collection is time-consuming and costly, and their design is often open to recall and selection bias.[2,3] Large, population-based studies are therefore desirable.

Recent years have seen advances in information technology that have facilitated access to large clinical databases. This gives clinicians the possibility to assess disease outcomes on a large scale. Clinical databases are an attractive source for epidemiological research for many reasons: they are readily available, they contain large amounts of data that otherwise could not be obtained, they carry little risk of bias, and they afford low-cost data access.[4,5] In addition, use of clinical databases for research fosters timely and early dissemination of information on specific clinical issues. The Danish Knee Ligament Reconstruction Register (DKRR) is one such population-based database, which has been monitoring the quality and developments in ACL reconstructions since 2005.[6]

It is of crucial importance to evaluate the registration completeness and to validate the data quality of key variables in the database to be able to draw valid and reliable conclusions. Furthermore, continuous improvement of the validity and reliability of data is important to the future use of national registries for clinical and research purposes.[5] In Denmark, national clinical registries for joint replacement have existed for several decades; they have been validated and are deemed highly reliable.[7] However, the validity of the DKRR data is not known.

Therefore, the objective of our study was to validate the data in the DKRR. Specifically, we aimed to (1) assess the registration completeness of the ACL reconstruction; (2) validate the data quality of key variables in the DKRR; and (3) validate the quality of patient-related outcome scores by tracing differences between responders and nonresponders, and differences in the Knee Injury and Osteoarthritis Outcome Scores (KOOS) and Tegner scores registered for these groups.

Methods and materials

Data sources

We conducted a validation study of the population-based national DKRR. Denmark has a population of 5.5 million people with free health care to all citizens. Patients with acute medical conditions are treated by specialists at public hospitals. Private hospitals are also accessible in Denmark, and they also have reimbursement agreements with the Danish state, as well as private insurance patients and self-paying patients. Danish citizens are registered in various administrative and medical registers with a unique personal security number. Because this personal identification number is consistently used in all Danish registries, it is possible to obtain precise individual-level data through data linkage among the Danish registries.

The Danish Knee Ligament Reconstruction Register (DKRR)

The DKRR is a nationwide clinical database that was established on July 1, 2005. The purpose of this registry was to improve the monitoring and quality of both primary and revision knee ligament surgery in Denmark.[6] According to Declaration number 459 of June 15, 2006, registration is compulsory, and all public (n = 24) and private (n = 27) hospitals report to this registry.[8] Using a standardized form and a secured internet portal, detailed preoperative, intraoperative, and 1-year follow-up data are recorded by the operating surgeon.[6] Furthermore, the patients report outcome scores on the functioning of their knee using the following self-assessment scores: the KOOS and the Tegner functional score.[9,10] These data are recorded online by the patient before surgery and 1 year after surgery.

The KOOS range from 0–100 with higher scores representing better results. KOOS is a patient-reported outcome measure used in the evaluation of knee function.[9] The KOOS was developed for younger, physically active patients with knee injuries and osteoarthritis and has proven to be a very responsive instrument. The KOOS consists of five subscores: sports, pain, quality of life, activities of daily living, and symptoms. The five subscores should be evaluated separately.

The Tegner scores range from 1–10, with higher scores representing better results. The Tegner score represents specific activities. Hence, a patient participating in competitive sports at the elite level is considered to have a Tegner score of 10, and an individual with sports activities at a recreational level is considered to have a Tegner score of 6. Patients on sick leave or those who are receiving a disability pension because of knee problems are considered to have a Tegner activity score of 0.[11]

Danish National Registry of Patients

The Danish National Registry of Patients (DNRP) includes data on 99.4% of all discharges from Danish nonpsychiatric hospitals since 1977, and outpatient visits since 1995.[12] Data in the DNRP include each individual's personal security number, admission and discharge date, discharge diagnosis, operations, and so on.[13] In Denmark, hospital discharge codes are registered by the International Classification of Diseases 10th Revision of 1994,[14] and operation codes are registered according to the Nordic Medico-Statistical Committee (NOMESCO), which was established in 1966.[15] These discharge and operation codes are recorded by the physicians, and without these registrations there will be no financial reimbursement from the Danish state to the hospitals.

In this study, we used the DNRP to identify patients with ACL reconstruction using the following NOMESCO codes: NGE45 (NGE45B, NGE45C, NGE45D, NGE45E): "Primary arthroscopic plastic repair of ACL of knee not using prosthetic material;"[15] and NGE55C: "Primary arthroscopic plastic repair of ACL of knee using prosthetic material."[15]

Medical records

For the validation of the key variables, we aimed to review medical records from a random sample of approximately 5% of all primary ACL reconstruction surgeries registered in the DKRR from January 1, 2008, until December 31, 2009 (n = 240). A computer-generated random sample was obtained from six different hospitals, both private and public, throughout Denmark. A 5% random sample was chosen to ensure a reasonable statistical precision of the estimated positive predictive values (PPVs), relying on the sample size used in the validation studies of registry data previously published in a similar area of research.[16] The medical records were systematically reviewed, and information was retrieved on these variables:

- Cartilage injury
- Meniscal injury treatment
- Activity leading to ACL rupture
- Diagnosis registered as ACL rupture
- Choice of graft
- Choice of femoral tunnel placement (anteromedial or transtibial technique)
- Number of femoral tunnels
- Date of operation
- Choice of technique for femoral and tibial fixation.

The medical record review was performed by a single independent researcher (LR-W), who was not involved in the treatment and who used a standardized form and the EpiData (EpiData Association, Odense, Denmark) program.

EpiData is a free data entry and data documentation program accessable on the Internet (http://www.epidata.dk). This program facilitates secure data entry owing to its different features of error detection. To optimize security in data entry in this study, preinstalled "checks" were made in the EpiData, which made it impossible to enter invalid numbers not previously defined by the reviewer. Furthermore, data entry and review were done twice.

Study population

Completeness of patient registration

In the first analysis, all operation codes for primary ACL reconstructions performed between July 1, 2005, and December 31, 2011 were identified in the DNRP and DKRR. The registration in the DNRP and DKRR was compared to compute the registration completeness of the ACL reconstruction surgeries in the DKRR.

We identified 14,943 primary ACL procedures in 14,721 patients from the DKRR. In a likewise fashion, we identified 17,276 primary ACL procedures in 16,734 patients from the DNRP. We performed matching between the DKRR and DNRP at the individual level using the unique personal security numbers. Records of which knee had been operated on were not available in 33% of the ACL reconstructions registered in the DNRP. Therefore, we decided to include only the first operation for all patients in the registry. This method implied exclusion of 222 operated knees from the DKRR and 542 operated knees from the DNRP. For 221 knees, the year of operation registered was not the same in the DNRP and DKRR. These knees were therefore excluded. This left us with 14,500 operated knees registered in the DKRR and 16,513 operated knees registered in the DNRP.

In accordance with Ytterstad et al,[17] large-volume hospitals were defined as hospitals performing more than 30 operations a year and small-volume hospitals as hospitals performing 30 or less operations per year.

Completeness was stratified on age because previous studies have shown that the risk for revision surgery seems to be higher in the young-age group than in the older-age group.[8,18]

Data quality of key variables

In the second analysis, we validated the data quality of key variables including cartilage damage, meniscal treatment, activity leading to ACL rupture, diagnosis registered as ACL rupture, choice of graft, choice of femoral tunnel placement (anteromedial or transtibial technique), number of femoral tunnels, date of operation, and choice of femoral and tibial fixation.

We randomly selected 240 patients registered in the DKRR with primary ACL reconstruction surgery from January 1, 2008 until December 31, 2009. This period was chosen to obtain an interval in which the database had been running for a certain amount of time so that the surgeons could familiarize themselves with the registration task.

Data quality of patient-related outcome scores

In the third analysis, we assessed the data quality of the recorded patient-related outcome scores (KOOS and Tegner scores). We performed the assessment by comparing the patients who gave their subjective scores 1 year after the operation (responders) with the patients who did not give their subjective scores 1 year after the operation (nonresponders). The aim was to evaluate if there were any differences in registered patient-related outcome data in the DKRR between the two groups.

We therefore conducted a study in which new KOOS and Tegner questionnaires were sent to 100 responders and to 100 nonresponders. To achieve 95% statistical power and a 5% probability that the null hypothesis is false, we made power calculations and randomly selected 100 patients for each group. The questionnaires were sent out in the spring of 2010 (ie, approximately 2 years after the primary ACL reconstruction surgery had been performed). After 2 months, the reminder was sent to the nonresponders. Sixty-two (62%) of the responders and 39 (39%) of the nonresponders answered this questionnaire, and an estimate of their mean scores was calculated.

Statistical analysis

Completeness of patient registration

The DNRP was used as a reference standard to calculate the registration completeness of the ACL reconstructions in the DKRR. Data from the DNRP and DKRR was merged on an individual level. The registration completeness was defined as the number of patients registered in both the DKRR and DNRP with ACL reconstruction, divided by the number of patients registered in the DNRP with ACL reconstruction in the same period. Analyses were stratified according to age, sex, and hospital volume to evaluate for any association between these variables and the completeness of the data registration.

Data quality of key variables

To validate data quality of selected key variables, we assessed the PPV using medical records as a reference standard. For each of the selected registered variables, we defined the PPV as the number of patients with a given variable registered in both the DKRR and medical records, divided by the total number of patients with a given variable registered in the DKRR.

Data quality of patient-related outcome scores

The percentage of registered KOOS and Tegner scores was calculated as the number of registered KOOS and Tegner scores divided by the total number of operations registered in the DKRR preoperatively and postoperatively. To evaluate if there was any difference in subjective scores (KOOS and Tegner scores) between the responders and nonresponders in the 1-year postoperative evaluation questionnaire, we calculated the mean score for each group; we tested data differences using Student's *t*-test.

For all estimates, a 95% confidence interval (CI) was calculated. We analyzed data using STATA version 12 (StataCorp LP, College Station, TX, USA). EpiData was used for data entry.

This study was approved by The National Board of Health and The Danish Data Protection Agency, journal number 2011-41-6320.

Results

In total, 18,050 patients were identified in the DKRR and DNRP from July 2005 to December 2011. A total of 12,963 patients (71.8%) were registered in both registries; 3550 (19.7%) were only registered in the DNRP, and 1537 (8.5%) were only registered in the DKRR. Patient demographics for these three groups are shown in Table 1.

Completeness of patient registration

The overall registration completeness of the ACL reconstruction in the DKRR was 78.5% (95% CI: 77.9%–79.1%) from

Table 1 Patient characteristics

Patient characteristics	Type of register		
	Both DNRP and DKRR, n (%) n = 12,963	**DNRP only, n (%) n = 3550**	**DKRR only, n (%) n = 1537**
Sex			
Male	7783 (60.0)	2208 (62.2)	937 (61.0)
Female	5180 (40.0)	1342 (37.8)	600 (39.0)
Mean age at surgery	29.7 (95% CI: 29.5–29.9)	31.0 (95% CI: 30.6–31.3)	31.9 (95% CI: 31.4–32.5)
Age at surgery (years)			
≤20	3449 (26.6)	773 (21.8)	299 (19.5)
>20	9514 (73.4)	2777 (78.2)	1238 (80.5)

Abbreviations: DNRP, Danish National Registry of Patients; DKRR, Danish Knee Ligament Reconstruction Register; n, number; CI, confidence interval.

2005–2011 (Table 2). The completeness increased from 60.3% (95% CI: 57.4%–63.1%) in 2005 to 86.3% (95% CI: 84.9%–87.7%) in 2011 (Figure 1).

There was no difference in completeness when data were stratified according to patient sex and age. However, a considerable difference was seen when data were stratified according to hospital volume: large-volume hospitals (81.6% [95% CI: 80.9%–82.2%]) had a higher degree of registration completeness than small-volume hospitals (64.5% [95% CI: 62.3–66.5]) (Table 2).

Accuracy of key variables

In general, the data quality of the key variables was good. The PPV ranged from 85%–100% (Table 3). The PPV was 96% for the use of transtibial placement of the femoral canal, 100% for "choice of graft," 85% for "cartilage damage," and 96% for "treatment of meniscal damage."

Data quality of patient-related outcome scores

Subjective outcome scores for both KOOS and Tegner were available for 4799 (33.1%) of 14,500 patients preoperatively; 1 year after surgery, these outcome scores were available for 3852 (26.6%) of 14,500 patients. No difference was found in either the five KOOS subscores or in the Tegner scores between responders and nonresponders in the 1-year postoperative questionnaire (Table 4).

Patient characteristics in the DKRR are outlined in Table 5. Nonresponders to the 1-year questionnaire were younger than the responders, and there were more males than females in the nonresponders. The amount of meniscal and cartilage lesions was comparable in the two groups. A small difference in graft choice was seen, yet more than 80% of patients underwent reconstruction with a hamstring graft in both groups. The percentage of revisions was low in both groups, but there were more revisions among responders (Table 5).

Discussion

Completeness of patient registration

The overall registration of ACL reconstruction procedures in the DKRR was good and has improved over time, as the surgeons have become familiar with the registration procedure. Sensitivity and specificity must generally be calculated to estimate the quality of the classification of hospital discharge and operative procedures. In accordance with Sorensen et al,[4] completeness is an estimate of the sensitivity, which we calculated in this study. The comparison between registries (the DKRR and DNRP) performed in this study does not give us the opportunity to measure specificity, but we assume that the specificity is close to one because our background population is large and the ACL reconstruction procedure is rare.[4]

The completeness of other databases has been evaluated in previous studies.[7,16,22] A study from the Norwegian

Table 2 Completeness of registration of ACL reconstruction surgery in the DKRR compared with the DNRP

	Type of register			Total (n)	Degree of completeness % (95% CI)
	Both DNRP and DKRR n (%)	DNRP only n (%)	DKRR only n (%)		
2005–2011	12,963 (71.8)	3550 (19.7)	1537 (8.5)	18,050	78.5 (77.9–79.1)
≤20 years	3449 (76.3)	773 (17.0)	299 (6.6)	4521	81.8 (80.6–82.9)
>20 years	9514 (70.3)	2777 (20.5)	1238 (9.2)	13,529	77.4 (76.7–78.1)
Male	7783 (71.3)	2208 (20.2)	937 (8.6)	10,928	77.9 (77.1–78.7)
Female	5180 (72.7)	1342 (18.8)	600 (8.5)	7122	79.4 (78.4–80.4)
Small volume[a]	1317 (56.0)	726 (30.8)	311 (13.2)	2354	64.5 (62.3–66.5)
Large volume[a]	11,646 (75.1)	2628 (17.0)	1226 (7.9)	15,500	81.6 (80.9–82.2)
2005	690 (52.2)	455 (34.5)	176 (13.3)	1321	60.3 (57.4–63.1)
2006	1870 (65.6)	758 (26.6)	224 (7.8)	2852	71.2 (69.4–72.9)
2007	1828 (67.5)	660 (24.4)	219 (8.1)	2707	73.5 (71.7–75.2)
2008	1737 (70.7)	480 (19.9)	231 (9.4)	2458	78.0 (76.2–79.7)
2009	2335 (77.3)	407 (13.5)	278 (9.2)	3020	85.2 (83.8–86.5)
2010	2323 (77.6)	433 (14.5)	238 (7.9)	2994	84.3 (82.9–85.7)
2011	2180 (80.8)	347 (12.9)	171 (6.3)	2698	86.3 (84.9–87.7)

Notes: Results were stratified according to patient sex, age, and small-volume versus large-volume hospitals. [a]196 ACL-reconstructed knees that could not be placed in either the small-volume or the large-volume group because of imprecise definition in the DNRP.

Abbreviations: ACL, anterior cruciate ligament; DKRR, Danish Knee Reconstruction Register; DNRP, Danish National Registry of Patients; n, number; CI, confidence interval.

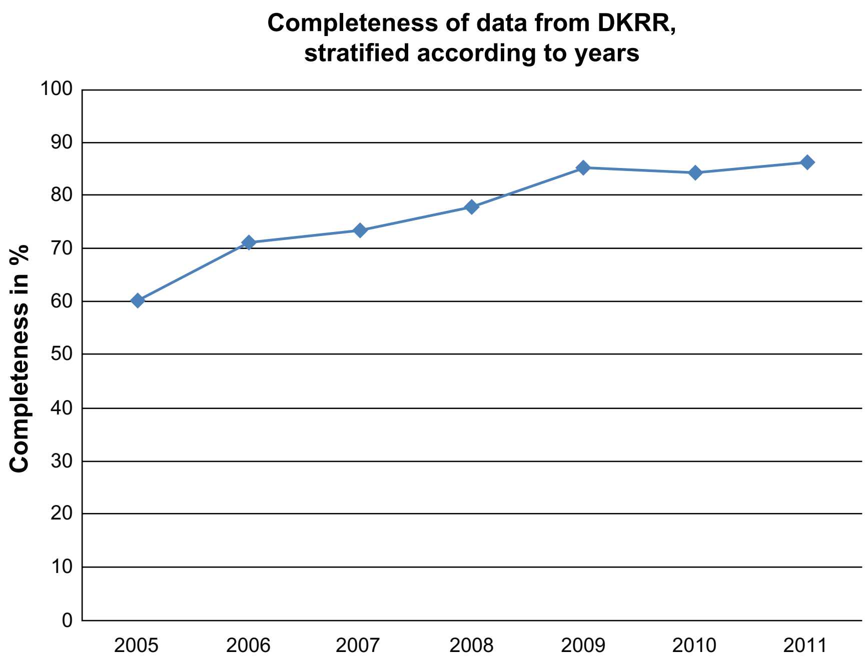

Figure 1 Development of data completeness in the DKRR.
Abbreviation: DKRR, Danish Knee Ligament Reconstruction Register.

Table 3 Validity of key variables registered in DKRR

	DKRR database	Medical record		Missing medical record	PPV% (95% CI)
		Yes	No		
Cartilage lesion	Yes	29	5	0	29/34 = 85 (69–95)
	No	27	127	12	
	Missing DKRR	13	26	1	
Treated meniscal lesions[a]	Yes	103	4	0	103/107 = 96 (90–99)
	No	26	107	0	
Sport as activity reason for the ACL rupture	Yes	172	29	1	172/201 = 86 (80–90)
	No	4	33	0	
	Missing DKRR	0	1	0	
Diagnosis of ACL lesion	Yes	240	0		240/240 = 100
	No	0	0		
Hamstring as graft choice[b]	Yes	208	0	2	208/208 = 100
	No	0	24	0	
	Missing DKRR	4	1	1	
Transtibial placement of femoral canal	Yes	136	6	60	136/142 = 96 (91–98)
	No	3	18	16	
	Missing DKRR	1	0	0	
One femoral canal (versus two)	Yes	237	0	2	237/237 = 100
	No	0	0	0	
	Missing DKRR	1	0	0	
OP date	Identical	238	0	1	238/239 = 99 (93–100)
	Not identical	0	1		
Method for fixation of graft in femur	Identical	217		7	217/233 = 93 (89–96)[c]
Method for fixation of graft in tibia	Identical	220		6	220/234 = 94 (90–97)[c]

Notes: Medical records were used as a reference standard, and 240 medical records were used. "Identical" indicates that the registration in the DKRR is identical to the registration in the medical records. [a]The registration of this variable in DKRR is to choose a treatment of the meniscal lesion. Hence, if no registration is made in this variable it can be etiher: no treatment or a missing value; [b]comparing if hamstring or bone–patellar tendon–bone graft is used. Other graft choices were deleted because they account for less than 2%; [c]About 20 different modes of fixation are possible in this variable. Therefore, calculation of completeness was made by inputing the number of variables registered identical in the DKRR and in the medical records into the numerator, and dividing them by all the cases registered in the denominator.
Abbreviations: DKRR, Danish Knee Ligament Reconstruction Register; PPV, positive predictive value; CI, confidence interval; ACL, anterior cruciate ligament; OP, operation.

Table 4 Results from questionnaires on KOOS and Tegner scores

Previously answered subjective measures	N	Pain mean (SD)	Symptom mean (SD)	Activity of daily living mean (SD)	Sport mean (SD)	Qol mean (SD)	Tegner mean (SD)
Yes (responders)	62	83.1 (15.0)	60.4 (13.8)	88.0 (15.7)	64.5 (26.9)	64.5 (25.4)	4.87 (2.0)
No (nonresponders)	39	78.5 (19.2)	59.8 (12.1)	83.7 (19.7)	56.9 (26.8)	59.3 (24.5)	4.56 (1.9)
P-value		0.09	0.38	0.12	0.97	0.82	0.72

Notes: Mean value of the different subjective scores in the group of patients who previously recorded subjective scores (responders) compared with the group of patients who did not previously record subjective scores (nonresponders).
Abbreviations: KOOS, Knee Injury and Osteoarthritis Outcome Score; N, number; SD, standard deviation; Qol, quality of life.

Registry of Knee Ligament Reconstruction reported a very high completeness (86%) when using hospital protocols as a reference standard and 84% when using the Norwegian National Patient Registry as a reference standard.[19] The higher completeness in the Norwegian study versus our study may be explained by several factors. First, the Norwegian study used another method for calculation of completeness. We defined completeness as a measure of the sensitivity, calculated as the number of cases registered in both registries (DKRR and DNRP) divided by the number of cases registered in the DNRP within the same period. The Norwegian study calculated completeness as the number of operations registered in the Norwegian National Knee Ligament Registry divided by the number of cases registered in the hospital protocols (or in the Norwegian National Patient Registry). Our completeness changed from 78.5% to 87.8% when we calculated our completeness from 2005–2011 using the same method as that used in the Norwegian study. Second, the Norwegian estimates were based on a selected population because the authors in the Norwegian study only used ten of 46 hospitals reporting to the registry. Our results are based on all hospitals in Denmark performing ACL reconstructions. Pedersen et al[7] showed a very good completeness of 94% of hip arthroplasty registration from 1995–2000 in the Danish Hip Arthroplasty Register. Again, this study differs from our study because they excluded patients operated on at private hospitals, which were mostly the small-volume hospitals with low registration completeness in our study. Likewise, the Norwegian Arthroplasty Register showed a high completeness of 98% for hip replacements, and 109% for hip revision surgery.[20] Again, the Norwegian Arthroplasty Register's calculation of completeness is different from ours. Also, we calculated the completeness at an individual level (because of the unique personal security number), which may not be the case in previous studies on completeness.[20] This trend may also explain some of the differences in results.

Table 5 Patient characteristics from the Danish Knee Reconstruction Registry with (responders) or without (nonresponders) subjective scores registered 1 year postoperatively

Patient characteristics	Subjective scores registered 1 year after operation	
	Yes, n (%)	No, n (%)
Sex		
Male	2240 (58.1)	6704 (62.9)
Mean age at time of surgery (years)	30.5 (95% CI: 30.1–30.8)	29.7 (95% CI: 29.5–29.9)
Age at time of surgery (years)		
≤20	965 (25.1)	2928 (27.5)
ACL revision		
Yes	144 (3.7)	255 (2.4)
Meniscal treatment		
Yes	1444 (37.5)	4227 (39.6)
Cartilage damage		
Yes	713 (18.5)	2369 (22.2)
Prior knee surgery		
Yes	1086 (28.2)	2935 (27.6)
Sport activity leading to tear		
Yes	3328 (86.4)	8761 (82.2)
Graft choice (hamstring)		
Yes	2974 (77.2)	8767 (82.3)

Abbreviations: n, number; ACL, anterior cruciate ligament; CI, confidence interval.

The differences in the design of these validation studies hamper their comparison. However, the abovementioned studies do indicate an overall high degree of registration in the Scandinavian registries, which makes them reliable for future research. Our review of the literature highlights the importance of reporting the completeness estimates and a thorough description of the calculation methods to be able to compare the results across countries.

In our study, registration completeness improved with time. This may be explained by the surgeons becoming more familiar with the registration task.[20,21] Although a declaration was issued by the authorities requiring all surgeons to register surgical procedures performed, no penalty is invoked by failure to register. Hence, the surgeon must become familiar with the registration procedure over time to achieve the overall goal of registration completeness. The goal for completeness in the DKRR is defined as more than 90%,[8] which has been reached by other registries in Scandinavia.[7,22] We stratified completeness according to small-volume versus large-volume hospitals and found that large-volume hospitals performed better than small-volume hospitals, which is in accordance with a recent study from the Norwegian National Knee Ligament Registry.[17] In the future, intensive feedback – primarily to small-volume departments – is necessary to improve completeness.

We regarded the DNRP as the reference standard in the study of completeness. However, we identified 1537 procedures in the DKRR that had not been registered in the DNRP, which shows that the DNRP is not a perfect reference. Approximately 79% of these 1537 missing patients in the DNRP underwent knee surgery at private hospitals. Private hospitals receive no financial reimbursement when treating insurance patients and self-paying patients. Hence, there is no financial incentive to register these procedures in the DNRP, which may explain why so many surgical procedures had not been registered.

Data quality of key variables

A high PPV (85%–100%) for key variables was shown in this study. In the DKRR, many data on "cartilage lesions" and "different sports activities leading to ACL rupture" were missing. This discovery has prompted an evaluation of the registration system, which found that registration of cartilage damage was imprecise. Therefore, registration of cartilage lesions has now been simplified, which will most likely improve registration of this variable.

The medical records showed a high percentage of missing data on the method used for femoral tunnel drilling (transtibial or anteromedial). The femoral tunnel was previously almost always drilled transtibially,[23] and, because the method is customarily used, surgeons may have deselected registration of this method for femoral tunnel drilling in the medical records. When only one method is available, the surgeon probably does not believe that it is essential to record this action. Therefore, improvement in registration completeness of the method of femoral tunnel drilling probably will not be achieved until the surgeons become fully accustomed to the existence of other methods and are faced with a choice between relevant alternatives.

Data quality of patient-related outcome scores

As expected, registration of subjective outcome scores was low, which has also been shown in other studies.[23,24] Therefore, it was important to evaluate if there was any significant and clinically important difference between the responders and the nonresponders in their subjective scores at the 1-year follow-up. No significant difference was noted in the mean estimates of the KOOS and Tegner scores between responders and nonresponders. However, these estimates are imprecise because of a low number of participants. Furthermore, these estimates tell us nothing about the difference between the second-time responders and "never-responders." Although the percentage of revision was low in both groups, there were fewer revisions among responders. The time at risk was not taken into account. We did not include survival analysis to compare the cumulative revision rates in this study because we found that it was out of the scope of our present study.

Study strengths and weaknesses

Our study was based on data from a national clinical registry; therefore, it had several strengths and weaknesses. That the DKRR and DNRP are large national databases is an obvious strength from a data quality perspective. Also, owing to the unrestricted and free access to health care in Denmark, the DKRR provides an unselected study population. Furthermore, the DKRR has the potential for extensive linkage to other important databases at the level of the individual, owing to the unique personal security numbers given to all Danish citizens. This linkage affords the possibility of individual measurements. Moreover, these nationwide population-based databases provide an excellent data source at low cost and with little risk of bias. Another strength of our validation study was the thorough evaluation of medical records, which allowed for validation of key variables in the DKRR and made the DKRR a valid tool for future research. Furthermore, the medical records were randomly picked by a computer program. The risk of information bias was low because previously designed forms were made in EpiData, and data entry was made twice. In addition, the reviewer of the medical records was blinded to the results in the DKRR and, hence, did not know the optimal result.

Through the years, the DNRP has been considered a valuable source of high-quality data information.[25] However, no validation of the ACL reconstruction code has been undertaken. Thus, a limitation in our study was the deviation in the quality of the data retrieved from the DNRP. Medical records are a valuable data source when validation studies are conducted.[5] Yet, they are not a perfect source of information, because it is up to the operating surgeon to decide which information he or she wishes to enter into the medical record. Some information is not considered to be of importance for the specific physician, and some variables will therefore be missing in the medical records. Although a number of missing variables were found in some of the key variables in our study, the high values of the PPV ensure satisfactory data quality.

As to the evaluation of responders versus nonresponders to the questionnaire at 1 year after surgery, we know nothing about the "never-responders," and the numbers of observations are low in this substudy compared with the entire study cohort.

Conclusion

In conclusion, this validation study showed good completeness of registration of the ACL reconstructions in the DKRR. We found a high PPV for most key variables in the DKRR. Thus, the DKRR is a valid and substantial resource for future epidemiological studies. However, a future effort to improve registration completeness from small-volume clinical departments is needed.

The KOOS and Tegner scores at the 1-year follow-up were comparable for responders and nonresponders. We therefore conclude that the DKRR data are a valid source for future clinical and epidemiological research.

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Disclosure

The authors report no conflicts of interest in this work.

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PAPER II

Title: *Is the use of oral contraceptives associated with operatively treated anterior cruciate ligament injury? A case-control study from the Danish Registry of Knee Ligament Reconstruction*

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Running title: Oral contraceptive use and risk of ACL injury

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Abstract

Background: The incidence of anterior cruciate ligament (ACL) injuries is 2-9 times higher in women than in men. Additionally, in vitro studies have demonstrated that ACL is an estrogen target tissue, and some studies have therefore suggested a protective association between oral contraceptives (OC) and the likelihood of sustaining ACL injury.

Hypothesis: We hypothesis a protective association between OC use and the likelihood of operatively treated ACL injury.

Study design: This was a population-based case-control study using data from Danish medical databases.

Methods: The study population included 4,497 female cases with an operatively treated ACL injury registered in the Danish Registry of Knee Ligament Reconstruction for the 2005-2011 period and 8,858 age-matched controls with no ACL injury.

The study evaluated exposure to OC use at the time of ACL injury (index date) and in the five previous years (ever user) or no OC use (never user). Ever users were further classified as either new users (patients who redeemed their first prescription within the first year before the index date), long-term users (redeemed additional prescriptions one to five years before the index date) or recent users (redeemed their most recent prescription more than one year before the index-date). Finally, a dose-response analysis of OC use was performed.

We used conditional logistic regression to calculate the relative risk (RR) with a 95% confidence interval (CI) of sustaining operatively treated ACL injury according to OC use.

Results: The adjusted RR associating OC with ACL injury was 0.82 (95% CI: 0.75 to 0.90) between ever users and never users. Furthermore, we found a decreased relative risk (RR) of sustaining operatively treated ACL injury of 0.80 (95% CI: 0.74 to 0.91) in long-term users and 0.81 (95% CI: 0.72 to 0.89) in recent users. Additionally, we found a trend towards a dose-response association. Using OC for more than four years did not seem to alter the likelihood of sustaining operatively treated ACL injury.

Conclusion: This population-based pharmaco-epidemiological study including 13,355 women indicates an association between OC use and a reduced likelihood of sustaining operatively treated ACL injury. No prior study has evaluated the association between OC and the likelihood of operatively treated ACL injury in a nationwide population-based setting, and only few clinical studies exist on this subject. Although our study does, indeed, indicate a protective association of OC use, OC should not be used as a prophylactic measure before additional clinical studies have further clarified the biological and causal association between OC use and the likelihood of sustaining operatively treated ACL injury.

Key Terms: Oral contraceptives, anterior cruciate ligament, ACL, injury

What is already known on this subject

In vitro studies have demonstrated that ACL is an estrogen target tissue and have indicated a possible association between OC and the likelihood of sustaining ACL injury. We found only two small clinical studies exploring the association between the use of OC and the likelihood of ACL injury, and they showed no association. Both studies are small and prone to information bias. On the other hand, one clinical study has shown a protective association between OC use and sport injuries and another study found an association between OC use and knee laxity, which could be a proxy for ACL injury.

What this study adds

- This study, which included a total of 13,355 women, indicates that there is a protective association between OC and the likelihood of sustaining operatively treated ACL injury.

- Compared with never users, the association was strongest for long-term users users of OC in whom a 20% reduction in the relative risk of sustaining operatively treated ACL injury was recorded.

Introduction

The incidence of anterior cruciate ligament (ACL) injury is reported to be 2-9 times higher in women than in men.[21, 24, 38, 41] The causes explaining the increased female incidence of ACL injuries are multifactorial and may include: a difference in femoral notch size, neuromuscular differences, valgus of the knee, differences in knee laxity and differences in core stability.[21,12, 20, 50] Additionally, hormonal effects have been proposed as an aetiological factor explaining the difference in the incidence of ACL injury.[1]

The menstrual cycle is controlled by the pituitary gland and results in a monthly hormone fluctuation of estrogen, luteinising hormone and progesterone.[3] Oral contraceptives (OC), which are used by 45-89% of women in Western countries at some point of their life, stabilise the hormone level during the menstrual cycle, preventing estrogen surge.[35, 51]

Results from basic science studies have shown that estrogen receptors are present on the human ACL and that the synthesis of collagen is reduced in the presence of an increased level of estrogen.[27] The conclusion is therefore that estrogen has an effect on tendon matrix composition. Others have found that the fluctuation in the serum estrogen level can lead to alterations in the ACL fibroblast metabolism, which may, in turn, result in structural and compositional changes of the ACL and hence contribute to an increased vulnerability of the female ACL.[28,19] Also, results indicate that women in the pre-ovulatory phase have a higher incidence of ACL injury and a greater knee laxity than in other phases of the menstrual cycle.[1, 7, 13, 25, 50, 55, 56] These findings suggest that cyclic hormonal changes may be one explanation for the increased female risk of ACL injury.[13, 28, 44] Furthermore, the findings indicate that the menstrual cycle and OC use may affect the ACL. Some of the studies are marred by information bias – such as recall bias – since the information collected relies on questionnaires on the menstrual cycle and OC use. They also introduce generalizability problems as some are based on a selected study population.[7, 13, 56]

To date we have found one clinical study suggesting a protective association between OC and the risk of sustaining sports injuries. The authors prospectively studied 108 female soccer players from the first through the third Swedish football league and followed them for 12 months. They found a lower rate of traumatic injuries, especially to the knee and ankle, in the group using OC compared with the group not using OC.[33]

However, in a case-control study including 93 cases and 93 controls, Ruedl et al. showed no difference in the incidence of OC use between ACL-injured and non-ACL-injured female recreational skiers.[46]

Any confirmed association between the use of OC and the likelihood of sustaining ACL injury in this young population could have a major clinical and public health impact as well as socioeconomic consequences. Therefore, we conducted the large nationwide population-based case-control study presented herein to evaluate the association between OC use and the likelihood of sustaining operatively treated ACL injury in a cohort of patients from a national patient registry. Specifically, the objective was to test the hypothesis of a protective association between OC use and the likelihood of sustaining operatively treated ACL injury.

Methods

Study setting

We conducted this study in the Danish population of females. The National Health Service provides tax-financed health care to all Danish residents, allowing free access to hospital care at medical, surgical and psychiatric departments as well as general practitioner visits. Danish citizens are registered in different administrative and medical registries, and all Danish citizens are registered with a unique personal identification number, which makes it possible to link data from various registries.

Data sources

The Danish Knee Ligament Reconstruction Register (DKRR)

The DKRR, a nationwide population-based clinical quality database, is described in details elsewhere.[42, 43]

The Danish Civil Registration System (CRS)

The CRS provides all Danish citizens with a unique ten-digit personal identification number at their date of birth. The CRS records information on changes in the vital status of all Danish citizens including changes in address, date of emigration and date of death since 1968.[40] Precise individual-level linkage between public Danish registers is possible owing to the personal identification number. In this study, the CRS was used to link various databases and to ensure complete follow-up on all patients.

The Danish National Registry of Patients (DNRP)

The DNRP holds data on 99.4%[37] of all discharges from Danish non-psychiatric hospitals since 1977 and outpatient visits since 1995.[5] Data in the DNRP include the personal identification number, admission and discharge dates, discharge diagnoses and operations, etc.[30] In Denmark, hospital discharge codes are registered in accordance with the International Classification of

Diseases, 10th revision (ICD-10) of 1994, and operation codes are registered according to the Nordic Medical Statistic Committee (NOMESCO), which was established in 1966.[58, 36] The attending physicians record these discharge and operation codes, and financial reimbursement from the Danish state to the hospitals is dependent on this registration. In this study, the DNRP was used to establish the medical history prior to the index date and to identify two controls for each case.

The Danish Prescription Registry

The Danish Prescription Registry contains records from 1994 onwards on date of redemption, type of drug, quantity dispensed, strength and other data.[23] Each time a prescription is redeemed at a pharmacy, a record of the patient's personal identification number, the date, and the type and quantity of the drug prescribed is recorded in the prescription database. The Danish Prescription Registry is reimbursement-driven and keeps records using automated bar-code data entry and hence provides data of a high quality and facilitates linkage with many other nationwide individual-level databases. In this study, the Danish Prescription Registry was used to identify the OC use in a five-year period leading up to the index date.

The integrated Database for Labour Market Research (IDA)

The database was established in 1980 and contains data on employment and income among other social conditions. The IDA is described in details elsewhere[60]

Study-population

ACL-reconstructed cases

We used the DKRR to identify all incident ACL-reconstructed women in Denmark from 1 July 2005 to 31 December 2011, i.e. the case population. This definition of ACL injury was chosen to facilitate identification of a cohort of patients with a high likelihood of having a validated injury to the ACL.[42] The date of ACL injury was considered the index date. Since only the month and year of injury was registered in the DKRR, the 15th of every month was chosen as the day of injury for all cases. In total, we identified 5,431 primary ACL-reconstructed women in 5,391 female patients. A total of 81 patients were excluded from the analysis due to use of middle- and high-dose OC. This was done to make the participants comparable. We included only the first operation if more than one ACL reconstruction had been performed in a patient. Hence, we excluded 40 knees because an operation had been performed on the contralateral knee. Since Danish Prescription Registry data were only available as from 1994, we excluded all patients (n=264) with an index day before year 2000 to ensure a reasonable follow-up time. Also, 549 patients were excluded due to incorrect or missing registration of the date of injury (n=218), and incorrect registration of redeemed OC (n=331), defined as more than 66 moths of redeemed prescriptions over a five-year period (Figure 1). This left us with 4,497 primary ACL procedures, which we included as cases in our analysis.

Population controls

We used the CRS to identify and match two female controls to each case registered in the DKRR. The cases and controls were matched by age on the year of ACL reconstruction of the case group. The controls were assigned index data identical to their cases. Controls were sampled using risk-set sampling; i.e., only individuals who were alive and had no prior history of ACL injury registered in the DNRP (i.e. not registered with one of the following ICD-10 diagnose-codes: DM236, DS835, DS835A-F) were eligible for selection.[39] Controls were excluded if they were using high- or middle-dose OC. Whenever a case was excluded due to the above criteria, the whole strata was excluded. Hence, each time a case was excluded, the two matched controls were also excluded to ensure that matching remained intact. In total, we included 8,858 for analysis. For 136 of the cases included in our analysis, it was possible to match only one control.

Exposures

Oral contraception use

OC contains estrogen and progesterone, and product refinement has decreased the daily dose of estrogen to les than 35 μg of estrogen in low-dose OC. Middle- and high-dose OC are classified as those containing between 35 and 50 μg of estrogen and more than 50 μg, respectively.

We used the Danish Prescription Registry to prospectively identify all OC prescriptions redeemed by the cases and controls before the index date. Next, we linked the data from the DKRR and the DNRP with information on redeemed prescriptions from the Danish Prescription Registry. OC exposure was identified using the Anatomical Therapeutic Chemical Classification code (ATC-codes) G03AA and G03AB. We only included low-dose OC. High- and middle-dose OC are no longer recommended due to their side effects and hence, rarely used and they were therefore excluded in order to make the populations comparable. We categorized exposure according to the number of prescriptions redeemed by each individual in the five years leading up to the index date, one redeemed prescription corresponding to three months of OC use. We identified the reference group ("never users") as individuals who had redeemed no OC prescriptions in the entire study period. "Ever users" were those who had redeemed one or more OC prescription during the whole study period. We further sub-divided "ever users" into two strata.

In the first stratum, we defined "current users" of OC as patients who redeemed their most recent prescription within one year of the index date. In order to evaluate whether the use of OC had any long-term association with ligament laxity, we further sub-categorised two groups of current users as described in other studies[48]: "new users" were defined as those who had redeemed their first prescription within the first year before the index date, and "long-term users" were defined as those who had redeemed additional prescriptions one to five years before the index date. We defined those who redeemed their most recent prescription more than one year before the index-date as "recent users".

In order to be able to investigate a potential cumulative association of OC use, in the second strata we further sub-classified ever OC users into groups with one, two, three, four and more than four years of OC use in the entire study period.

Patient characteristics and covariates

We included a number of covariates in the analysis because of their potential association with the exposure and the outcome of interest. Data on the potentially confounding factors were obtained from several registries including the CRS (age and immigration), the DNRP (obesity and pregnancy/birth), the National Danish Prescription Registry (medication use), and IDA (information on gross income). Relevant confounders were identified a priori using prior literature and by evaluating our data.[2, 4, 6, 9, 15, 26, 11, 17] In order to capture patients who may be physically inactive, we used obesity as a proxy for physical inactivity. We identified patients with obesity (ICD-10: E65.8 and E66) in the five years leading up to the index date (yes versus no) and used it as confounder in our analysis. Since non-steroidal anti-inflammatory drugs (NSAIDs) may be used more in physically active people, we chose to include this as a confounder to our analysis. NSAID drug use (ATC-code: M01A) was recorded if two prescriptions or more had been redeemed in the five years leading up to the index date. Since immigration status and gross income could be associated with using OC and attending pivoting sports and hence with a risk of sustaining ACL injury, we also included these two variables in our final model. Information on gross income was an average of the three years before the index date. To address other means of hormonal changes in the female, pregnancy and birth was also used as a confounder in our analysis. We identified pregnancy and giving birth (ICD-10: DO00-DO99) within five years prior to index date (yes versus no).

Statistics

We used conditional logistic regression to compute the crude and adjusted odds ratio with 95% confidence intervals (CI) assorting OC use and the likelihood of operatively treated ACL injury. Given the risk set sampling design and the fact that operatively treated ACL injury is a rare outcome, the odds ratio can be interpreted as a relative risk (RR).[39] We fitted the model controlling for the relevant confounders listed in Table 1. We used multiple imputation to examine the potential influence of missing values, which generated 20 imputed datasets. RRs were calculated as the average RRs of the 20 datasets, corrected for between- and within-imputation variation.[45, 52] The imputation models included all of the available measured covariates listed in Table 1 and were used as the adjusted measures. We used Wald's test to test for trend of significance in the dose-dependent analysis.

We conducted a sensitivity analysis to examine the potential influence of missing values by comparing results on RR estimates with and without multiple imputations and using the multiple imputation results in our final estimates. Furthermore, we conducted a sensitivity analysis to examine the potential of any compliance problems. This was done by performing an analysis that defined never users as those redeeming one or less than one prescription during the entire study period and ever user as those with two or more redemptions during the study period. This was deemed necessary since redeeming only one prescription may indicate that other means of anti-conception have been initiated, and, hence, if only one prescription was redeemed, it may not have been used.

Finally, two sensitivity analyses were made defining new users as those who had redeemed their first prescription within the first three or six months before the index date, and long-term users as those who had redeemed additional prescriptions from three or six months to five years before the index date. In this sensitivity analysis, we defined people who redeemed their most recent prescription more than three or six months before the index date as recent users. This analysis was performed to evaluate if the cases and controls were actually on an OC at the time of their injury or not.

We used Walds test to test for trend of significance in the dose-dependent analysis.

The study was approved by the Danish Data Protection Agency. Matching was performed using SAS, and all other statistical analyses were computed using Stata, version 12 (Stata release 12, College Station, Texas, USA).

Results

Patient characteristics

Descriptive data are presented in Table 1 for the whole study population counting 4,497 cases and 8,858 controls. On the index date, the median age of the cases was 24.0 years (interquartile range (IQR): 17.1 to 37.9 years), the majority being between 16 and 20 years of age. NSAID use was more common in the case group than in the control group, and cases also had a higher gross income than controls. Obesity, pregnancy and immigrant status were more common among controls.

Likelihood of operatively treated ACL injury

To identify ACL-injured patients, we used the DKRR to find all incident ACL-reconstructed patients as a proxy for ACL injury. In the case group, 2,047 (45.5%) used OC at some point over a five-year period compared with 4,218 (47.5%) in the control group. Compared with never users, ever users of OC had a lower likelihood of sustaining operatively treated ACL injury: adjusted RR = 0.82 (95% CI: 0.75 to 0.90). Long-term and recent OC users also had a lower likelihood of operatively treated ACL injury as seen in the adjusted RR of 0.80 (95% CI: 0.74 to 0.91) and 0.81 (95% CI: 0.72 to 0.89), respectively. No association between new users and likelihood of operatively treated ACL injury was found (Table 2). There was a trend towards a dose-response association, with a RR of 0.83 (95% CI: 0.74 to 0.94), 0.78 (95% CI: 0.68 to 0.90) and 0.75 (95% CI: 0.64 to 0.90) of sustaining an operatively treated ACL injury if using OC for 1, 2 and 3 years within a five-year period, respectively. Using OC for more than four years did not seem to alter the likelihood of sustaining operatively treated ACL injury, RR = 0.88 (95% CI: 0.77 to 1.01) (Table 3). Wald's test on the trend of duration of OC use showed a significant level ($p < 0.00$).

The results of the sensitivity analysis did not change when the other definition of OC use was employed; nor when three or six months were used as the cut-off for the new user group or when never users were defined as those redeeming one or less than one prescription during the entire study period and ever users as those with two or more redemptions during the study period. Similarly, the sensitivity analysis on multiple imputations did not alter the result.

Discussion

This is the first nationwide pharmaco-epidemiological study to evaluate the association between OC use and the likelihood of sustaining operatively treated ACL injury. The primary finding of this large population-based case-control study was that OC use was associated with a reduced likelihood of sustaining operatively treated ACL injury, with a slight trend towards a dose-dependent association. The decrease in the RR for sustaining operatively treated ACL injury was 11-19%.

Previous to this study, OC had been associated with a protective effect and a decreased risk of ovarian, endometrial and colorectal carcinoma.[16, 34 34] The speculation that OC might have an effect on the ACL was introduced by in vitro studies in the 1990s. Liu et al. were the first to demonstrate that the human ACL is an estrogen target tissue by identifying estrogen receptors in the ACL specimens from 13 women and four men.[27] In their study, the specimens were obtained from an older population (average age 57 years) with varying degrees of pathology (tumors, osteoarthritis and ACL tears). This is a major limitation compared to the young ACL-injured group of patients. Supporting these findings, an in vitro study has shown a dose- and time-dependent association between 17β-estradiol and ACL cells derived from a 32-year-old woman who underwent total knee arthroplasty. In this study, the authors observed a decrease in fibroblast proliferation with increasing 17β-estradiol and suggested that rhythmic variation in estrogen during the menstrual cycle might have an effect on the ACL fibroblast metabolism.[59] However, in an in vitro study of 12 male ACL specimens and 14 female ACL specimens from ACL-reconstructed patients, Faryniarz et al. showed that there was no difference in the expression of estrogen receptors between men and women. On the basis of these findings, they concluded that estrogen alone may not play a role in gender differences in ACL injuries.[14] They did not account for the higher serum estrogen level in women than in men, and their finding of an equal number of receptors therefore does not rule out that estrogen levels may influence the female ACL. The study by Faryniarz is supported by an immunohistochemical study by Seneviratne et al. from 2004.[49] In this study, the authors exposed cultured ovine ACL fibroblasts to physiological levels of estrogen and demonstrated no effect on collagen synthesis. They concluded that it is unlikely that a monthly 2-3-day increase in circulating estrogen can result in rapid, clinically significant alterations in the material properties of the ACL in vivo.

Supporting our results, an in vitro animal study indicated an association between estrogen levels and the mechanical properties of the ACL as an increased failure load and an increased toughness of the ACL were observed in the estrogen-treated group.[57] Hence, they concluded that chronic exogenous steroid treatment in rats - dosed to mimic OC use in humans - was associated with better mechanical properties in the OC-treated group than in the control group.

To date, only one clinical study has shown that women taking OC have a lower rate of sports injuries than women not taking OC..[32, 33] In a prospective study, the authors followed 108 women soccer players from the first through the third Swedish football league for 12 months. The women answered a questionnaire on their menstrual-cycle history, use of contraceptives and menstrual disorders. All traumatic injuries in the study period were recorded. The authors found a lower rate of traumatic injuries, especially to the knee and ankle, in the group using OC than in the group not using OC. Also supporting the protective effect of OC, a study by Martineau et al. showed a higher anterior knee laxity for non-users of OC than for users.[31] Hence, the authors concluded that OC yields a significant decrease in knee laxity.

Some studies have questioned the hypothesis of a protective association between OC and ACL injury,[3, 29, 46, 54] but only a few of these studies have evaluated the association of OC with the risk of sustaining ACL injury directly.[3, 46] A case-control study by Ruedl et al. showed no difference in OC use between 93 ACL-injured and 93 non-ACL-injured female recreational skiers.[46] In this study, the external validity was low due to the restricted population of recreational skiers, since it is reasonable to believe that recreational skiers may differ from OC users in the general population. Also, no information on recent user status or the duration of OC use was given; and due to the study design, there is a significant risk of information and selection bias. In a prospective study on OC use, Agel et al. showed no difference in non-contact injuries between users and non-users of OC. In this study, no information on recent user, new user or duration of OC use was given. The findings from a recent animal study on 24 monkeys, which were either sham-operated or ovariectomised, support these clinical results. The authors of this animal study found no difference in the mechanical properties of the ACL in the two groups and therefore concluded that there is no direct effect of estrogen on the mechanical and material properties of the ACL.[54] The complex interplay among hormones and their relationship to ligamentous laxity and ACL injury remains unclear. As mentioned, several studies do show a relationship between the menstrual cycle and OC use and the risk of sustaining ACL injury/increased knee laxity. These are small studies with plenty of limitations. The risk of selection bias due to exclusion criteria is considerable. The risk of information and recall bias is also notable in these studies since some rely on questionnaires. Furthermore, in several studies power analyses were not done. The contradictive results, then, are probably due to small sample sizes, and the results could be due to chance. Hence, previous studies give us no clear answer to the question if there is any protective association between the use of OC and the likelihood of sustaining operatively treated ACL injury. Although our study does suggest that an association exists between OC use and the likelihood of sustaining operatively treated ACL injury, our results have to be considered preliminary. We still need more clinical studies and RCTs to further clarify the biological and causal association between OC use and the likelihood of operatively treated ACL injury.

Strengths and limitations

Several issues should be considered when interpreting our results. Our study is based on data from a national clinical registry and it therefore has several strengths and limitations. The fact that the DKRR is a large national database is an obvious strength from a data quality perspective. Also, owing to the unrestricted and free access to healthcare in Denmark, the DKRR provides an unselected study population. Furthermore, the DKRR has the potential for extensive linkage to other important databases at the level of the individual owing to the unique personal identification number given to all Danish citizens. This linkage affords the possibility of individual measurements. Moreover, these nationwide population-based databases provide an excellent data source at low cost and with little risk of bias. Additionally, the population-based design in the context of a tax-supported health-care system principally removes the risk of selection bias although matching the cases and control the year of operation does introduce a minor risk of selection bias. Data from the prescription database regarding redeemed prescription enjoy a high validity and are virtually complete.[23] Also, in Denmark it is not possible to redeem OCs without a prescription, thus it is unlikely that “never users” have obtained and taken OCs, and this is a clear strength. However, redeemed prescriptions do not provide definitive information on compliance. Thus, we might have categorised some women as recent OC users who are actually never users because they did not take their OC. Furthermore, differences in compliance between exposure groups could introduce information bias. Since patients not taking the redeemed prescriptions are independent of the outcome (having operatively treated ACL injury), this misclassification is non-differential and it will hence produce bias towards the null, thereby supporting the association found in this study. Additionally, our sensitivity analysis using the other definition for OC use did not alter the results, which also reduces the risk of compliance problems.

Although we found only a trend towards a dose-dependent association, this result does strengthen the validity of our results not being due to chance.

Furthermore, since NSAIDs are available over the counter, some authors have questioned the information on NSAID use from databases such as the NDPD.[53] It is generally accepted to use NSAID prescriptions to measure associations of NSAIDs since regular users of NSAIDs have an economic incentive to obtain the drugs by prescription due to the reimbursement provided by the Danish State.[22, 48] A recent Danish study has quantified the proportion of total sales made on prescription and concluded that the potential for identification of individual-level use of NSAIDs from prescription registries in Denmark is high.[47] Therefore, we assess that the risk of information bias due to NSAID use is low.

Also, data based on national clinical registries encounters several potential limitations. One problem is the data-completeness. We chose to sample cases from DKRR opposed to using the DNRP. This was done since the diagnose code of ACL injury in the DNRP has not been validated. Also, the ACL diagnosis in the DKRR has been validated and revealed a positive predictive value of 100% having ACL injury in the ACL reconstructed patients. Hence, using the DKRR to identify cases we were thereby able to truly identify patients who actually sustain ACL injury.[42] Nevertheless, using the DKRR to identify ACL reconstruction as the outcome in this study is looking at only one definition of ACL injury. Some patients are not willing to undergo surgery, accepting instead a reduction in their activity level and chronic knee instability. In other cases, surgeons do not find that patients are suitable for surgery and, finally, elite athletes may be more susceptible to ACL reconstruction than other patients. Our case population therefore is only ACL injury patients treated operatively and hence, our findings may differ from those of patients with ACL injury who have not undergone surgery and this could introduce bias. Thus, we may only draw conclusion on ACL injured patients treated operatively.

In our multivariate analysis, we included important confounders. Although we adjusted for a number of potential confounding factors, our study – like all observational studies – may suffer from unmeasured and residual confounding. For example, data on sports activity level, smoking habits, alcohol consumption were not available in the DKRR, the DNRP or through Denmark Statistics.

A risk of residual confounding may be present in this study since the coding of obesity in the DNRP is considered to be incomplete as these information only rely on hospital contacts and thus, likely underestimates the true prevalence of obesity in the population.

One of the potentially important unmeasured life-style confounders in this study is if our subjects were athletes or not. Although few studies show no association between being an OC user and being an athlete or between the use of OC and the extent of physical activity,[8-10, 18] there is no clear evidence to determine if use of OC differs between athletes and the general population. Hence, we cannot rule out "being an athlete" as a potential unmeasured confounder in our study.

Conclusion

This national population-based pharmaco-epidemiological study including 13,355 women shows an association between use of OC and a reduced likelihood of operatively treated ACL injury. Though, our results have to be considered as preliminary and hence, we still need more clinical studies and RCTs to further clarify the biological and causal association between OC use and the likelihood of operatively treated ACL injury.

Tables and figures

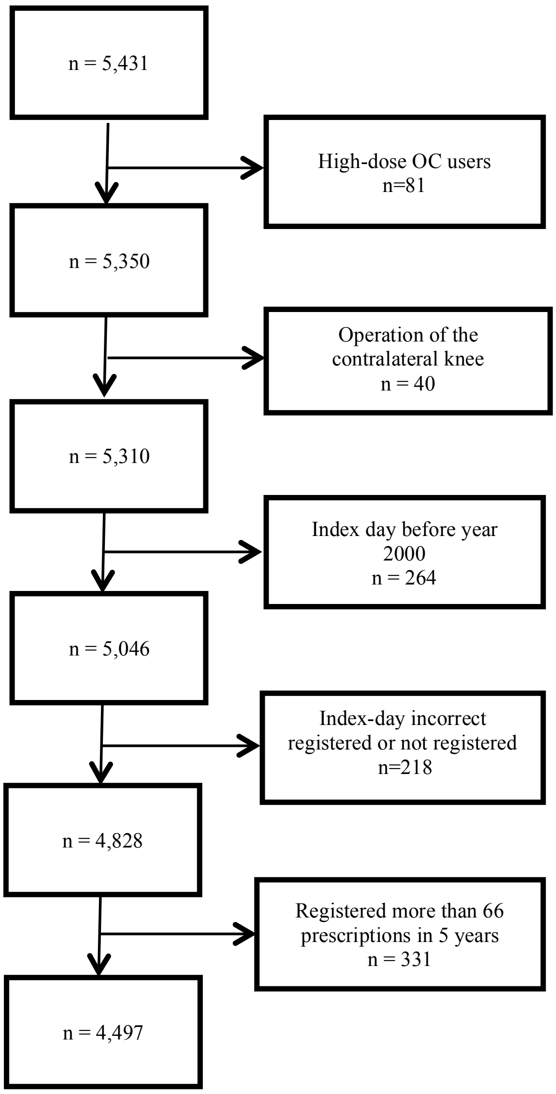

Figure 1: Flow chart showing patients (cases) included in this study. Inclusion criteria were women registered in the DKRR with an ACL reconstruction (n = 5,431) and two age matched controls. This figure shows the exclusion criteria. When excluding a cases using the criteria listed above we excluded the whole strata, hence excluding the 2 matched controls to ensure that matching remained intact. We ended up including 4,497 cases in our cohort and 8,858 controls. For some cases it was not possible to match one control. In total we had 13,355 people in our cohort.

Table 1: Patient characteristics: total population n = 13,355

	Cases (n= 4,497)	**Control (n=8,858)**
Age, median (index date)	24.0 (iqr= 17.1 – 37.9)	23.7 (iqr = 17.0 – 37.7)
	n (%)	**n (%)**
Age ≤ 15 years (n= 1,285)	415 (9.2)	870 (9.8)
Age > 15 and ≤ 20 years (n= 4,233)	1,429 (31.8)	2,804 (31.7)
Age > 20 and ≤ 30 years (n= 2,515)	849 (18.9)	1,666 (18.8)
Age > 30 and ≤ 40 years (n= 2,685)	915 (20.4)	1,769 (20.0)
Age > 40 years (n= 2,638)	889 (19.8)	1,749 (19.7)
Obese	70 (1.6)	236 (2.7)
Pregnancy/birth	631 (14.0)	1,667 (18.9)
NSAID use within five year, yes	1,009 (22.4)	1,719 (19.4)
Immigrants and descendants, yes	109 (2.4)	608 (6.9)
Gross income < 26,800 Euro/year	2,326 (51.7)	4,935 (55.7)
Exposure variables	**n (%)**	**n (%)**
Never users† (reference) (n= 7,090)	2,450 (54.5)	4,640 (52.4)
Recent users** (n= 1,715)	538 (12.0)	1,177 (13.3)
New users§ (n= 842)	283 (6.3)	559 (6.3)
Long-term users£ (n= 3,708)	1,226 (27.3)	2,482 (28.0)
Cumulative OC use	**n (%)**	**n (%)**
Total use: 1 year (n= 1,759)	554 (12.3)	1,205 (13.6)
Total use: 2 year (n= 1,193)	361 (8.0)	832 (9.4)
Total use: 3 year (n= 785)	241 (5.4)	544 (6.1)
Total use: 4 year (n= 873)	284 (6.3)	589 (6.7)
Total use: > 4 year (n= 1,656)	607 (13.5)	1,048 (11.8)

Abbreviations: iqr: inter quartile range, OC: oral contraceptives

†Never users = users, who redeemed no prescriptions in the five year period before ACL injury
§New user = Current user, first prescription redeemed ever within one year before index-date
£Long-term user = Current user, first prescription redeemed more than one year before index-date
**Recent user = users, who redeemed their first prescription more than one years before the index-date and no prescription within the first year before index date

Table 2: Relative risk (RR) for sustaining operatively treated ACL injury using Oral contraceptives (OC) or not

	Crude RR	Adjusted* RR
Never users†, (n= 7,090)	1.0 (ref)	**1.0 (ref)**
Ever users‡, (n= 6,266)	0.89 (0.81-0.96)	**0.82 (0.75-0.90)**
New-users§, (n= 842)	0.96 (0.82 – 1.12)	**0.89 (0.76 – 1.05)**
Long-term users£, (n=3,708)	0.90 (0.81 – 0.99)	**0.80 (0.74 – 0.91)**
Recent users**, (n= 1,715)	0.83 (0.73-0.93)	**0.81 (0.72 - 0.89)**

Abbreviations: RR= relative risk; OC= oral contraceptives;
*****Adjusted for age, obesity, pregnancy/birth, income, ethnicity, NSAID-use
†Never users = users, who redeemed no prescriptions in the five year period before ACL injury
‡Ever users = users, who redeemed ≥ one prescription in the five period before ACL injury
§New user = Current user, first prescription redeemed ever within one year before index-date
£Long-term user = Current user, first prescription redeemed more than one year before index-date
**Recent user = users, who redeemed their first prescription more than one years before the index-date and no prescription within the first year before index date

Table 3: Dose response analysis according to duration of OC use on the risk of sustaining operatively treated ACL injury

Number of years using OC	**Crude RR**	**Adjusted* RR**
Never users, (n= 7,090)	1.0 (ref)	**1.0 (ref)**
Cumulative OC use		
Total use: 1 year (n= 1,759)	0.85 (0.76 – 0.96)	**0.83 (0.74 – 0.94)**
Total use: 2 years (n= 1,193)	0.80 (0.70 – 0.92)	**0.78 (0.68 – 0.90)**
Total use: 3 years (n= 785)	0.81 (0.69 – 0.96)	**0.75 (0.64 – 0.90)**
Total use: 4 years (n= 873)	0.89 (0.76 – 1.05)	**0.81 (0.69 – 0.96)**
Total use: more than 4 years (n= 1,656)	1.08 (0.95 – 1.23)	**0.88 (0.77 – 1.01)**

Abbreviations: RR=incidence rate ratio. OC= oral contraceptives, Never users = users who redeemed no prescription in the entire study period

*****Adjusted for age, obesity, pregnancy/birth income, ethnicity and NSAID-use

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PAPER III

Increased Risk of Revision After Anteromedial Compared With Transtibial Drilling of the Femoral Tunnel During Primary Anterior Cruciate Ligament Reconstruction: Results from the Danish Knee Ligament Reconstruction Register

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Purpose: The goal was to study revision rates and clinical outcome after anterior cruciate ligament (ACL) reconstruction using the anteromedial (AM) technique versus the transtibial (TT) technique for femoral drill hole placement. **Methods:** A total of 9,239 primary ACL reconstruction procedures were registered in the Danish Knee Ligament Reconstruction Register between January 2007 and December 2010. The failure of the 2 different femoral drilling techniques was determined using revision ACL reconstruction as the primary endpoint. As secondary endpoints, we used the pivot-shift test and instrumented objective test as well as patient-reported outcome, registered in the Danish Knee Ligament Reconstruction Register. Relative risks (RRs) with 95% confidence intervals (CI) were calculated. **Results:** We identified 1,945 AM and 6,430 TT primary ACL procedures. The cumulative revision rates for ACL reconstruction after 4 years with the AM and TT techniques were 5.16% (95% CI: 3.61%, 7.34%) and 3.20% (95% CI: 2.51%, 4.08%), respectively. The adjusted overall RR for revision ACL surgery in the AM group was 2.04 (95% CI: 1.39, 2.99), compared with the TT group. Use of the AM technique increased from 13% of all operations in 2007 to 40% in 2010. AM technique was further associated with increased RRs of positive pivot shift of 2.86 (95% CI: 2.40, 3.41) and sagittal instability of 3.70 (95% CI: 3.09, 4.43), compared with the TT technique. **Conclusions:** This study found an increased risk of revision ACL surgery when using the AM technique for femoral drill hole placement, compared with the TT technique, in the crude data as well as the stratified and adjusted data. Our finding could be explained by technical failures resulting from introduction of a new and more complex procedure or by the hypothesis put forward in prior studies that compared with a nonanatomic graft placement, a greater force is carried by the anatomic ACL reconstruction and, hence, there is a concomitant higher risk of ACL rupture. **Level of Evidence:** Level II, prospective comparative study.

Femoral tunnel position in anterior cruciate ligament (ACL) reconstruction is critical to a good outcome, with incorrect tunnel placement cited as the most common cause of clinical failure.[1-3] Generally there are 2 alternatives for femoral tunnel placement: the anteromedial (AM) approach and the transtibial (TT) approach. The traditional TT approach for femoral tunnel placement is limited by the angulation of the tibial tunnel, which restricts placement of the femoral tunnel and places the femoral tunnel higher in the intercondylar notch.[4,5] To overcome these limitations created by the tibial tunnel and to increase rotational stability in the single-bundle ACL reconstruction, the AM surgical approach to the femoral tunnel was introduced. Reaming through a medial parapatellar tunnel in 1995, O'Donnell and Scerpella were the first to describe an alternative method for femoral tunnel placement.[6] Bottoni et al. followed in 1998 by inserting the femoral guide through the AM portal for better femoral tunnel placement.[7] This led to increased use of the AM portal for femoral drill hole placement owing to better ability to reach a more anatomical ACL footprint.[1,8-10] By using this AM technique, the surgeon is able to visualize and position the femoral tunnel

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independent of the tibial tunnel. Although it is more challenging because of the lack of "easy-to-use" guides for femoral drill hole placement and the necessity for hyperflexion during drilling, the AM drilling technique has increased in popularity in recent years as a result of the trend of anatomic ACL reconstruction.[11]

Also, cadaveric studies have shown better rotational stability with AM placement of the femoral canal than with TT placement.[12] In several studies, TT placement of the femoral tunnel has also been shown to be unable to capture the center of the native femoral footprint,[1,5,11-13] whereas the AM portal gives the surgeon a more unrestricted possibility of placement of the femoral tunnel.[11,13,14] Anatomic ACL reconstruction has also led to increased interest in double-bundle ACL reconstruction.[15] However, single-bundle endoscopic ACL reconstruction remains the gold standard and is the most commonly used operative technique for ACL reconstruction.

The impact of the shift in ACL reconstruction technique from TT to AM portal femoral tunnel placement on patient outcome has not been investigated before in Denmark. The Danish Knee Ligament Reconstruction Register (DKRR)[16] has monitored the quality and development of ACL reconstructions since 2005 and has registered femoral drilling techniques since 2007. Therefore, the objective of this population-based cohort study was to compare the revision rates and clinical outcomes between AM and TT drill hole placement in primary ACL reconstruction in the DKRR and, hence, test the hypothesis of no difference between TT and AM femoral tunnel position.

Methods

This study was designed as a prospective population-based cohort study using the DKRR linked to the Civil Registration System (CRS), studying the risk of revision in the AM technique for femoral drill hole placement compared with that in the TT technique.

Data Sources

Danish Knee Ligament Reconstruction Register. The DKRR is a nationwide clinical database that was established July 1, 2005, for the purpose of improving the monitoring and quality of both primary and revision ACL surgery in Denmark.[16] All private (n = 27) and public (n = 24) hospitals report to this register, and registration is compulsory according to Declaration No. 459 of June 15, 2006; 85% of all ligament reconstructions have been reported to the DKRR over the last 6 years.[17] Since January 2007, anatomic ACL reconstruction measures such as femoral tunnel drilling technique and double-bundle reconstructions have been registered. In Denmark, most surgeons are subspecialized so most of ACL reconstructions are performed by surgeons specialized in sports traumatology, although fellows and residents also perform this kind of surgery as part of their training.

Detailed preoperative, intraoperative, and 1-year follow-up data are recorded by the operating surgeon using a standardized form and a secured Internet portal.[16] The mean follow-up time was 1.05 years (95% confidence interval [CI]: 1.05, 1.06). At the 1-year follow-up visit, the pivot-shift test was performed; patients were tested for sagittal instability and to determine if ligaments were loose medially or laterally. Also at the 1-year follow-up, patients were asked about complications and if they had had revision surgery. Furthermore, patients independently reported subjective scores of knee function using the self-assessment score, the Knee Injury and Osteoarthritis Outcome Score (KOOS),[18] and the Tegner functional score.[19] These data are Web-recorded by the patient before and 1 year after surgery. KOOS scores range from 0 to 100, and Tegner scores, from 1 to 10, with higher scores representing better results. $KOOS_4$, a validated average of 4 KOOS scores (quality of life, sport, pain, and symptoms), was also calculated.[20]

Civil Registration System. All Danish citizens receive a unique personal identification number at birth. The Civil Registration System (CRS) has recorded information on changes in vital status of all Danish citizens, including changes in address, date of emigration, and date of death, since 1968. Precise individual-level linkage between public Danish registers is possible because of the personal identification number. The CRS was used to obtain complete follow-up data on all patients.

Study Population

Denmark has a population of 5.5 million, and free health care is available to all citizens including general practitioner visits and hospital visits at medical, surgical, and psychiatric departments. In this study, we identified 9,239 primary ACL procedures in 9,202 patients from the DKRR between January 1, 2007 and December 31, 2010. A total of 85 patients emigrated during the study period. For 20 operated knees, the patients resided in Greenland, and for 37 operated knees, the nationality was other than Danish. These 2 groups were not subject to proper follow-up and were therefore excluded. Finally, 806 knees (8.7% of the total) were excluded because of missing information on femoral drill hole placement. One patient had revision surgery registered before primary surgery and was therefore excluded. No patients were registered as emigrated or dead before revision surgery. In total, we included 8,375 primary ACL procedures for further analysis.

Exposure

In this study we investigated the results of the use of either the AM or TT technique for femoral drill hole placement on our outcome measures.

Outcomes

The primary outcome was revision ACL surgery, defined as new surgery with exchange of primary ACL. Patients who were diagnosed with suspected lesions of their ACL, but did not undergo revision ACL surgery, were not included as revision outcomes. All primary ACL procedures in the 2 groups were followed up from the day of primary ACL surgery to the day of revision of primary ACL if revision occurred, or time of death, or on status date, which is the end of the study period (December 31, 2010).

The secondary outcomes were parameters of objective knee stability in terms of instrumented sagittal knee stability testing (e.g., Rolimeter or KT-1000 tests) and pivot-shift scores. The pivot-shift test is a dynamic but passive test of the knee that measures the rotational and anterior tibial translation stability of the ACL. The pivot-shift test is graded on a 4-point scale, where 0 = normal, 1 = glide, 2 = clunk, and 3 = gross.[21] The pivot-shift data were divided into negative pivot-shift tests (n = 3,402) and positive pivot-shift tests (n = 607). The sagittal stability test measures the difference in sagittal stability between the operated knee and the healthy knee. Patients were categorized as having a side-to-side difference ≤2 mm or >2 mm.

Finally, we used patient-related outcomes, the KOOS and Tegner scores at 1 year after surgery, if reported. These data, both preoperatively and postoperatively were linked to femoral drill-hole placement data. KOOS and Tegner scores are validated subjective patient-related outcome scores calculated according to published standards.[18,19] $KOOS_4$ is a validated patient-related outcome computed from the 4 most responsive KOOS subscores[20] including symptoms, pain, sport, and quality of life. Preoperative and postoperative KOOS and Tegner scores were available on 3,059 patients (37%) and 2,563 patients (31%), respectively. Data were linked to the CRS to obtain information about emigration and death. Furthermore, the data were linked to revision surgical procedures in the DKRR for primary endpoint evaluation.

Confounding Factors

At time of surgery, we obtained data from the DKRR on gender, age (≤20 and >20 years of age), cartilage damage >1 cm^2 present (no/yes or missing data), operated meniscal damage (yes/no or missing data), choice of graft (bone—patellar tendon—bone autograft or semitendinosus gracilis autograft), prior surgery to the knee (yes/no), and activity leading to primary ACL rupture (sport or other circumstances such as traffic accidents, an activity of daily living, or a work-related incident). For meniscal damage we registered the proportion of treated meniscal damage in each group.

Statistics

By applying the Kaplan-Meier method we estimated the revision probability at different follow-up periods in the AM and TT groups. We used Cox regression analysis to compare the revision risk after primary ACL surgery among patients operated with the AM and TT techniques. We computed the hazard ratios as a measure of relative risk (RR) with 95% confidence interval (95% CI) for patients operated with the AM compared with the TT technique, both crudely and adjusted for potentially confounding factors. The assumption of the Cox regression model was assessed with use of log—log plots and Schoenfeld residuals and was found suitable.

Further, using Cox regression analysis we calculated the adjusted RR of having a positive pivot-shift test or >2 mm of sagittal instability to the operated knee compared with the healthy knee in the AM and TT groups. For the sagittal instability test, we excluded 2 patients who had registered postoperative stability tests on both knees.

Median values of the KOOS and Tegner scores preoperatively and 1 year postoperatively for the patients who underwent surgery using the AM and TT techniques were compared using the Student *t* test or Wilcoxon rank-sum test. The distribution of potentially confounding factors between the AM and TT groups was compared (Table 1) using the χ-square test. $P < .05$ was considered statistically significant.

All statistical analyses were computed using Stata Version 12 (Stata Release 12, College Station, TX). The study was approved by The Danish National Board of Health and the Danish Data Protection Agency.

Results

Patient characteristics are outlined in Table 1, and causes of revision surgery, in Table 2. No statistically significant difference in cause of revision was found between the 2 groups using the χ-square test.

Over a 4-year period, use of the AM technique increased from 13% of all operations in 2007 to 40% in 2010. In the AM group, 39 of 1,945 knees were revised, and in the TT group, 102 of 6,430 knees were revised over the 4-year observation period. The average time of follow-up was 22.2 months (95% CI: 21.8, 22.4) for the whole cohort and 16.2 (95% CI: 15.6, 16.8) and 24.0 (95% CI: 23.6, 24.3) months for the AM and TT groups, respectively.

The Kaplan-Meier 4-year cumulative revision rate was 5.16% (95% CI: 3.61%, 7.34%) in the AM group and 3.20% (95% CI: 2.51%, 4.08%) in the TT group (Fig 1). The revision rate was 1.09 (95% CI: 0.65%, 1.85%), 3.28 (95% CI: 2.30%, 4.66%), and 4.71 (95% CI: 3.34%, 6.63%) among patients operated on with the AM technique compared with 0.44 (95% CI: 0.29%, 0.65%), 1.78 (95% CI: 1.42%, 2.23%), and 2.57 (95% CI: 2.09%, 3.16%) among patients operated on with the TT technique, after 1, 2, and 3 years, respectively.

Table 1. Demographics

Demographic	Femoral Tunnel Placement Technique: Anteromedial (n = 1,945)	Transtibial (n = 6,430)	P (χ^2)
Gender			
Male	1,193 (1,193/1,945 = 61%)	3,812 (3,812/6,430 = 59%)	.11
Female	752 (752/1,945 = 39%)	2,618 (2,618/6,430 = 41%)	
Age at time of surgery			
≤ 20 years	527 (27%)	1,680 (26%)	.40
> 20 years	1,417 (73%)	4,751 (74%)	
Meniscal treatment			
Yes	779 (40.1%)	2,448 (38.1%)	.12
No/missing	1,166 (59.9%)	3,982 (61.9%)	
Cartilage damage			
Yes/missing	348 (17.9%)	1,405 (21.9%)	.00
No	1,597 (82.1%)	5,025 (78.1%)	
Prior surgery on the knee*			
Yes	441 (22.8%)	1,701 (26.6%)	.001
No	1,491 (77.2%)	4,699 (73.4%)	
Sport activity leading to tear*			
Yes	1,562 (80.4%)	5,189 (81%)	.57
No	380 (19.6%)	1,216 (19%)	
Graft choice†			
BPTB	183 (10.0%)	879 (14.3%)	.00
STG	1,646 (90.0%)	5,242 (85.7%)	

BPTB, bone–patellar tendon–bone autograft; STG, semitendinosus/gracilis autograft.

*"Prior surgery on the knee" and "Sports activity leading to tear" do not add up to 3,875 because some data were not registered by the operating surgeon.

†Four hundred twenty-six variables are either missing or other graft types which are not included in this table.

The crude overall RR for revision surgery in the AM group compared with the TT group was 2.01 (CI: 1.39, 2.92). The overall RR for revision adjusted for the mentioned confounders (age, gender, cartilage damage, operated meniscal damage, choice of graft, prior surgery to the knee, and activity leading to lesion) was 2.04 (CI: 1.39, 2.99). Furthermore, the adjusted RRs of revision after 1 and 2 years were 2.32 (CI: 1.17, 4.57) and 2.04 (CI: 1.33, 3.14), respectively.

Table 2. Causes of Revision Surgery

Cause	Femoral Tunnel Placement Technique: Anteromedial	Transtibial
New trauma	16 (42.1%)	40 (38.8%)
Tunnel widening	1 (2.6%)	3 (2.9%)
Suboptimal placement of graft in tibia	3 (7.9%)	8 (7.8%)
Suboptimal placement of graft in femur	3 (7.9%)	13 (12.6%)
Infection	5 (13.2%)	6 (5.8%)
Unknown reason for instability	7 (18.4%)	23 (22.3%)
Other ligament failure	1 (2.6%)	5 (4.9%)
Other	2 (5.3%)	5 (4.9%)
Total	38 (100.0%)	103 (100.0%)

The AM technique for drill-hole placement was associated with an increased risk of positive pivot-shift test for rotational instability compared with the TT technique, with an adjusted RR of 2.86 (95% CI: 2.40, 3.41) (Table 3). Furthermore, we observed that the patients who had the AM technique for drill-hole placement had an increased risk of having a difference in sagittal instability >2 mm between the operated and the healthy knee compared with the TT group, with an adjusted RR of 3.70 (95% CI: 3.09, 4.43) (Table 3). Because of a substantial number of missing data at the 1-year postoperative clinical control visit, pivot-shift and sagittal instability data were recorded only for 49% and 47% of the operations, respectively. The KOOS and Tegner scores, both preoperatively and 1 year after surgery, were comparable in the 2 groups (Table 4).

Stratified Analyses

We conducted stratified analyses on all the covariates listed above under confounding factors and compared the risk of revision between the AM and the TT techniques in each group. The AM technique was associated with an increased risk of revision compared with the TT technique irrespective of gender, age, cartilage damage, and meniscal damage. Stratified analyses suggest that the AM technique is associated with an increased risk of revision compared with the TT technique among patients who received hamstring grafts of 2.20 (95% CI: 1.48, 3.27), whereas no association was found (RR for revision of 0.55%; 95% CI: 0.07, 4.21) among patients who received bone–patellar tendon–bone (BPTB) grafts. Further, the increased risk of revision for AM versus the TT technique was confirmed in the group that had not had prior surgery (RR = 2.49; 95% CI: 1.67, 3.72), whereas no association was seen in the group that had prior surgery to the knee (RR = 0.28; 95% CI: 0.03, 2.07).

Discussion

This is the first nationwide register-based cohort study comparing the results of use of the AM and TT techniques for femoral drill-hole placement in primary ACL reconstruction. Our study showed that introduction of the AM technique into ACL reconstruction has resulted in a higher risk of revision ACL surgery than with the traditional TT technique. Further, AM drill hole placement was associated with more objective instability. The lack of association between the AM technique and revision risk among patients who received BPTB graft and those who had prior surgery to the knee should be interpreted with caution because of the very few revisions in these groups; a larger cohort will be needed to clarify this issue.

Our results are in accordance with a meta-analysis by Alentorn-Geli et al. comparing the TT and AM portal techniques in BPTB ACL reconstructions.[11] They

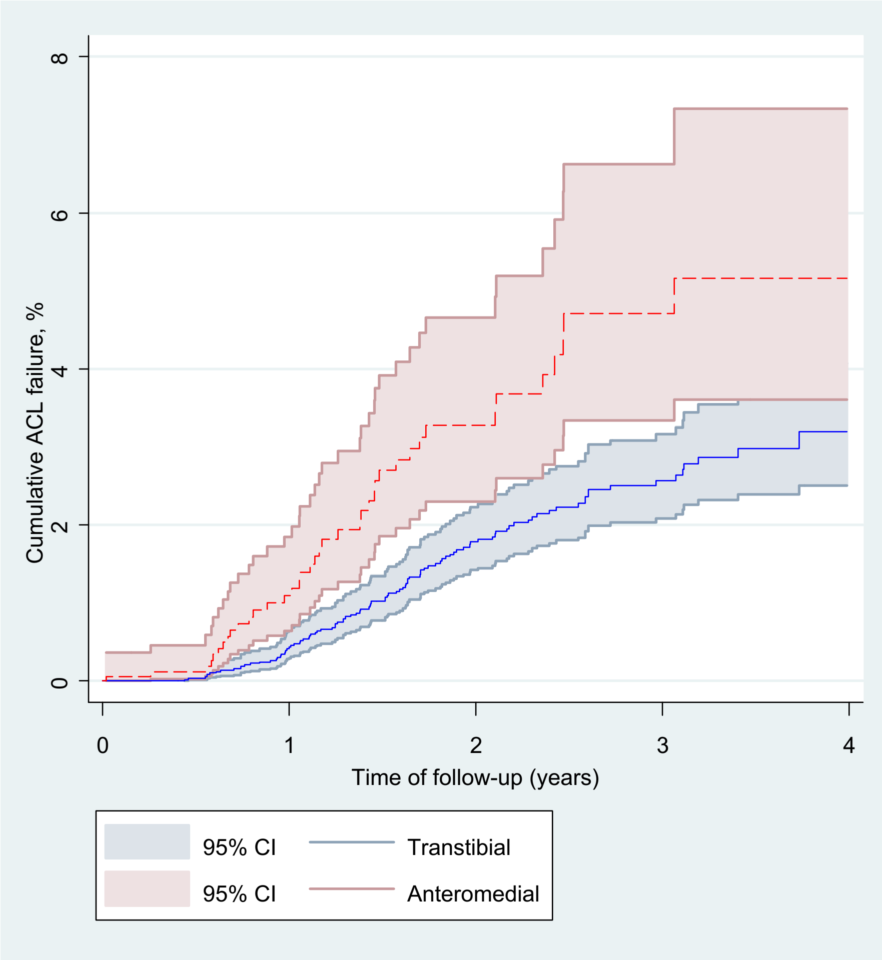

Fig 1. Kaplan-Meier failure curves for primary anterior cruciate ligament (ACL) reconstructions using either the anteromedial (AM) or transtibial (TT) approach for femoral drill hole placement. The primary endpoint is revision ACL reconstruction. (CI, confidence interval.)

obtained a graft revision rate of 5.7% in the AM group compared with 2.3% in the TT group. However, all included studies were case series, and none of the studies was comparative. Some studies have indicated better rotational stability with the AM technique than with the traditional TT technique.[12,22,23] In a cross-sectional study, Alentorn-Geli et al. showed, in a cohort of 47 patients, better objective knee stability in the AM group than in the TT group.[10] Likewise, in a cadaveric study, Bedi et al. found better knee stability in the AM group than in the TT group using Lachman and pivot-shift tests.[12] This is in contrast to our cohort study in which we found that significantly more knees had positive pivot-shift and sagittal instability in the AM group than in the TT group. Moreover, Markolf et al., in a cadaveric study, questioned the rationale of moving the femoral tunnel from the standard location to a more oblique position in the notch as no difference was seen in pivot-shift kinematics in their study.[24]

Table 3. Results of Pivot-Shift Test for Rotational Instability and Instrumented Sagittal Knee Instability (e.g., Rollimeter or KT-1000) 1 Year After Surgery

	Femoral Tunnel Placement Technique		
Objective Test	Transtibial	Anteromedial	*P* value
Pivot-shift test for rotational instability			
Positive	401 (13.6%)	206 (19.5%)	<.000
Adjusted RR* (95% CI)	1.0 (reference)	2.86 (2.40; 3.41)	
Instrumented sagittal instability			
>2 mm	320 (11.4%)	208 (19.8%)	<.000
Adjusted RR* (95% CI)	1.0 (reference)	3.70 (3.09; 4.43)	

NOTE. Shown here is the difference in risk and adjusted RR of having a positive pivot-shift test or rotational instability >2 mm on instrumented sagittal instability tests in the anteromedial group compared with the transtibial group.

RR, relative risk; CI, confidence interval.

Additionally, studies have shown that a greater force is carried by the anatomic ACL reconstruction than on a nonanatomic graft placement. Xu et al.[25] showed that an anatomic reconstructed AM bundle showed a significantly higher in situ force than did nonanatomic high placement of the AM bundle. Hence, a greater load is carried by an anatomic reconstructed graft, which makes it more vulnerable than the nonanatomically placed graft because it transfers more load to other

Table 4. Preoperative and 1-Year Postoperative KOOS and Tegner Scores for Primary Anterior Cruciate Ligament Procedures Using the Anteromedial and Transtibial Approaches

	Transtibial	Anteromedial	*P* value
	Preoperative		
	n = 2,360 (37%)	n = 699 (36%)	
KOOS subscore			
Symptoms	70.9 (70.2; 71.5)	70.7 (69.5; 71.8)	.72
Pain	70.9 (70.2; 71.6)	70.9 (69.6; 72.2)	.96
Activities of daily living	78.0 (77.2; 78.6)	78.1 (76.8; 79.3)	.79
Sports	38.0 (36.9; 39.0)	38.1 (36.2; 40.0)	.76
Quality of life	39.1 (38.5; 39.8)	39.4 (38.1; 40.6)	.78
$KOOS_4$	54.7 (54.1; 55.3)	54.8 (53.6; 56.0)	.78
Tegner score	2.95 (2.9; 3.0)	2.9 (2.7; 3.0)	.58
	Postoperative		
	n = 1,905 (30%)	n = 658 (34%)	
KOOS subscores			
Symptoms	76.9 (76.1; 77.7)	76.7 (75.5; 78.0)	.56
Pain	83.4 (82.7; 84.3)	82.5 (80.9; 84.1)	.08
Activities of daily living	89.0 (88.4; 90.0)	88.3 (87.1; 89.2)	.07
Sports	62.1 (60.7; 63.4)	61.2 (58.5; 63.8)	.62
Quality of life	59.1 (58.2; 60.1)	57.4(55.9; 59.0)	.08
$KOOS_4$	70.3 (69.5; 71.1)	69.4 (68.1; 70.8)	.21
Tegner score	4.9 (4.8; 5.0)	5.0 (4.8; 5.2)	.35

NOTE. KOOS and Tegner scores are median values with 95% confidence intervals (in parentheses).

structures in the knee.[25] This could be part of the explanation as to why in our study the revision rate in the AM group is greater than that in the TT group.

Several problems have been encountered using the AM technique. In a cadaveric study, Bedi et al. showed a decrease in tunnel length and an increased tendency to compromise the posterior wall when using the AM technique.[26] On the other hand, they also showed a greater coronal obliquity of the femoral tunnel. Likewise, other studies have shown the AM technique results in significantly shorter tunnel lengths compared with the TT technique, entailing potential problems with graft selection, fixation method, and inadequate amount of graft in the tunnel.[27,28] Damage to the peroneal nerve, iatrogenic cartilage damage, or slipping of the aimer during hyperflexion have also been described as problems to overcome when using the AM technique.[29] Because several technical challenges are connected to use of the AM technique, we also propose a learning curve as part of the explanation of our present findings. Our study period represents a transition period in which nearly half of the ACL surgeons learned the AM technique. Despite that, the transition to the AM technique is an attempt to do more anatomic reconstructions, but we have no data to show to what extent this actually was accomplished. One can speculate that a proportion of the tunnel placements were inadequate because of technical problems of poor visualization.

Several studies on ACL reconstruction outcome have used subjective patient-related outcome measures.[20,30,31] We also evaluated patient-related outcome measures to see if there were any correlations between these and choice of technique for femoral drill hole placement. Our subjective scores did not show any significant difference between the 2 groups, which is in accordance with other studies.[10] With the current interest in double-bundle ACL reconstruction,[32,33] it would be of interest to compare anatomic single-bundle with double-bundle ACL reconstruction in large prospective cohorts as in a national registry. In Denmark, however, surgeons have been cautious in introducing double-bundle reconstruction, with less than 1% of reconstructions using the double-bundle technique. Therefore, the DKRR will not be able to compare single- and double-bundle ACL reconstruction outcomes.

Whether revision rates improve when the AM portal technique becomes routine needs to be determined in future national registry studies. Ongoing monitoring of the results with the AM approach is therefore necessary and exemplifies the importance of a national registry.

Methodological Considerations

This study was based on data from a national clinical registry and, thus, has several limitations. One problem is the completeness of the data and patient compliance with on-line subjective patient registrations. Only about 37% of patients reported preoperative, and only 31% of patients reported postoperative, patient-related outcome scores. This could lead to information bias if missing data on patient-related outcomes are related to both drill hole placement technique and later revision. Because the data collection is prospective and registration of primary ACL is independent of registration of later revision, the risk of information bias is very limited. Nevertheless, a previous validity study showed no difference in patient-related outcome scores between respondents and nonrespondents in the DKRR (unpublished data). We therefore ascribed our subjective data a value despite the incompleteness of our data.

In this multivariate analysis we included important confounders that have previously been associated with the risk of revision surgery.[11,31,34,35] These adjustments did not alter the RR. The sensitivity analysis made for the 802 missing data showed the same tendency in RR as the actual analyzed RR, and we therefore concluded that it did not have any significance with respect to our results.

A substantial amount of data was missing at the 1-year postoperative clinical control visit; hence, pivot-shift data were recorded for 49% of operations and sagittal instability data were recorded for only 47%. The challenge of getting a large percentage of patients to clinical follow-up is substantial when dealing with a national cohort. Again, because of the prospective collection of data, it is unlikely that the lack of these data is associated with both drill hole placement technique and subsequent revision. The 1-year follow-up examination was, at most hospitals, performed by the operating surgeon, who was not blinded, which could result in information bias.

By using revision ACL reconstructions as the primary outcome in this study, we do not capture all ACL failures. Some patients accept a chronic unstable knee and reduce their activities, and others are not suitable for second operations. Hence, the real number of ACL failures is probably higher than the number of ACL revision surgeries. However, there is no reason to believe that total ACL failure rates and ACL revision rates differ in the AM and TT groups.

Our study is based on a large sample size ensuring the high precision of the risk estimates presented. Although we adjusted for a number of potential confounding factors, our study, like all observational studies, may suffer from unmeasured and residual confounding. For example, data on patients' medication use, physical activity during the follow-up period, or quality of rehabilitation were not available from the DKRR.

Conclusions

Both the crude data and the stratified and adjusted data from this study indicate that the risk of revision ACL surgery increases when the AM technique, compared with the TT technique, is used for femoral drill hole placement. Our finding could be explained by the technical failures resulting from introduction of a new and more complex procedure or by the hypothesis stated in prior studies that a greater force is carried by an anatomic anterior cruciate ligament reconstruction than a nonanatomic graft placement, and hence, there is a concomitant higher risk of anterior cruciate ligament rupture.

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APPENDIX 1-7

APPENDIX 1

Appendix 1: Literature search study I: validity studies on national knee ligament registries and national registries on joint replacement

Author, Year, journal, reference	Design	Study population, country	Exposure, follow up time	Study weakness (bias, confounding)	Outcome	Results
Barr CJ, 2012, J. Arthroplasty[173]	Validity study	6,912 primary arthroplasty (THA) and revision THA from Harris Joint Registry (HJR) of Boston, USA	HJR compared to the golden standard defined as Research Patient Registry 2000 2009	Unclear how they measure the completeness and no number available to check the calculation. Research Patient Registry is not a perfect source of information	Completeness of data in HJR	Completeness of data: Primary THA: 91% Revisions THA: 85%
Espehaug B., 2006, Acta Orthop[174]	Validity study	37,673 Primary and revision THA from the Norwegian Arthroplasty Registry (NAR)	NAR compared to the golden standard defined as Norwegian Patient Registry 1999 2002	Their calculation of completeness is not a measure for the sensitivity as recommended by Sorensen et al[53], making their estimates of completeness higher than expected. No individual matching possible, and hence no validity of data at a personal level Norwegian Patient Registry is ot erfect source of information	Registration of completeness in he AR	Data completeness: Primary THA: 97% Revision THA: 106%. Total knee replacement: 99% Revision knee surgery: 97%
Pedersen AB, 2004, Acta Orthop Scand[137]	Validity study	27,076 primary and revision hip THA in anish ip Arthroplasty Registry (DHAR)	DHAR compared to the golden standard defined as Danish National Registry of Patient (DNRP) 1995 2000	Excluded patients operated at private hospitals The DNRP is not a perfect source of information	Registration completeness in he HAR	Registration rate: Primary THA: 94% Revision THA: 81% Finding a lower completeness at university hospitals
Solumshengslet, 2007, Idrettsmedicin [51]	Validity study	285 primary ACL reconstructions in the Norwegian Knee Ligament Registry (NKLR)	NKLR compared to the golden standard defined as hospital protocols or the Norwegian National Registry of Patient 2004 2005	Their calculation of completeness is not a measure for the sensitivity as recommended by Sorensen et al[53], making their estimates of completeness higher than expected. The estimates were based on a selected population since they only used 10 out of 46 hospitals reporting to the registry. Can result in selection bias Norwegian Patient Registry is ot erfect ource f information	Registration completeness	Completeness: 86% when using NPR and 84% when using hospital records as gold standard
Södermann P, 2000, J. Arthroplasty [172]	Validity study	95,060 primary and revision THA from the Swedish Arthroplasty Registry (SAR)	SAR compared to discharge Register (DR). 1986 1995	No individual matching possible, and hence no possibility of investigation into validity of data at a personal level DR is ot erfect ource f formation	Registration completeness	Registration rate: Primary THA: SAR: 84,884 and DR: 83,137 Revision THA: SAR: 10,176 and DR: 11,323
Ytterstad, 2012, Acta Orthop[52]	Validity study	2,393 primary and revision ACL reconstructions in the NKLR from public and private hospitals.	Norwegian ACL registry compared to Norwegian Registry of Patient (NRP). Small volume hospitals: less than 30 operations pr year. 2008 2009	Their calculation of completeness is not a measure for the sensitivity as recommended by Sorensen et al[53], making their estimates of completeness higher than expected. Excluding one private hospital due to gross counting error, which could weaken their estimates. The NPR is not a perfect source of information	Registration completeness	Registration rate: Total: 86% Small volume hospitals: 69% Large volume hospitals: 89%
Ytterstad, 2011, Tidskr Nor Legeforen[45]	Validity study	195 primary ACL reconstructions from the NKLR	Norwegian ACL registry compared to NPR and electronic medical journals. 2005 2006	Their calculation of completeness is not a measure for the sensitivity as recommended by Sorensen et al.[53] In ome f he alculation ot lear ow as een calculated. They only used data from 14 out of 53 hospitals, hence the risk of selection bias	Registration completeness	Registration rate: 97 99%

APPENDIX 2

Appendix 2: Literature search from study II: Impact of the use for OC on the risk of sustaining operatively treated ACL injury

Author, Year, journal, ref.	n	Design	Study population, country	Exposure, follow up time	Study weakness (bias, confounding.)	Outcome	Results
Agel J, 2006, Med Sci Sports Exerc[78]	3150	Prospectively collected data on OC use and injury.	2026 nonusers; 1024 OC users; United States	OC use	Risk of information bias high, due to information on exposure and outcome relay on questioners	Noncontact ACL injuries; Ankle sprains	No difference in the risk of sustaining ACL injury nd nkle prain etween he ser nd nonuser of OC
Bell DR/ 2011/ Clin J Sports Med[67]	30	Causal comparative, research laboratory	15 OC users 15 non OC users	OC use	Low sample size. Selection bias due to selection of OC user. Hamstring stiffness only surrogate measure	Hamstring stiffness and hamstring neureomechanics	No difference between the OC users and non users was observed in hamstring stiffness as well as no difference was noted during the menstrual cycle
Faryniarz DA, 2006, In Vitro Cell Dev Biol Anim [63]	26	*In vitro* study	Specimen from 12 men and 14 female ACL	Monoclonal antibody to human estrogen receptors	They only quantified the number of receptors no study on the function of the receptors.	Number of estrogen receptors on the human ACL	No difference in the expression of estrogen receptors between men and women
Hicks-Little CA, 2007, J Sports Med Phys Fitness[74]	53		25 OC user and 28 non OC users. All female athletes.	OC use	No sample size calculation No blinding No adjustment for confounders	Anterior tibial displacement using KT 1000	OC had increased laxity f he nee ompared to those without treatment with OC The menstrual cycle does influence on the laxity f he knee
Komatsuda, 2006, Acta Orthopaedica[56]	40	*In vitro* Rabbit study	40 ovariectomized rabbits	Estrogen levels in rabbits. Rabbits stimulated with estrogen in 4 different concentrations	Animal study, caution extrapolation data to human No samle size calculation Small sample size No adjustment was done and no matchning	Mechanical properties of the ACL of rabits	Ultimate tensile stress and linear tiffness were lower in the group treated with high dose estrogen.
Liu, 1996, J Orthop Res[62]	17	Immunohistoce hmestry study.	13 ACL specimen from women and four from men	Estrogen receptor antibodies	Specimens were obtained from an older population (average age 57 years) and with varying degrees of pathology (tumors, osteoarthritis, and ACL tears).	Identify strogen and progesteron target cell on the human ACL using immunohistocheme stry	Estrogen target cells identified on the human ACL
Liu, 1997, Am J Sports Med[65]		*In vitro* animal study	Rabit fibroblast in cell culture	Estrogen (17 beta estradiol)	Animal study, caution extrapolation data to human	ACL fibroblast metabolism	Estrogen stimulation resulted in ecreased fibroblast proliferation and collagen synthesis.
Lobato, 2012, Knee Surg Sports Traumatol Arthrosc[79]	40	Prospective single center study	20 OC users 20 non OC users Brazil	OC use	Low sample size	Hip and knee kinematics using ant stair descent	OC does not influence the hip and knee kinematics during anterior stair descent.
Martineau PA, 2004, Clin J Sports Med[59]	87	Single center study. Retro spective study	42 OC users 36 non users Canada	OC use	Risk of information and selection bias high. Outcome only surrogate for ACL injury	Anterior posterior translation using KT 1000 (measured by one blinded examiner)	Higher anterior knee laxity for the nonuser in both knees. They concluding that OC yields significant decrease in knee laxity
Moller-Nielson, 1989, Med Sci Sports Exc[82]	84	Prospective study, information collected using questioner	84 women soccer players from the first to third leagues in Sweden.	OC use and menstrual cycle phase	Risk of Information and selection bias moderate due to prospectively collected data and exclusion criteria Outcome only surrogate for ACL injury	Unspecific sports injuries reventing the player from attending in exercise session	Lower rate of sports injuries in women using OC Higher rate of injuries during the premenstrual and menstrual period.

Ruedl G, 2009, Knee Surg Sports[60]	93 + 93	Case control study, 2006 08; Case: women with ACL injury Control: no ACL injury	93 cases; recreational skiers 93 controls age matched recreational skiers Austria.	Frequency of OC use.	Risk of information bias high due to study design with questionnaire. No information on how much or how long OCs had been used, Very gross classification of the use of OC with risk of residual confounding. Only recreational skiers, hence, low external reproducibility	Non contact ACL injury	No difference in the risk of ACL injury was shown between OC users and non users.
Seneviratne A, 2004, Am J Sports Med[76]		*In vitro* immunohistochemical animal study	ACL fibroblasts from sheep knees	Estrogen exposure to ovine ACL firborblasts	Animal study, caution extrapolation data to human	ACL fibroblast proliferation and collagen synthesis in	No difference in fibroblast proliferation and collagen synthesis regardless of estrogen concentration
Yu WD, 1999, Clin Orthop Relat Res[176]		*In vitro*	Cells derived from a 32 year old woman who underwent total knee arthroplasty	17β estradiol		ACL fibroblast proliferation	Decreased fibroblast proliferation with increasing 7β estradiol Suggesteing that the cyclic variation in omen predispose to ACL injury
Wentorf, 2006, Am J Sports med[77]	26	Animal study	26 monkeys either sham operated (estrogen maintained; = 2) r ovariectomized (n = 14)		Animal study, caution extrapolation data to human No male specimen for comparison	Mechanical properties of the ACL	Endogeneous estrogen did not affect the mechanical properties of the ACL
Woodhouse, 2007, Knee Surg Sports Traumatol Arthrosc[64]	35	Rat study	35 rats; 16 cases and 19 controls United States	Reproductive hormones	Animal study, caution extrapolation data to human Exposure only surrogate of real OC use. External validity, is it comparable to humans?	Experimental dynamic load on ACL until failure	Hormone treated rats was associated with greater elongation, more energy absorbed prior to failure, and higher toughness compared to controls

APPENDIX 3

Appendix 3: Literature search from study III: Impact on the choice of the use of either the AM or TT technique for femoral tunnel drilling during ACL reconstruction

Author, Year, journal, ef.	N	Design	Study population, country	Exposure	Study weakness (bias, confounding)	Outcome	Results
Alentorn Geli E, 2010, International Orthopaedics[178]	47	Retrospective ross sectional study	Forty seven 16 35 year old male soccer players. 21 in the TT group; 26 in the AM group	AM vs. TT technique for femoral tunnel drilling	Low external reproducibility (only male soccer players) TT had longer follow up that the AM group No blinding of examiner Not all patients were included, risk of selection bias	IKDC, T1000, achman, pivot shift test, ROM, Lysholm and Tegner scores	The AM group revealed better clinical outcomes and stability and higher IKDC scores. No difference in Lysholm and Tegner scores.
Alentorn Geli E, 2010, Knee Surg Sports Traum Arth[99]	859	Meta analysis	859 patients from 21 studies. Eight studies used the AM technique and 13 studies used the TT technique	Indirect omparison of the AM and the TT technique	None of studies made a direct comparing the AM and the TT technique, hence, only an indirect comparison of the two technique. Half of the AM sample came from the same population hence, a low external validity. Graft failure rate was measure with different follow up time hence, these results should be interpreted with caution	Return to sport, ROM, graft failure rate, IKDC, Lysholm, Lachman test, KT1000 and pivot shift test	Improved ange f otion, tability, nd return to play in the AM group compared to the TT group. Graft failure rate was higher in the AM (5.7%) group compared to the TT (2.3%) group
Bedi A, 2010, Arthroscopy[93]	18	Cadaveric study	12 knees in the AM and 5 patients in the TT group	AM vs. TT technique for femoral tunnel drilling	Not clear if blinded evaluation was performed	Coronal obliquity Tunnel length	AM technique allowed greater femoral tunnel obliquety, but also horter unnel and higher risk of posterior wall blow out
Bedi A, 2011, Arthroscopy[97]	10	Cadaveric study	5 knees in the AM and in he T roup	AM vs. TT technique for femoral tunnel drilling	Performed on older cadavers with a mean age of 64 years. Not comparable to the age of the usual ACL patient. No blinding of which technique was performed	Anterior draw, Lachman test and pivot shift test	The AM technique revealed better clinical result using the Lachman and pivot shift test
Bowers AL, 2011, Arthroscopy[91]	30	Retrospective comparison study	15 patients in each group	AM vs. TT technique for femoral tunnel drilling		MRI evaluation of tunnel position	AM technique restores the native anatomy better than the TT technique. TT decreased obliquity
Chhabra A, 2006, Artrhroscopy[182]	75	Retrospective comparative study	41 patients in the TT group and 34 I the AM group	AM vs. TT technique for femoral tunnel drilling in ACL reconstruction using hamstring graft	Possibility for confounding factors high. Only hamstring grafts, selection bias.	Tunnel widening	Femoral tunnel expansion lower in the AM group.
Chalmers PN, 2013, Arthroscopy[98]	9	Systematic review	Nine studies were identified irectly comparing AM with the TT technique.	AM vs. TT technique for femoral tunnel drilling	Does not include all relevant articles in the area and includes one article without the actual outcome of interest.	Review of different papers on AM and TT technique	Describing and comparing the results from different studies on AM or TT technique for femoral tunnel drilling.
Chang CB, 2011, Arhroscopy[90]	105	Case series	50 patients in he M and 55 patients in the TT group	AM vs. TT technique for femoral tunnel drilling	Different time periods evaluated in the two groups Only ACL reconstruction using hamstring grafts was included troducing election ias	Placement of the femoral tunnel, length and obliquety evaluated using X ray	AM technique shorter tunnels and more oblique.
Dargel, 2009, Knee Surg Sports Traum Arth[177]	100	Retrospective study	50 patients in the AM and 50 patients in the TT group	AM vs. TT technique for femoral tunnel drilling	Possible confounding factors not adjusted for They conclude more rotational stability in the AM group from this study, which is not possible to conclude from this study	Evaluating the placement of the femoral tunnel, using X ray	AM technique results in a more posterior tunnel and the femoral tunnel is inclined more towards the lateral cortex of the lateral emoral ondyle

Debandi A, 2012, Knee Surg Sports Traum Arth[106]	16	Animal study of porcine knees	8 knees in the AM and in he T perated group	AM vs. TT technique for femoral tunnel drilling	Use of a porcine model There was no follow up on the quality of the placement of the tunnels, if it was anatomic or not Variance in measures using X ray	pivot shift test	The AM operated group showed a better rotational stability than the TT operated group.
Gadikota, 2012, Am J Sports Med[21]	8	Cadaveric study	8 specimen each used for three drilling techniques	Comparing of the AM, TT and outside in technique for femoral tunnel drilling	Performed on older cadavers with a mean age of 56 years. Not comparable to the age of the usual ACL patient. All three techniques was used on each specimen filling the tunnels with cement, introducing a risk of bias	Placement of the femoral tunnel evaluated using 3 dementinal solid modeling software	AM technique captured the center of the native femoral footprint better than the TT technique
Gavriilidis, 2008, Knee[102]	10	Cadaveric study	10 specimen each drilled AM and TT	AM vs. TT technique for femoral tunnel drilling	Unknown age and sex of the cadavers	Placement of the femoral tunnel evaluated by dissection	AM technique captured the center of the native femoral footprint better than the TT technique
Hantes ME, 2009, nee Surg Sports Traum Arth[94]	56	Retrospect ive	56 patients operated from 2002 2004 by a single surgeon. 30 patients in the TT technique and 26 with the AM technique.	Comparing femoral tunnel placement using the TT or the AM technique	Risk of confounding factors not accounted for. No randomization of patients	Femoral tunnel placement evaluated using MRI	The TT technique showed a decreased obliquity
Ilahi, 012, Arthroscopy[104]	115	Retrospect ive comparati ve study	35 patients in the TT group and 80 patients in he M roup.	AM vs. TT technique for femoral tunnel drilling	No randomization Risk of confounding, since no adjustment was made Length was measured directly under surgery, hence not blinked, risk of bias	Femoral tunnel length measured during surgery	Femoral tunnel length was significantly shorter in the AM group compared to the TT group.
Herbort, 2010, Knee Surg Sports Traum Arth[103]	9	Cadaveric study	3 different techniques were tested for femoral tunnel drilling	using different placement of the grafts resembling the AM vs. TT technique for femoral tunnel drilling	Mean age was 65 years which does not represent the usual age for an ACL reconstructed patient.	Knee kinematics/anterior tibial translation using robotic technology, simulation a KT1000 test	The AM AM reconstruction, resembling the anteromedial tunnel placement technique, restored the intact knee kinematics more closely than the other techniques.
Kim MK, 2011, Knee Surg Relat Res[107]	66	Retro spective trial	33 patients in the AM group and TT group. All operated by the same surgeon	AM vs. TT technique for femoral tunnel drilling	Lack of sufficient description of surgical technique for tunnel placement. No blinding of examiner. The examiner was the same who performed the surgery. This can introduce bias. No randomization was done	Lachmna test, pivot shift test, KT2000 and IKDC score.	Better rotational stability in the AM group measured using pivot shift test. No statistical significant difference in IKDC score, Lachman test or KT1000
Lim HC, 2012, Clin Orthop Surg[96]	14	Cadaveric study	7 knees randomly assigned to either AM or TT technique	AM vs. TT technique for femora l unnel drilling	Mean age was 63 years. The rotational test is only an indirect measure of the pivot shift test	Maximal anterior force and anterior force combined with tibial rotation.	No difference was seen in anterior draw AM group had a better stability when anterior tibial draw was combined with tibial rotation.
Mardani kivi M, 2012, Med Sci Monit[108]	124	Cross sectional study Iran	60 patients in the TT group and 64 patients in he M roup.	AM (2009 10) vs. TT (2006 08) technique for femoral tunnel drilling	No matching was performed which gives problems with selection bias and confounding. No randomization, risk of confounding and selection bias. AM operations were done by the same surgeon as the TT operations but 2 years later No blinding of examiner	Lachman, IKDC, return to sport and patient satisfaction	The AM group had a higher satisfaction higher Lysholm and IKDC score and returned more rapid to prior sports activities than the TT group. No difference in achman est.

Miller, 2011, Arthroscopy[105]	20	Cadaveric study	10 knees in each group	AM vs. TT technique for femoral tunnel drilling	Age of cadaveric ranged from 73 to 89 not resembling ACL reconstructed patients No adjustment for confounding factors was made.	Femoral tunnel length	The AM group showed shorter femoral tunnels than the TT group.
Noh JH, 2013, arthroscopy[114]	64	RCT	32 male patient randomized to the AM group and 32 to the TT group	AM vs. TT technique for femoral tunnel drilling using Achilles allograft.	No comparison was made between the actual position of the femoral tunnel and the clinical outcome. Risk of information and selection bias low, due to study design.	Lysholm, Lachman, IKDC, pivot shift test, Tegner score, Telos test, and radiological assessment using MRI scan	No difference in DC, ivot hift est nd Tegner score between the two groups. The AM group had a higher Lysholm score of 3, and the position of the femoral tunnel was more posterior than in the TT group
Pascual Garrido, 2013 Knee Surg Traum Arthr[92]	50	Retrospective case series	25 in the AM group 25 in he T roup	AM vs TT technique for femoral tunnel placement	No randomization can lead to bias No adjustment for confounders Evaluation was done by radiographs not MRI which makes the result imprecise	Obliquity of the femoral tunnel	The AM technique made more oblique tunnels than by the TT technique.
Schairer WW, 2011, Arthroscopy[109]	21	Retro spective cohort study.	9 patients in the TT group 12 patients in the AM group.	AM vs. TT technique for femoral tunnel drilling	No randomization, risk of selection bias. Risk of confounding since the AM group was chosen later in time when the surgeon had more experience and new MR hardware was on the marked, hence different MR hardware was used. Also, no adjustment on age, graft size and gender, which also introduces he risk f onfounding.	Translational and rotational kinematics of the knee measured using MR scans	Better knee rotational stability in the AM operated group compared to the TT operated group.
Silva, 2012, Knee Surg Sprots Traum Arthr[100]	40	Prospective study	20 patients in each group.	AM vs. TT technique for femoral tunnel drilling	No randomization made, risk of bias No sample size calculation was made.	Placement of the femoral tunnel within the ACL footprint, reveled by CT scan	The AM technique placed the femoral tunnel closer to the ACL footprint than did the TT technique.
Sim JA, 2011, Am J Sports Med[110]	8	Cadaveric study	8 cadaveric knees operated with the AM and the TT technique. United states.	AM vs. TT technique for femoral tunnel drilling	Performed on older cadavers with a mean age of 56 years not comparable to the age of the usual ACL patient. The same specimen was used for the different procedures, filling the bone with cement in between operations	Anterior tibial translation	No difference in knee joint laxity
Tudisco C, 2012, Orthopedics[111]	12	Cadaveric study	6 cadaveric knees in the AM and in the TT operated group	AM vs. TT technique for femoral tunnel drilling	Performed on older cadavers with a mean age of 68 years gives some limitations to compare to the normal ACL reconstructed population. The entire lower limb was not used in this study No blinding of examiner	Pivot shift test and KT1000 measurements	No difference in KT1000 measures post operative AM group had better pivot shift test post operatively.
Xu Y, 2011, Arthroscopy[112]	72	Retrospective comparative study	53 patients in the TT group and 19 patients in he M roup.	AM vs. TT technique for femoral tunnel drilling	No randomization, risk of bias arise No adjustment was made for confounding factors	Tunnel enlargement KT 1000 measures IKDS	The AM technique created a more posterior and less vertical graft No difference in IKDS or KT 1000 measures
Yau WP, 2013, Arthrosopy[95]	42	Case control study	21 controls in he T group and 21 cases in the AM group.	AM vs. TT technique for femoral tunnel drilling	No randomization was made, risk of bias No adjustment for potential confounders of the results were made	Clockwise evaluation of the placement of the femoral tunnel using MRI	Using the AM technique led to a better tunnel placement
Zhang Q, 2012, Acta Cir Bras[113]		Lower quality RCT	38 patients in each group.	AM vs. TT technique for femoral tunnel drilling	Lack of sufficient description of methodology (treatment allocation). No blinding of examiner No power analysis, risk of power problem and type II error	KT1000 measurements	No difference in KT1000 measurements.

APPENDIX 4

Knee injury and Osteoarthritis Outcome Score (KOOS), English version LK1.0

KOOS KNEE SURVEY

Today's date: _____/______/______ Date of birth: _____/______/______

Name: ____

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to perform your usual activities.
Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms
These questions should be answered thinking of your knee symptoms during the **last week**.

S1. Do you have swelling in your knee?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S3. Does your knee catch or hang up when moving?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S4. Can you straighten your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

S5. Can you bend your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

Stiffness
The following questions concern the amount of joint stiffness you have experienced during the **last week** in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

S6. How severe is your knee joint stiffness after first wakening in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

S7. How severe is your knee stiffness after sitting, lying or resting **later in the day**?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Pain

P1. How often do you experience knee pain?

Never	Monthly	Weekly	Daily	Always
☐	☐	☐	☐	☐

What amount of knee pain have you experienced the **last week** during the following activities?

P2. Twisting/pivoting on your knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P3. Straightening knee fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P4. Bending knee fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P5. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P6. Going up or down stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P7. At night while in bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P8. Sitting or lying

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P9. Standing upright

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A1. Descending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A2. Ascending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A3. Rising from sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A4. Standing

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A5. Bending to floor/pick up an object

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A6. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A7. Getting in/out of car

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A8. Going shopping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A9. Putting on socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A10. Rising from bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A11. Taking off socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A12. Lying in bed (turning over, maintaining knee position)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A13. Getting in/out of bath

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A14. Sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A15. Getting on/off toilet

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A17. Light domestic duties (cooking, dusting, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, sports and recreational activities

The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the **last week** due to your knee.

SP1. Squatting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP2. Running

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP3. Jumping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP4. Twisting/pivoting on your injured knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP5. Kneeling

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Quality of Life

Q1. How often are you aware of your knee problem?

Never	Monthly	Weekly	Daily	Constantly
☐	☐	☐	☐	☐

Q2. Have you modified your life style to avoid potentially damaging activities to your knee?

Not at all	Mildly	Moderately	Severely	Totally
☐	☐	☐	☐	☐

Q3. How much are you troubled with lack of confidence in your knee?

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

Q4. In general, how much difficulty do you have with your knee?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Thank you very much for completing all the questions in this questionnaire.

APPENDIX 5

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Tegner Activity Scale

Activity Level Before Injury	Current Activity Level	Activity Level Following Surgery if applicable	
◯	◯	◯	Competitive sports Soccer - national and international elite
◯	◯	◯	Competitive sports Soccer, lower divisions Ice hockey Wrestling Gymnastics
◯	◯	◯	Competitive sports Bandy Squash or badminton Athletics (jumping, etc.) Downhill skiing
◯	◯	◯	Competitive sports Tennis Athletics (running) Motorcross, speedway Handball Basketball Recreational sports Soccer Bandy and ice hockey Squash Athletics (jumping) Cross-country track findings both recreational and competitive
◯	◯	◯	Recreational sports Tennis and badminton Handball Basketball Downhill skiing Jogging, at least five times per week
◯	◯	◯	Work Heavy labor (*e.g.*, building, forestry) Competitive sports Cycling Cross-country skiing Recreational sports Jogging on uneven ground at least twice weekly
◯	◯	◯	Work Moderately heavy labor (*e.g.*, truck driving, heavy domestic work) Recreational sports Cycling Cross-country skiing Jogging on even ground at least twice weekly
◯	◯	◯	Work Light labor (*e.g.*, nursing) Competitive and recreational sports Swimming Walking in forest possible
◯	◯	◯	Work Light labor Walking on uneven ground possible but impossible to walk in forest
◯	◯	◯	Work Sedentary work Walking on even ground possible
◯	◯	◯	Sick leave or disability pension because of knee problems

APPENDIX 6-7

Appendix 6: Patient demographics in study III: Comparison of patients registered with pivot shift data one year after surgery and patients not registered with pivot shift data one year after surgery.

Patient characteristics		Registered pivot shift test registered Yes N =4,138 (49%)	No N =4,237(51%)
Gender	Male	2,411 (58%)	2,594 (61%)
	Female	1,727 (42%)	1,643 (39%)
Age at the time of surgery (years)	≤ 20 years	1,161 (28%)	1,051 (25%)
	> 20 years	2,977 (72%)	3,186 (75%)
Technique for femoral tunnel drilling	AM	1,086 (26%)	859 (20%)
	TT	3,052 (74%)	3,378 (80%)
Meniscal treatment	Yes	1,559 (38%)	1,668 (39%)
	No/missing	2,579 (62%)	2,569 (61%)
Cartilage damage	Yes/missing	818 (20%)	935 (22%)
	No	3,320 (80%)	3,302 (78%)
Prior surgery to the knee$	Yes	1,035 (25%)	1,107 (26%)
	No	3,085 (75%)	3,102 (74%)
Sport activity leading to tear$	Yes	3,417(83%)	3,334 (79%)
	No	711 (17%)	885 (21%)
Graft choice£	PT	599 (15%)	463 (12%)
	HT	3,363 (85%)	3,525 (88%)

Abbreviations: PT: atellar endon raft; T: amstring raft; M: nteromedial; T: ranstibial
$: Does not add up to 8,375 due to unregistered data
£: Does not add up to 8,375 due to unregistered data variables and registration of other graft choices.

Appendix 7: Patient demographics in study III: Responders and non responders to the KOOS and Tegner questionnaire one year after surgery.

Patient characteristics		Recorded KOOS and Tegner scores one year after surgery	
		Yes N =2,563 (31%)	No N =5,812(51%)
Gender	Male	1,436 (56%)	3,569 (61%)
	Female	1,127 (44%)	2,243 (39%)
Age at the time of surgery (years)	≤ 20 years	632 (25%)	1,580 (27%)
	> 20 years	1,931 (75%)	4,232 (73%)
Technique for femoral tunnel drilling	AM	658 (26%)	1,287 (22%)
	TT	1,905 (74%)	4,525 (78%)
Meniscal treatment	Yes	953 (37%)	2,274 (39%)
	No/missing	1,161 (63%)	3,538 (61%)
Cartilage damage	Yes/missing	467 (18%)	1,286 (22%)
	No	2,096 (82%)	4,526 (78%)
Prior surgery to the knee$	Yes	642 (25%)	1,500 (26%)
	No	1,906 (75%)	4,281 (74%)
Sport activity leading to tear$	Yes	2,145(84%)	4,606 (80%)
	No	413 (16%)	1,183 (20%)
Graft choice£	PT	411 (17%)	651 (12%)
	HT	2,037 (83%)	4,851 (88%)

Abbreviations: PT: patellar tendon graft; T: hamstring graft; M: nteromedial; T: transtibial;
$: Does not add up to 8,375 due to unregistered data
£: Does not add up to 8,375 due to unregistered data variables and registration of other graft choices.