REVISION ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION – CURRENT EVIDENCE, PREDICTORS AND OUTCOME

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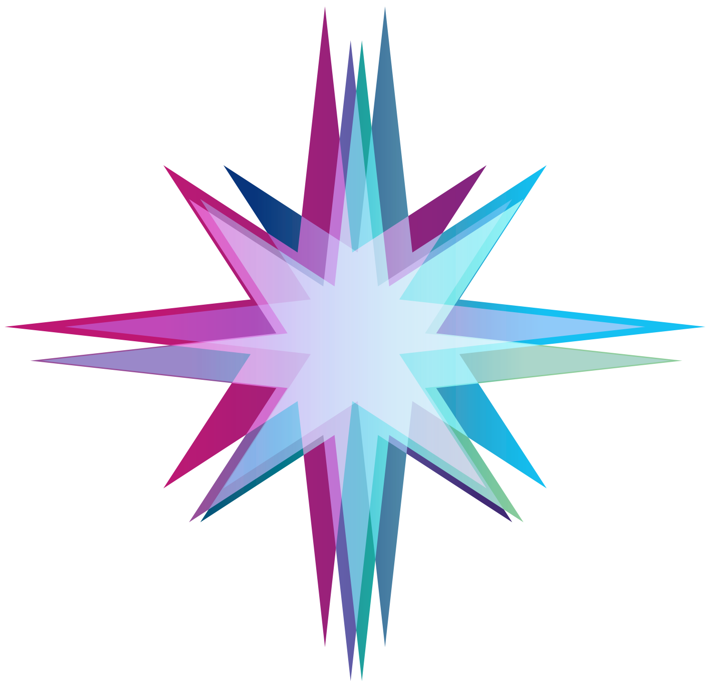

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01 ABSTRACT

Despite extensive research in the field of anterior cruciate ligament (ACL) reconstruction, primary ACL reconstruction failure and a high re-rupture rate remain a problem. Far too many patients experience a second devastating hit – the need to undergo a revision ACL reconstruction. This thesis aims to review current evidence, predictors and outcome related to revision ACL reconstruction. For this purpose, seven studies were conducted and they were stratified into three distinct themes – Current evidence, The impact of a concomitant medial collateral ligament (MCL) injury and Outcome after revision. Registry-based data formed the foundation of this thesis, for which the Swedish national knee ligament registry and a local rehabilitation registry were utilized. Additionally, evidence from all three Scandinavian knee ligament registries was synthesized.

In Theme I, the evidence provided from the Scandinavian knee ligament registries was systematically reviewed to find predictors of ACL revision and to determine the robustness of these predictors by applying the Fragility index. Young age was the strongest and most robust predictor of ACL revision, where an approximately 5-fold increase in the risk of revision was found for adolescents compared with the oldest age group (patients over 35 years of age). Patient sex did not influence the risk of revision. The use of hamstring tendon (HT) autografts was associated with an increased risk of revision compared with patellar tendon (PT) autografts, although a larger HT graft diameter was protective in terms of ACL revision. Notably, there was great variability in current Scandinavian knee ligament registry studies in terms of the statistical robustness of significant predictors of ACL revision. Nearly one third of the analyses had a fragility index of zero, which indicates high statistical fragility and questions the robustness of current predictors of revision reported by the registries.

Theme II explored the impact of a concomitant MCL injury on the risk of ACL revision and how the treatment of these injuries affects outcome. Patients without a concomitant MCL injury ran an approximately 30% lower risk of revision ACL reconstruction compared with patients who had a concomitant MCL injury at primary ACL reconstruction. Specifically, the risk of ACL revision was increased for patients in whom the concomitant MCL injury was treated non-surgically, while patients receiving surgical treatment for an MCL injury did not display any difference in the risk of revision compared with patients without a concomitant MCL injury. The ACL graft choice between HT and PT did not influence the risk of revision in patients undergoing ACL reconstruction with a concomitant non-surgically treated MCL injury. In terms of functional outcome, patients with and without a non-surgically treated MCL injury were able to attain similar outcomes in terms of return to sport, tests of muscle function and patient-reported outcome (PRO) at one year postoperatively. However, only 10% of the patients with a concomitant non-surgically treated MCL injury had returned to their pre-injury level of sport, compared with 26%

of the patients without an MCL injury at one year after ACL reconstruction.

In Theme III, a systematic review of the Scandinavian knee ligament registries found that the PRO was significantly lower after an ACL revision compared with the primary ACL reconstruction, although a few assessments between the 1- to 5-year follow-ups revealed a clinically relevant difference. The largest impairments after a revision compared with a primary ACL reconstruction were found in sport and recreational activities, as well as in quality of life. In Study VII, when a cohort that had undergone both a primary and a revision ACL reconstruction was assessed, there were minor differences between the two occasions according to the one-year PRO. However, the prevalence of cartilage injuries increased significantly at the revision ACL reconstruction (35.1%) compared with the primary ACL reconstruction (18.3%), which could indicate potential for a further deterioration in knee function after ACL revision with time. Clinically relevant predictors of significantly inferior PROs one year after revision ACL reconstruction were the use of an allograft and a concomitant injury to the posterolateral corner at the time of revision ACL reconstruction.

02 SAMMANFATTNING

Trots omfattande forskning kring kirurgisk rekonstruktion av främre korsbandsskador är andelen patienter som behöver genomgå en revisionsoperation fortsatt stor, där anledningarna kan vara exempelvis utebliven inläkning av korsbandsgraftet eller en re-ruptur. Syftet med denna avhandling var att undersöka nuvarande evidens, prediktorer och utfall relaterat till revision av främre korsbandsrekonstruktion. Avhandlingen är indelad i tre övergripande teman – nuvarande evidens, betydelsen av en samtidig inre sidoledbandsskada och utfall efter revision. Grunden i denna avhandling är registerdata från det svenska korsbandsregistret samt ett rehabiliteringsregister. Den innehåller även systematiska översiktsartiklar där data från samtliga skandinaviska korsbandsregister har sammanställts.

Tema I inkluderar systematiska översiktsartiklar av de skandinaviska korsbandsregistren med syfte att finna prediktorer för revisionsoperation samt undersöka den statistiska robustheten av sådana prediktorer genom beräkning av ett fragilitets index. Ung ålder var den mest robusta prediktorn för revisionsoperation, där tonåringar löpte en drygt 5 gånger högre risk för revisionsoperation jämfört med patienter över 35 år. Det var ingen skillnad i risk för revision mellan könen. Revisionsrisken var högre efter korsbandsrekonstruktion med hamstringsenegraft jämfört med patellarsenegraft. Risken för revision minskade dock med ökad diameter av hamstringsenegraftet. Variationen i den statistiska robustheten var stor. Drygt en tredjedel av alla signifikanta prediktorer för revision som presenterats från de skandinaviska korsbandsregistren hade ett fragilitets index på noll, vilket indikerar stor statistisk fragilitet och ifrågasätter robustheten av nuvarande evidens kring prediktorer för revisionsoperation.

Tema II undersökte betydelsen av en samtidig skada på det inre sidoledbandet vid en främre korsbandsrekonstruktion. Risken för revisionsoperation var 30% lägre bland patienter utan en samtidig inre sidoledbandsskada jämfört med de som hade en kombinationsskada av främre korsband och inre sidoledband. Risken för revisionsoperation var specifikt ökad när den inre sidoledbandsskadan behandlades icke-kirurgiskt. Valet av hamstring- eller patellarsenegraft påverkade inte risken för revision hos patienter med en samtidig icke-kirurgiskt behandlad inre sidoledbandsskada. Det var ingen skillnad i patientrapporterat utfall, muskelfunktionstester eller återgång till idrott mellan patienter som genomgått en främre korsbandsrekonstruktion med eller utan en samtidig icke-kirurgisk behandlad inre sidoledbandsskada. Dock hade endast 10% av patienter med en samtidig inre sidoledbandsskada återgått till sin tidigare aktivitetsnivå ett år efter den främre korsbandsrekonstruktionen, vilket kan jämföras med 26% i patientgruppen utan en samtidig inre sidoledbandsskada.

Tema III fann sämre patientrapporterat utfall efter revisionsoperation jämfört med primär korsbandsrekonstruktion, sett till kumulativ evidens från de skandinaviska korsbandsregistren. Störst försämring efter revisionsoperationen sågs i utfall för sport och aktivitet, samt livskvalitet. I Studie VII undersöktes en population begränsad till patienter som genomgått både en primär och en revisionsrekonstruktion av det främre korsbandet, utan att finna några kliniskt relevanta skillnader mellan ingreppen ett år postoperativt. Prevalensen av samtidiga broskskador var högre vid revisionsoperationen (35.1%) jämfört med den primära korsbandsoperationen (18.3%), vilket skulle kunna indikera risk för ytterligare försämring efter revisionsoperationen med längre uppföljningstid. Att använda allograft samt att ha samtidiga skador på posterolaterala strukturer av knäleden vid revisionsoperationen var prediktorer för sämre patientrapporterat utfall.

03 LIST OF PAPERS

This thesis is divided into three themes, which include the following studies referred to by their Roman numerals.

THEME I – CURRENT EVIDENCE

I. Factors associated with additional anterior cruciate ligament reconstruction and register comparison: a systematic review on the Scandinavian knee ligament registers

Svantesson E, Hamrin Senorski E, Baldari A, Ayeni OR, Engebretsen L, Franceschi F, Karlsson J, Samuelsson K

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II. Strength in numbers? The fragility index of studies from the Scandinavian knee ligament registries

Svantesson E, Hamrin Senorski E, Danielsson A, Sundemo D, Westin O, Ayeni OR, Samuelsson K

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THEME II – THE IMPACT OF A CONCOMITANT MEDIAL COLLATERAL LIGAMENT INJURY

III. Increased risk of ACL revision with non-surgical treatment of a concomitant medial collateral ligament injury: a study on 19,457 patients from the Swedish National Knee Ligament Registry

Svantesson E, Hamrin Senorski E, Alentorn-Geli E, Westin O, Sundemo D, Grassi A, Čustović S, Samuelsson K

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IV. Graft Choice for Anterior Cruciate Ligament Reconstruction With a Concomitant Non-surgically Treated Medial Collateral Ligament Injury Does Not Influence the Risk of Revision

Svantesson E, Hamrin Senorski E, Östergaard M, Grassi A, Krupic F, Westin O, Samuelsson K

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V. Only 10% of patients with a concomitant MCL injury return to their preinjury level of sport one year after ACL reconstruction: a matched comparison with isolated ACL reconstruction

Svantesson E, Piussi R, Beischer S, Thomeé C, Samuelsson K, Karlsson J, Thomeé R, Hamrin Senorski E

Submitted manuscript.

THEME III – OUTCOME AFTER REVISION

VI. Factors that affect patient reported outcome after anterior cruciate ligament reconstruction -a systematic review of the Scandinavian knee ligament registers

Hamrin Senorski E, Svantesson E, Baldari A, Ayeni OR, Engebretsen L, Franceschi F, Karlsson J, Samuelsson K

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While modern medicine evolves continuously, evidence-based research methodology remains: how register studies should be interpreted and appreciated.

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Knee Surg Sports Traumatol Arthrosc. 2017 Aug;25(8):2305-2308.

Clinical outcomes after anterior cruciate ligament injury: panther symposium ACL injury clinical outcomes consensus group.

Svantesson E, Hamrin Senorski E, Webster KE, Karlsson J, Diermeier T, Rothrauff BB, Meredith SJ, Rauer T, Irrgang JJ, Spindler KP, Ma CB, Musahl V; Panther Symposium ACL Injury Clinical Outcomes Consensus Group.

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04 ABBREVIATIONS

ACL	Anterior Cruciate Ligament
ACL-RSI	The Anterior Cruciate Ligament – Return to Sport after Injury
ADL	Activities of daily living
AM	Anteromedial
BMI	Body Mass Index
CI	Confidence Interval
DKRR	Danish Knee Ligament Reconstruction Registry
EBM	Evidence-Based Medicine
EQ-5D	European Quality of Life Five Dimensions
HR	Hazard Ratio
HT	Hamstring Tendon
ICRS	International Cartilage Repair Society
IKDC	International Knee Documentation Committee
KOOS	Knee injury and Osteoarthritis Outcome Score
K-SES	Knee Self-efficacy Scale
K-SES$_{18}$	The 18-item version of the Knee Self-efficacy Scale
LCL	Lateral Collateral Ligament
LSI	Limb Symmetry Index
MCL	Medial Collateral Ligament
dMCL	deep Medial Collateral Ligament
sMCL	superficial Medial Collateral Ligament
MRI	Magnetic Resonance Imaging

NKLR	Norwegian Knee Ligament Registry
OA	Osteoarthritis
PASS	Patient Acceptable Symptom State
PCL	Posterior Cruciate Ligament
PL	Posterolateral
PLC	Posterolateral Corner
POL	Posterior Oblique Ligament
PRISMA	The Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported Outcome
PT	Patellar Tendon
QoL	Quality of Life
QT	Quadriceps Tendon
RCT	Randomized Controlled Trial
RTS	Return to Sport
SNKLR	Swedish National Knee Ligament Registry
ST	Semitendinosus
ST-G	Semitendinosus and Gracilis
Tegner	Tegner activity scale
TP	Transportal
TT	Transtibial
VAS	Visual Analogue Scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

05 DEFINITIONS

ACL reconstruction	A reconstruction of the native ACL using a graft.
Bias	A systematic error that influences the results or interpretation of a trial and increases the risk of a deviation from the truth.
Allograft	A graft that originates from a donor of the same species as the recipient.
Autograft	A graft that originates from another location of the same individual's body.
Case-control study	A retrospective study type in which the cases (individuals with a certain disease or outcome) are compared with controls (individuals without the disease or outcome) to determine whether prior exposure is associated with the disease or the outcome of interest.
Case series	A study reporting the outcome for one group or series of individuals that have usually received the same intervention.
Cohort study	An observational study in which a cohort is followed over time. The outcomes of interest are compared between subsets of the cohort to study whether exposure to an intervention, for example, is associated with outcome.
Confidence interval	A measurement of uncertainty in a statistical analysis, representing a range where the true value is expected to lie. Usually, a 95% CI is given for a study result, meaning that the true value could be expected to lie within this interval with 95% certainty.
Confounder	A factor that is independently associated with both the intervention or exposure and the outcome.
Content validity	The extent to which a test or outcome measurement truly measures what it is intended to measure.
External validity	Refers to the generalizability of a study result, i.e. the extent to which the results could be applied to another population than that studied.
Fragility Index	A calculation that could be performed for two-arm analyses where a significant difference has been found. The fragility index describes the minimum number of individuals in the study arm with the fewest events that are required to change the outcome from a non-event to an event in order to change the result from significant to non-significant.
Hazard ratio	The ratio of the hazard rates between two groups in a survival analysis. The hazard ratio represents the probability of an event occurring per a unit of time in one study group divided by that probability in the other study group.
Internal validity	The extent to which a study is designed and conducted to minimize the risk of bias in the study result.
Intraclass coefficient (ICC)	A coefficient of reliability. The ICC assesses the consistency of multiple measurements, for example, a test-retest of a PRO or the repeatability of measurements between multiple examiners.
Limb symmetry index	The result for the injured leg in relation to the uninjured leg. The ratio between the legs is expressed as a percentage (injured/uninjured x 100).

Multivariable model	A statistical model where the relationship between multiple independent variables and the outcome (or dependent variable) is assessed.
Null hypothesis	The hypothesis that no difference will exist between the study groups.
Odds	Describes the probability of an event in one group. Odds are a ratio of events to non-events.
Odds ratio	The ratio of the odds for an event between two groups.
P-value	The probability of obtaining a similar or more extreme result than the observed result, if the null hypothesis is true.
Power	The probability of finding a significant difference in the given outcome if a true difference truly exists. It is calculated as 1 minus the probability of a type-II error.
Predictor	A variable that is associated with an increased risk of a given outcome.
Randomized controlled trial	The study groups are randomly allocated to a treatment or intervention and are followed prospectively. RCTs are regarded as level 1 evidence and are the gold standard to determine the efficacy of a treatment.
Regression model	Statistical modeling of the association between one or more independent variables and one or more dependent variables.
Relative risk	A ratio of the risk of an event in one group compared with the risk of an event in another group.
Reliability	The extent to which a measurement or observation yields consistent results
Revision ACL reconstruction	The event of undergoing a new ACL reconstruction to replace a previous ACL reconstruction.
Scandinavian knee ligament registries	Refers collectively to the national knee ligament registries established in Denmark, Norway and Sweden.
Systematic review	A systematic search of the literature to answer a predefined research question by summarizing the results of eligible studies. A systematic review may or may not include a meta-analysis of the data.
Survival analysis	A statistical approach that is based on a time-to-event analysis. The survival analysis takes account of the expected duration of time until an event occurs, for example, the event of ACL revision. Cox regression modeling is commonly used in conjunction with a survival analysis, where independent variables could be entered in the model to study its impact on the risk of an event.
Type I error	A false rejection of the null hypothesis, i.e. concluding that there is a true difference or a treatment effect for an intervention when in fact there is not.
Type II error	A failure to reject a false null hypothesis, i.e. concluding that there is no difference or no treatment effect for an intervention when in fact there is.
Univariable analysis	A statistical model where the relationship between only one independent variable and the outcome (or dependent variable) is assessed.

06

INTRODUCTION

6.1 ANATOMY AND BIOMECHANICS OF THE KNEE JOINT

6.1.1 The knee joint

The knee joint is the largest and one of the most complex joints in the body. Three articulations make up the knee joint – the medial femorotibial, the lateral femorotibial and the patellofemoral.[104] The construction must provide smooth movement, while also providing stability in the lower extremities and withstanding the large loads applied to the joint.

The femorotibial joints consist of the articulations between the convex femoral condyles and the flattened tibial plateaus on the medial and lateral sides respectively. The medial femoral condyle has a larger radius compared with the lateral, but its curvature is less than that of the lateral femoral condyle.[80] The bony morphology creates a biomechanical pattern where the center of knee rotation changes with the degree of knee joint flexion.[165] During knee range of motion, there are elements of both rotation and sliding of the femoral condyles on the tibial plateau. Femoral rotation in the transverse plane occurs because of the larger curvature of the lateral condyle. Since the lateral compartment reaches full extension earlier than the medial, the femur rotates while the medial compartment continues to extend.[80, 104]

The patellofemoral joint is formed by the largest sesamoid bone in the body, the patella, and the femoral trochlea, and plays a particular role in the extensor mechanism of the knee joint.[80] The patella is embedded in the quadriceps tendon, which is formed by the confluence of the vastus musculature. At the level of the patella, the quadriceps tendon shifts to become the patellar tendon, which is a direct extension of the quadriceps tendon attaching at the tibial tubercle. This construction increases the moment arm of the force generated by the quadriceps musculature, thereby reducing the force needed for knee joint extension.[71]

The capsule surrounding the knee joint provides stability and produces the synovial fluid which contains important nutrients for the intra-articular structures.[214] The stabilizing properties of the capsule are due to the distinct collagen fibers of the external capsular layer and the proprioceptive reflex circuits for active muscle stabilization, provided by the free nerve endings in the capsule (Figure 1).[214]

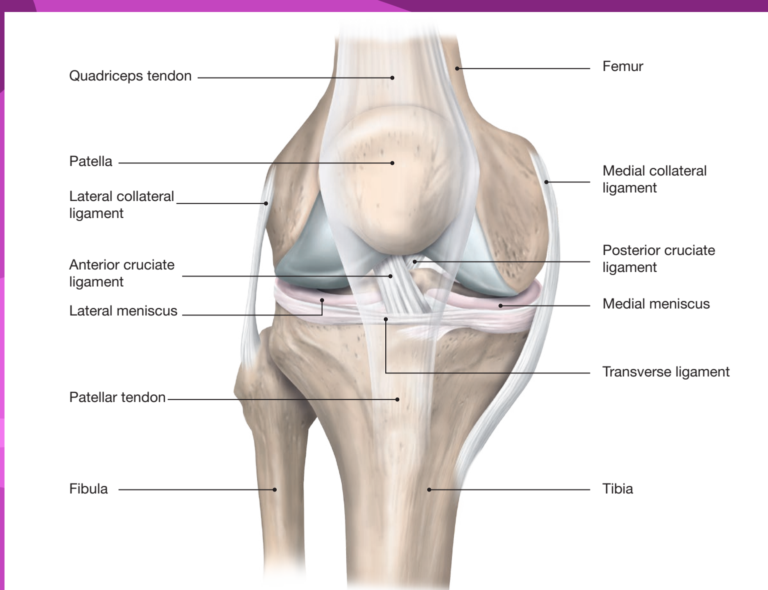


FIGURE 1
The knee joint anatomy.

6.1.2 The menisci

The two menisci are located between the femur and tibia in the lateral and medial compartment respectively. The architecture of the menisci, with a thick external margin that gradually tapers to a thin margin in the central part of the joint, creates a socket for the convex femoral condyles for stable articulation with the tibial plateaus.[80] The anterior and posterior horns of the menisci are attached to the tibial plateau and multiple ligaments connect the menisci to each other (Figure 2).[70, 104] The firm attachment of the medial meniscus to the deep fibers of the MCL puts it at particular risk of injury when shearing and rotational forces are applied to the knee joint.[80] The lateral meniscus, on the other hand, is far more mobile, since the peripheral attachment is only to the capsule. From the external to the internal part of the meniscus, the neurovascular supply gradually decreases and only 10-25% of the adult peripheral meniscus is vascularized (Figure 3).[18] This explains why the menisci have limited spontaneous healing capacity, especially in the central zone. In addition to providing knee joint stability,[183, 248] the menisci are essential for shock absorption and load transmission within the knee joint.[1] The menisci also play a role in the lubrication of the knee joint and provide nutrients to the articular cartilage.[70]

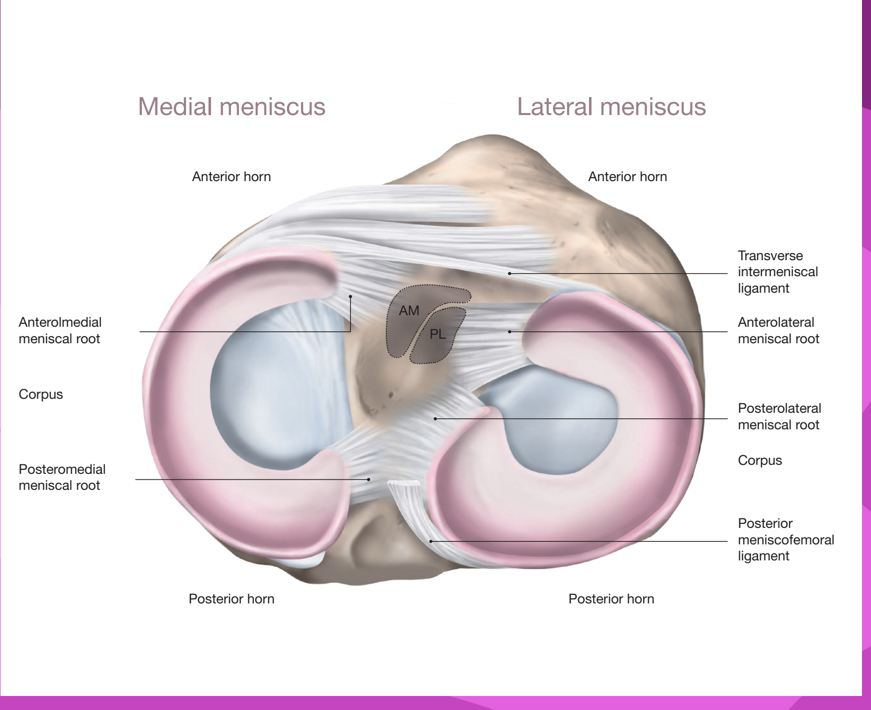


FIGURE 2
The anatomy of the menisci on the tibial plateaus. The insertion sites for the anteromedial (AM) and posterolateral (PL) bundles of the anterior cruciate ligament on the tibia are marked.

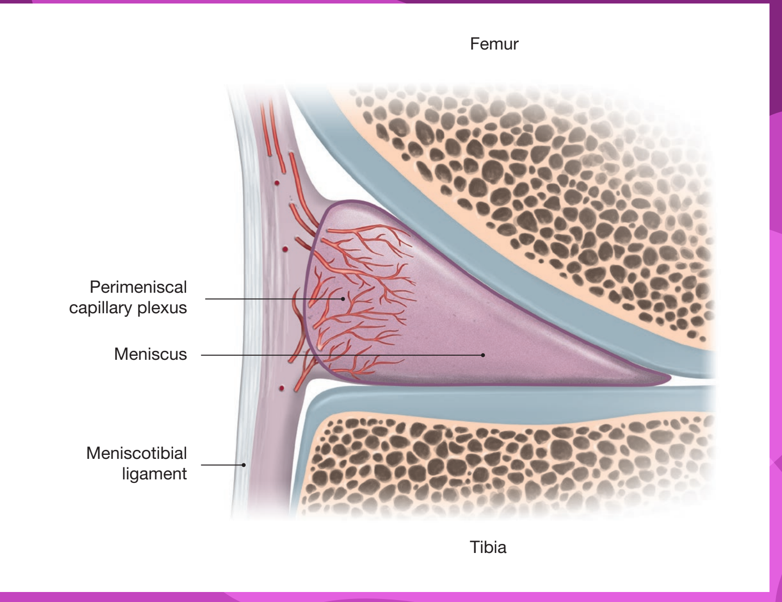


FIGURE 3
The external part of the meniscus is thick and vascularized.

6.1.3 The articular cartilage

The articular cartilage envelops the bony surfaces within the knee joint to minimize friction and provide smooth articulation. Another important function is to facilitate load transmission in synergy with the menisci. To maintain these properties, the cartilage is dependent on the production of proteoglycans by chondrocytes and the interaction with the synovial fluid for the diffusion of nutrients and lubrication.[37] The proteoglycans are complex protein structures with coupled glycosaminoglycan chains. These molecules have a great capacity to bind water, which is an important reason for the shock-absorbing properties of the cartilage.[224]

6.1.4 Ligaments of the knee joint

There are four main ligaments of the knee joint – two are extra-articular and two are intra-articular. The two collateral ligaments are extra-articular structures and are located on each side of the knee joint. The cruciate ligaments have been named after their intra-articular relationship, with the appearance of forming a cross in the center of the knee joint.

THE ANTERIOR CRUCIATE LIGAMENT

From its origin at the posteromedial aspect of the lateral femoral condyle, the ACL runs obliquely through the knee joint and inserts anteriorly on the medial tibia.[286] It has been reported that the length of the ACL is in mean 32 mm (ranging from 22 to 41 mm), with a width ranging from 7 to 12 mm.[286] The ligament consists of two separate bundles named after the location of their tibial insertion site – the posterolateral and the anteromedial bundles. Two bony landmarks mark the margins of the femoral origin – the intercondylar ridge and the bifurcate ridge.[66] The intercondylar ridge marks the anterior border of the footprint and no fibers insert antero-superiorly to this ridge. Recent descriptions of the femoral insertion suggest that the fibers that originate immediately posterior and parallel to the intercondylar ridge are predominantly load-bearing fibers. They have been described as the direct fibers, while the fibers covering the remaining footprint are indirect fibers that "fan out" from the direct fibers but have less strength and load-bearing function.[186] Perpendicular to the intercondylar ridge is the bifurcate ridge which divides the femoral footprint in two, forming the insertional sites for the AM and the PL bundle respectively. The area of the femoral footprint is approximately 3.5 times larger than the cross-sectional area of the ACL midsubstance.[98] The idea of a two-bundle anatomy of the ACL has, however, been contradicted by others, who have instead suggested that the ACL is a flat, ribbon-like structure with a flat insertion site at the intercondylar ridge, which is in continuity with the posterior femoral cortex.[234, 235] Following the theory of a ribbon-like structure, the macroscopic appearance of the ACL as two separate bundles has been explained as an illusion caused by the twisting of the ligament when the knee moves from extension to flexion.[235]

The tibial insertion site is approximately 20% larger than the femoral[98] and is located between the medial and lateral tibial spine. The tibial attachment has traditionally been described as oval to triangular in shape, although the descriptions of a flat, ribbon-like ACL have questioned this and instead suggest that the site is C-shaped and that the center of the insertional site is confluent with the anterolateral meniscal root.[143, 232] Additionally, it has been shown that the size of the insertion sites for the ACL varies considerably between individuals, with the tibial insertion site length ranging from 12-22 mm.[129]

The ACL has the appearance of an hourglass-shaped ligament that twists with knee range of motion.[117, 286] The femoral footprint is oriented horizontally in knee flexion and the AM bundle then originates from the most posterior part of the femoral footprint, while the PL bundle originates anteriorly. As the knee is extended, the relative positions change and the AM bundle fibers insert at the most proximal part and the PL originates distally in the extended position. Depending on the degree of knee joint flexion, the variable tension pattern between the bundles provides a synergistic relationship to ensure both anteroposterior and rotatory stability during full range of motion (Figure 4). The AM bundle is approximately 35 mm long and the PL bundle measures about half that length. The AM bundle is more vertically oriented compared with the PL bundle, which means that it has a greater ability to provide anteroposterior stability, while the PL bundle is most important for rotatory stability due to a more horizontal orientation. Knee extension tightens the PL bundle, which makes it primarily responsible for stability in knee extension. On the other hand, the AM bundle is taut in flexion and the majority of the stabilizing function is therefore provided by the AM bundle in knee flexion.[38]

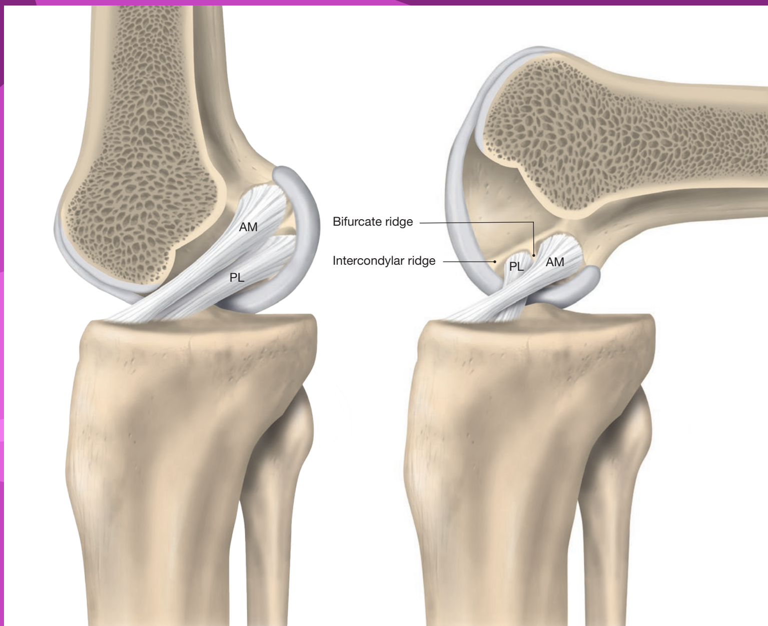


FIGURE 4

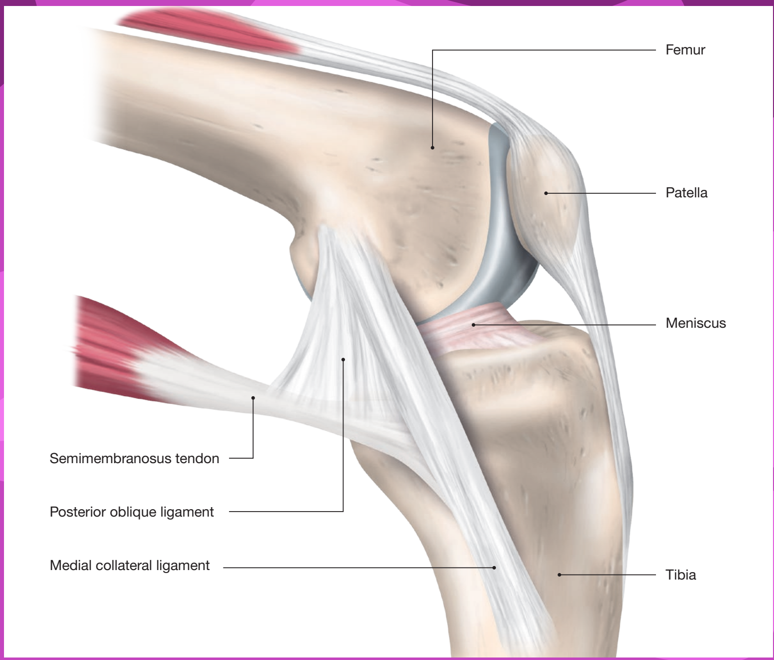
The relative positions of the anteromedial (AM) and posterolateral (PL) bundles change with knee range of motion. The intercondylar ridge marks the anterior border of the footprint and the bifurcate ridge separates the insertion sites for each bundle.

THE POSTERIOR CRUCIATE LIGAMENT

The PCL is the largest intra-articular knee ligament.[262] The ligament originates at the lateral aspect of the medial femoral condyle and inserts into a facet on the posterior aspect of the tibia, approximately one centimeter distal to the joint line. Like the ACL, the PCL is divided into two bundles – one anterolateral and one posteromedial bundle which function in a synergistic manner to provide stability during full knee range of motion.[262] Specifically, the primary function of the PCL is to prevent the excessive posterior translation of the tibia and to restrain rotatory forces.[138]

THE MEDIAL COLLATERAL LIGAMENT

The MCL could be viewed as a ligament complex comprising three distinct structures: the sMCL, the dMCL and the POL.[141] The sMCL is the largest ligamentous structure over the medial aspect of the knee. While some studies have reported that the sMCL originates posterior to the medial femoral epicondyle,[141, 161] there have also been findings of the medial epicondyle located in the center of the sMCL origin.[275] Fibers of the sMCL have been reported to attach both anteriorly and posteriorly to the medial epicondyle, with an equal distance to the center of origin.[275] The sMCL inserts at two separate sites on the tibia, in close relation to the semimembranosus tendon and the pes anserinus (Figure 5).[141] Directly under the sMCL is the dMCL, which also consists of components from the meniscofemoral and meniscotibial ligaments.[141] The dMCL originates slightly distally and posteriorly to the medial femoral epicondyle. From here, the ligament runs dis-



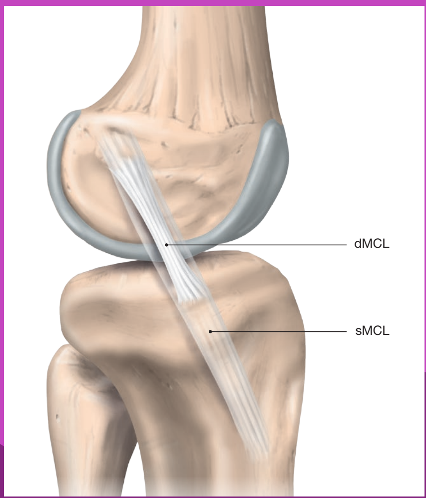


FIGURE 5
The anatomy of the medial side of the knee joint.

FIGURE 6
The deep medial collateral ligament (dMCL) is located under the superficial medial collateral ligament (sMCL) and runs in an oblique manner.

tally in an oblique manner in an antero-distal direction. The attachment anteromedially on the tibia is wider than the femoral origin, giving rise to the fan-like shape of the dMCL (Figure 6).[275] The POL is a fibrous extension of the semimembranosus that blends with the posteromedial joint capsule and thereby reinforces this part of the joint capsule.[141]

The primary role of the MCL is to function as a valgus constraint. However, the MCL complex also functions as a restraint to anteroposterior motion and is a stabilizer for internal and external tibial rotation.[91, 161, 241] The sMCL is the most important valgus constraint, while the fiber orientation of the dMCL should make it an ideal structure to resist external rotation.[275] In the extended knee, the dMCL has been shown to be the primary restraint to tibial external rotation.[20] However, controversies exist relating to the role of the MCL complex and the phenomenon of anteromedial rotatory instability in the ACL-deficient knee, since there have also been reports that the sMCL is most important for counteracting anteromedial rotatory instability, with little effect by the dMCL on rotatory stability.[270] With regard to the POL, it has been established as an important stabilizer in full or near-full knee extension for valgus loads, posterior translation and internal rotation.[270, 275]

THE LATERAL COLLATERAL LIGAMENT AND THE POSTEROLATERAL CORNER

The most important stabilizing structures of the PLC are the popliteus tendon, the popliteo-fibular ligament, the LCL and the posterolateral capsule.[228, 240] The LCL originates slightly proximally and posteriorly to the lateral femoral epicondyle and attaches on the lateral aspect of the fibular head. In knee extension, the LCL is taut, while flexion of the knee slackens the ligament. The LCL is a primary varus stabilizer, while it also limits the external tibial rotation of the flexed knee.[34, 142] The popliteus muscle arises from the lateral aspect of the femur and runs obliquely in a posterior and distal direction to insert at the posteromedial tibia. The muscle is thus located on the posterior aspect of the knee, also known as the popliteal fossa. The muscle then becomes tendon in the lateral third of the popliteal fossa. From there, the tendon runs partially intra-articularly and rounds the posterior aspect of the lateral femoral condyle to its insertion at the popliteal sulcus. The musculotendinous junction of the popliteus muscle is the origin of the popliteo-fibular ligament which consists of two bundles, one anterior and one posterior (Figure 7).[169] Injuries to the lateral ligaments of the knee joint are not as common as injuries to the other ligaments of the knee, which is likely the reason why these injuries are not seldom overlooked. Moreover, a PLC injury rarely occurs in isolation but is often associated with injury to the ACL or PCL and neurovascular structures.[35, 48, 76, 145] The relationship between the stabilizing properties of the ACL and PLC is important and significantly increased forces act on the ACL in the event of PLC deficiency.[144]

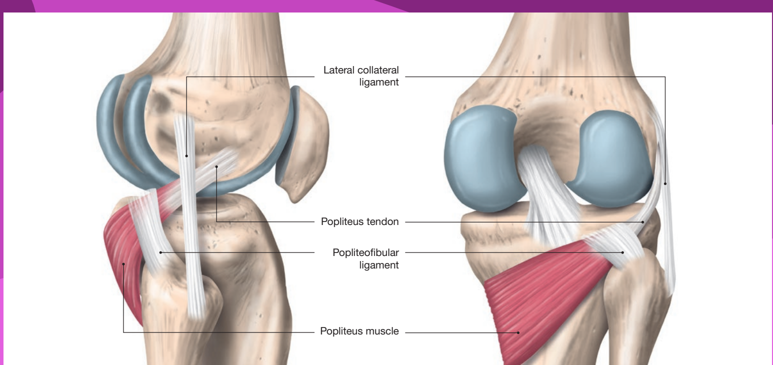


FIGURE 7
The posterolateral corner of the knee joint.

6.2 ANTERIOR CRUCIATE LIGAMENT INJURY

6.2.1 Epidemiology

Injury to the ACL is one of the most common orthopedic and sport-related injuries worldwide and it most commonly affects the young and athletic population. The incidence has been reported to be 80 per 100,000 inhabitants/year in Sweden.[189] Approximately 4,000 primary ACL reconstructions are performed annually in Sweden,[281] indicating that around 50% of the ACL-injured patients choose to undergo non-surgical treatment.

The mean age for undergoing primary ACL reconstruction in Sweden is 28 years for both females and males, while the mean age for undergoing revision ACL reconstruction is 25 years for females and 28 years for males. Of the patients registered in the SNKLR, 45% are females.[281] In international ACL registries, patients under the age of 30 years account for between 58% and 66% of all primary ACL reconstructions.[209]

6.2.2 Etiology

An ACL injury occurs in non-contact situations in the vast majority of cases. The mechanism of injury usually involves movements such as pivoting, cutting or deceleration maneuvers. Soccer is the most common activity at the time of ACL injury in Sweden (29% of ACL injuries for females and 49% for males), followed by downhill skiing (females 29% and males 10%).[281] Controversy exists in terms of the exact mechanism of injury and various patterns involving combinations of factors such as knee extension, rotation, anterior tibial translation and valgus collapse have been proposed. According to video analysis and visual inspection, valgus collapse in combination with external tibial rotation are common features of the ACL injury mechanism.[29, 132, 211] Increased lateral trunk motion, a flatfoot position at initial ground contact and increased hip flexion have also been observed as factors that differ when an athlete performs the same movement without sustaining an ACL injury.[29, 132, 211]

6.2.3 Risk factors

Young age, female sex and sports participation are among the most evident risk factors for sustaining an ACL injury.[103] Females run an approximately three times higher risk of sustaining an ACL injury compared with males[210, 243] and ACL injuries peak in the late teenage years, where earlier competitive and more intense sports participation in the adolescent population are associated with an increased risk.[137] Interestingly, the differences between the sexes start to appear after puberty.[14, 103] This supports the belief that the hormonal milieu may affect the risk of ACL injury.[101] Other factors relate to neuromuscular control, biomechanical factors, anatomy and knee joint laxity.[103] Generalized joint hypermobility is a risk factor for ACL injury[242] and may be one factor in the heritable component of the risk of sustaining an ACL injury.[30, 69] There are also knee morphology factors, such as increased tibial slope, that could influence the risk of ACL injury.[23]

6.2.4 Concomitant injuries

A review of patients presenting with acute hemarthrosis revealed that only 12% of all ACL injuries were isolated.[195] When the restraining capacity of the ACL suddenly disappears at the moment of rupture, the direction of the underlying forces continues to act on concomitant structures in the knee joint.

MENISCAL INJURIES

Meniscal injuries are common with an ACL rupture and are present in up to 40-60% of all ACL injuries.[190, 195] From a long-term perspective, combined ACL and meniscal tears result in a higher prevalence of OA compared with isolated ACL injuries.[39, 194] There is a variety of injury patterns for the menisci and, in recent years, there has been an increased emphasis on ramp and root lesions, since failure to address these injuries could result in persistent laxity.[178, 231] A root lesion is defined as a radial tear of the meniscus within 1 cm of its posterior insertion or an avulsion of the posterior insertion site, which could lead to the inability of the meniscus to convert axial loads into transverse hoop stresses.[172] This in turn increases the contact pressures between the femur and tibia, which poses a risk for degenerative changes in the knee joint and, in fact, emulates a state of meniscectomy.[139, 172] Lateral meniscus root lesions are more frequently associated with traumatic ACL ruptures than medial[168] and the repair of lateral root tears appears to play an important role in restoring stability in the ACL-reconstructed knee.[249] The term "ramp lesion" refers to the separation of the posterior horn of the medial meniscus from the posteromedial capsule and a recent study reported that there was a strong association between ramp lesions and injury to the MCL. Specifically, 93.7% of the patients with a ramp lesion had an injury to the sMCL.[274] The presence of a ramp lesion increased the odds of having a simultaneous sMCL injury by a factor of 13 and the odds of having a simultaneous injury to the dMCL by a factor of 5.[274] Since ramp lesions could contribute to anteromedial rotatory instability,[52, 178] and could be difficult to detect,[250] careful inspection of the knee joint during ACL reconstruction is important. There is consensus that the menisci should be repaired whenever possible, due to the high risk of OA following meniscectomy[157] and the importance of meniscal integrity for knee joint function and stability.

MEDIAL COLLATERAL LIGAMENT INJURIES

An isolated MCL injury is the most commonly sustained knee ligament injury[12, 155] and the combination of ACL, MCL and meniscus injury was acknowledged as the "the unhappy triad" back in the 1960s.[193] A concomitant MCL injury has been reported in approximately 20-40% of all ACL injuries[195, 284] and therefore represents the most commonly injured knee ligament concurrently with an ACL injury. In contrast to isolated MCL injuries, which usually involve contact trauma with a valgus-directed force applied to the lower leg,[155] an MCL injury in conjunction with an ACL injury most frequently occurs in non-contact situations with combined rotational and valgus forces. The mechanism of combined ACL and MCL injury should logically involve an anterior or external rotatory subluxation of the medial tibial plateau. This mechanism of injury could also cause a ramp lesion when the medial femoral condyle moves posteriorly, rides over the medial meniscus and ruptures the posteromedial capsule. This mechanism of injury is supported by studies reporting a high proportion of bone edemas located at the posterior medial tibial plateau and the medial femoral condyle in association with a ramp lesion.[51, 133, 274]

Although an ACL rupture is generally thought to occur after initial ground contact,[126] there has been speculation that an ACL rupture may actually occur in the flight before landing as a result of strong quadriceps contraction.[50] The mean strain to failure of the ACL has been reported to range between 15.0% and 17.9%,[21] while it is 23.0% for the MCL.[122] The dMCL is, however, weaker than the sMCL and therefore ruptures prior to the sMCL.[121] A recent study evaluated the strain profiles of the ACL and MCL in simulated landings and analyzed the changes in strain before initial ground contact and after initial contact.[21] The study grouped the cadaveric specimens in different risk profile groups for ACL injury, where higher risk groups had higher knee abduction moment and internal tibial torque applied to the knee joint. Interestingly, a summation of the ligament strain before initial contact, after initial contact and the baseline ligament strain resulted in strains high enough to rupture the ACL, while the sum of MCL strain was substantially lower than the ultimate failure strain for the MCL.[21] It thus appears that the ACL is more vulnerable to injury during valgus loads in landing compared with the MCL and that higher loads and other types of injury mechanism are required for combined ACL and MCL injuries.

The clinical assessment of an MCL injury is graded in three severity grades, depending on the medial side joint opening when applying valgus stress. A grade I-II MCL injury is generally thought to be a sprain or partial rupture of the superficial fibers, while a grade III (>10 mm) joint opening could indicate a total rupture of the MCL.

CARTILAGE INJURIES

Sustaining a concomitant injury to the articular cartilage at the time of ACL injury poses a severe risk for future knee impairment and could contribute to the development of post-traumatic OA.[120] An epidemiologic study of six large ACL registries reported that the proportion of patients with a concurrent cartilage injury at the time of ACL reconstruction ranged from 20-33%.[209] According to data from the Norwegian and Swedish national knee ligament registries, 20.2% of ACL-injured patients had partial-thickness cartilage injuries, while full-thickness cartilage injuries were observed in 6.4%.[223] One of the most commonly used classification systems for cartilage injuries is the International Cartilage Repair Society (ICRS). This system uses grading from 0 to 4 based on lesion depth, where 0 is normal cartilage without notable defect, 1-2 involve less than 50% and 3-4 involve more than 50% of the cartilage thickness.[32]

6.3 ACL INJURY TREATMENT

A completely ruptured ACL has no potential to heal because of its location in the intra-articular milieu. The results of primary repair of the ACL have been discouraging in a long-term perspective for the majority of patients.[191, 252] Innovative solutions using intraligamentary stabilization and scaffolds used for the primary repair of the ACL have been proposed[6] and it is possible that this could be an option for a subset of patients with further evaluation of the technique.[182] Nevertheless, the current gold standard for restoring the integrity of a ruptured ACL is to perform a ligament reconstruction. This is, however, not equivalent to claiming that an ACL reconstruction is necessary for all patients, since both reconstructive and non-reconstructive treatment can result in satisfactory patient-reported knee function, even among young and active patients.[73, 74, 215] The few RCTs on the topic have, however, shown that a large proportion of patients who were primarily treated non-surgically subsequently opted for an ACL reconstruction[73, 74, 215] and that knee laxity was greater among the non-surgically treated patients compared with the surgically treated patients at a 2- to 5-year follow-up.[73, 74] Generally, the indication for ACL reconstruction becomes stronger with increased activity level, knee joint instability and concomitant injuries. The term "coper" is commonly used for patients that achieve satisfactory knee function and stability without surgical treatment and a period of rehabilitation after injury might elucidate whether or not an ACL reconstruction should be performed.[68, 254]

6.3.1 ACL reconstruction techniques

The arthroscopic technique for ACL reconstruction was introduced during the 1980s and is a hallmark for modern ACL reconstruction.[47] In the early arthroscopic era, isometric and non-anatomic graft placement was performed when the TT technique started to become popular. With the TT technique, the femoral tunnel is drilled via the tibial tunnel, which frequently results in the malposition of the femoral tunnel due to limited visualization of the native femoral footprint and limited room to maneuver the angle of drilling through the tibial tunnel. A non-anatomic placement of the tunnels results in a high, vertical graft placement, giving the graft limited capability to restrain rotatory forces.[128] The establishment of the TP technique facilitated the performance of anatomic ACL reconstruction, since the technique enables the direct visualization of the native insertion sites and independent tunnel drilling. In the conventional TP technique, one anterolateral portal is used as the viewing portal and one anteromedial portal is used as the working portal through which the femoral tunnel drilling is performed.[42] Because of this, the nomenclature for the TP drilling technique has commonly been used interchangeably with "the AM drilling technique" in the literature. It should, however, be distinguished from the use of an accessory anteromedial portal, which is a third portal that even further facilitates anatomic ACL reconstruction by improving the visualization of the native femoral footprint.[15, 42, 260] Figure 8 illustrates the TT and the TP/AM arthroscopic techniques.

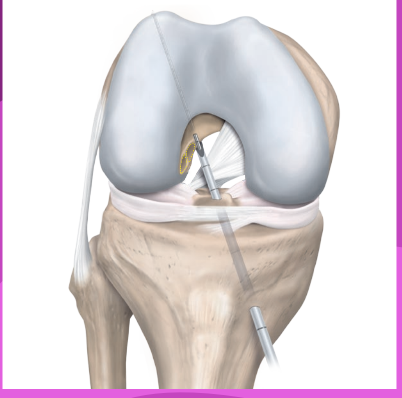


FIGURE 8a
The transtibial technique in which the femoral tunnel is drilled via the tibial tunnel.

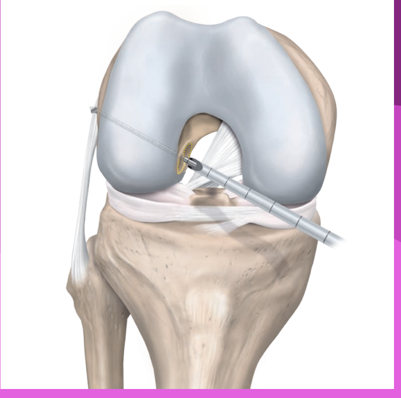


FIGURE 8b
The transportal or anteromedial technique in which the femoral tunnel is drilled via an independent portal. The yellow lines mark the femoral footprint of the anterior cruciate ligament.

6.3.2 Anatomic ACL reconstruction

An anatomic ACL reconstruction aims to replicate the native femoral and tibial insertion anatomy, restore the function and tension pattern of both native ACL bundles and individualize the reconstruction according to each patient's unique anatomy and injury.[105, 119] An anatomic graft placement better recreates the physiologic restraining properties of the ACL[119] and most surgeons today agree that an ACL reconstruction should aim to restore native anatomy, even if there is less agreement on how this is optimally achieved. The TP/AM technique results in the superior restoration of both anteroposterior and rotatory stability compared with the TT technique[46, 154, 219] and offers better visualization and flexibility when it comes to positioning the bone tunnels. This has led many surgeons to abandon the TT technique, although others argue that anatomic graft placement could still be achieved with the TT technique and advocate the use of it.

The double-bundle ACL reconstruction is another area that should be mentioned with respect to anatomic ACL reconstruction. The double-bundle ACL reconstruction technique was developed with the aim of better mimicking the native anatomy of two bundles. In the double-bundle ACL reconstruction, two bone tunnels are drilled in the femur and tibia respectively. Two separate grafts, one AM bundle and one PL bundle, are subsequently inserted. The idea of two bundles for ACL reconstruction rapidly attracted interest because of the closer resemblance to the native anatomy. However, the current evidence suggests that there are likely no major differences in outcome between single- and double-bundle ACL reconstructions in patients with an average ACL insertion size.[113, 251] A satisfactory outcome could therefore be achieved by either a single- or a double-bundle ACL reconstruction in the majority of patients[167] and the decision-making relating to the technique should be individualized while considering the pros and cons of either technique.

6.3.3 Graft choice

For a long time, the PT autograft was the gold standard graft choice for ACL reconstruction, but its use has declined in Sweden over the past decade, whereas it is still frequently used in Norway and the US, for example.[209] The main advantages of the PT are the bone-blocks at both ends, facilitating ingrowth, and the predictable size of the tendon which can be assessed on preoperative MRI. The main disadvantage is the risk of donor-site morbidity causing anterior knee pain.[36] The HT autograft has been shown to have significantly less donor-site morbidity compared with the PT autograft and it is currently the most frequently used graft for primary ACL reconstruction in Sweden.[281] The HT autograft can include the ST tendon alone or be complemented by the additional harvesting of the gracilis tendon, depending on the necessary graft diameter. The HT grafts can be constructed in many ways, using different folding and suture techniques, thus displaying greater variability compared with PT grafts. The disadvantages of using HT autografts include tissue-to-bone healing, which takes longer compared with PT bone-to-bone healing, and the ligamentization process is likely also longer for the HT compared with the PT (around 12-24 months compared with 6-12 months).[201] Furthermore, there is a risk of hamstring muscle strength deficits caused by the HT tendon harvest.[127]

Recently, interest in using QT autografts has increased, with comparable outcomes compared with the PT and HT autograft.[177] The QT autograft can be harvested with and without a bone block and offers a larger cross-sectional area than the PT autograft.[26, 109, 230] The harvest of the QT tendon also causes less donor-site pain compared with PT tendon harvest.[177] Additionally, it has been shown that the postharvest tensile strength of the remaining part of the QT is higher than the strength of the PT after harvest. Thus, the harvest of QT may superiorly preserve extensor mechanism strength compared with PT.[2]

The choice of allograft avoids problems related to donor-site morbidity in terms of muscle deficits and pain, which may facilitate part of the rehabilitation and recovery.[130] On the other hand, its use is associated with higher costs, a prolonged healing time and an increased risk of re-rupture.[108] Specifically, irradiated allografts run a greater risk of failure since the irradiation affects the structural properties of the fibers and reduces the mechanical strength of the tissue.[159] Interestingly, non-irradiated allografts have been found to produce a similar outcome compared with autografts.[87] However, because of the increased rates of graft failure observed for allografts compared with autografts and the prolonged incorporation time, the use of allografts is questionable in young, active patients.[108] The primary indications for allografts are instead in the population with less knee-demanding activity, revision cases and in multiligament injuries.[45, 108]

6.3.4 Graft fixation

The graft needs to be properly fixated in the femoral and tibial tunnel to allow for complete graft incorporation and prevent the migration of the graft. The different methods of graft fixation can be broadly divided into four categories – cortical suspensory fixation, adjustable cortical suspensory fixation, intratunnel transfixation and interference screws. With regard to the effect of graft fixation on outcome after ACL reconstruction, there is to date no firm evidence in the literature in favor of one optimal graft fixation technique compared with another.[107, 110, 115, 264]

6.4 MANAGEMENT OF COMBINED ACL AND MCL INJURIES

The MCL has good healing potential and successful outcomes after the non-surgical treatment of isolated MCL injuries have led many surgeons to advocate this treatment also in the setting of an ACL rupture, with early or delayed ACL reconstruction.[205, 272] Cadaveric and biomechanical studies have, however, raised concerns that increased forces are applied to the newly reconstructed ACL if medial-side laxity persists after non-surgical MCL treatment, which has been proposed to increase the risk of ACL graft failure.[22, 288] There is, however, a shortage of clinical studies of the management of combined ACL and MCL injuries and limited diagnostic benchmarks for the amount of medial-side laxity that indicates the need for surgical intervention to the injured MCL.[114] Nor is there any consensus on the optimal timing of ACL reconstruction if the non-surgical treatment of the MCL is employed. Some advocate delayed ACL reconstruction to allow time for MCL healing and the initiation of physical therapy prior to the ACL reconstruction, which could reduce the risk of early loss of motion.[84, 205] However, successful outcomes have also been reported with early ACL reconstruction (within 23 days of injury) and non-surgical MCL treatment,[93] which could in theory be beneficial in terms of providing the early stabilization of the knee joint, thereby enhancing MCL healing.[276]

The spontaneous healing seen for sMCL injuries might not be applicable to injuries involving the deeper parts of the MCL and the surgical reconstruction or repair of the MCL might be needed to fully restore medial-side stability in patients with grade III MCL injuries or in patients where medial-side laxity persists after an initial period of non-surgical treatment. Several techniques for the surgical treatment of the MCL have been described and found to produce successful outcomes, although reconstruction likely yields superior outcomes compared with repair.[84, 161] With regard to MCL reconstruction, the MCL complex is not by nature isometric. Since there are fibers attaching both anteriorly and posteriorly to the center of rotation (the medial femoral epicondyle), there are length changes in the MCL complex depending on knee joint angle.[125, 275] An isometric position has, however, frequently been proposed for the surgical reconstruction of the MCL, since it has been considered beneficial to avoid strain on the reconstructed MCL, potentially risking persistent laxity. The position of the femoral attachment of the MCL is most important when surgically reconstructing the MCL, since small changes in the positioning of the femoral attachment have significant effects on the graft length change pattern.[125] When reconstructing the POL, it should be tensioned near knee extension to mimic its native state,[125, 275] while the MCL should be tightened at 30° of knee flexion and in slight varus.[272]

Another issue that has been raised through biomechanical cadaveric studies is that medial-side stability could be further compromised by HT harvest for ACL reconstruction in patients with a concomitant MCL injury.[100, 131] It has been hypothesized that the removal of the valgus-stabilizing properties provided by the ST and the gracilis increases the forces of the ACL and potentially leads to inferior outcomes in the clinical setting. Nonetheless, the clinical importance of the findings presented in preclinical studies has not yet been proven in the clinical setting and the majority of clinical studies of combined ACL and MCL injuries are of a low level of evidence. The clinical impact of the presence and treatment of a concomitant MCL injury at ACL reconstruction therefore remains to be determined.

6.5 MORBIDITY

Despite advances in treatment strategies, the literature shows that the risk of developing OA remains high in the mid- to long-term perspective after ACL injury.[153, 194, 217, 269] Although it should be remembered that radiographic evidence of OA is not associated per se with perceived symptoms of OA,[206] approximately 50% of ACL-injured patients show radiographic evidence of OA 10 to 20 years from injury.[153] There is a four times higher risk of OA after ACL injury compared with an uninjured knee in a 10-year perspective and this risk increases to six-fold when a concomitant meniscal injury is present.[208] To date, there is insufficient evidence to conclude whether ACL reconstruction provides protection from the development of OA compared with non-surgical treatment.[149, 269] A systematic review of the literature found that ACL reconstruction did not reduce the prevalence of OA compared with non-surgical treatment.[269] However, it has been shown that patients who undergo ACL reconstruction need to undergo future total knee replacement surgery to a lesser extent compared with patients treated non-surgically.[150]

Persistent knee joint laxity is another cause of morbidity after ACL injury, which could not only have a direct functional impact but also lead to changes in knee joint kinematics and altered chondral loads, thereby contributing to the development of OA.[116] Failure to restore native knee joint stability is not uncommon after ACL reconstruction and the degree of residual knee joint laxity strongly correlates with functional outcome.[19, 218] Persistent symptoms of instability after ACL reconstruction may also restrict patients in terms of physical activity and it has been shown that, although the majority are able to return to some kind of sport after ACL reconstruction, only 65% return to their pre-injury level of sport, while 55% return to a competitive level.[16]

6.6 REVISION ACL RECONSTRUCTION

The need for a revision ACL reconstruction is a dreaded outcome for both the patient and the physician and an indubitable indication of failed primary ACL reconstruction. The terms "graft failure" and "graft rupture" are commonly used interchangeably, although they may in fact represent a considerably different etiology. The underlying causes of a revision ACL reconstruction are most commonly traumatic re-injury (graft rupture) or graft failure caused by technical errors or biological factors.[148, 164, 258] The most common technical error causing the need for revision is the malpositioning of the femoral tunnel placement.[164, 258] Biological failure is not unanimously defined, although it often refers to the failed incorporation of the graft. Incorporation is a complex process that includes cell proliferation, revascularization and the ligamentization of the graft.[40]

The overall cumulative revision probability at seven years from primary ACL reconstruction is approximately 4% in the SNKLR, while it ranges between 2.8 and 3.7% in other large knee ligament registries during the first three years after primary ACL reconstruction.[209] The literature has shown an ACL graft rupture rate of 5.8% at five years after primary ACL reconstruction[279] and 7.9% at ten years.[158] However, certain patient groups run a much higher risk of requiring an ACL revision. It has been reported that one in four patients under the age of 25 years could be expected to sustain a second ACL injury to either the ipsilateral or the contralateral knee.[271] In fact, this age group runs a 30-40 times greater risk of sustaining a new injury compared with their uninjured counterparts of the same age.[271] Although female sex is an established risk factor for ACL injury,[175] there is insufficient evidence when it comes to whether this applies to the risk of ACL revision. Overall, there appears to be no major difference between the sexes in the risk of ipsilateral re-injury.[118, 199, 247]

One explanatory factor for the large increase in the risk of ACL revision among young patients is that the younger population is generally more active compared with the older population. Patients who return to pivoting sports after primary ACL reconstruction run a four times higher risk of ACL revision compared with those that do not return.[89, 268] Time to RTS is another factor for ACL revision, since it has been shown that the majority of all ACL re-injuries occur shortly after RTS.[89, 136, 200] The greatest risk when it comes to sustaining a second ACL injury is during the first two years after ACL reconstruction when returning to sport.[184] This has raised concerns that patients are allowed to return too early to sports, as a 51% reduction in the re-injury rate has been found for every month's delay to RTS until 9 months after surgery.[89] It has even been proposed that delaying RTS for up to two years may be a strategy for avoiding re-injury.[184] The main factor in delaying RTS would, however, be to allow the patient to regain knee function and muscle strength. Failure to fulfill the RTS criteria in terms of functional performance testing before RTS is allowed is associated with a significantly increased risk of sustaining a new injury.[89, 136]

6.6.1 Surgical considerations

A revision ACL reconstruction poses several technical challenges for the surgeon, not to mention challenges for the patient in terms of a second period of surgery and rehabilitation. Revision surgery may be performed using a one- or two-stage approach.[43] Generally, a one-stage approach could be chosen if either the original bone tunnels are correctly positioned or if they are so far away from the optimal tunnel placement that new tunnels could be drilled without interfering with the original ones. In a one-stage procedure, the remainder of the previous graft is removed, any concomitant injuries are managed and a new graft is inserted into tunnels that are newly drilled or the original tunnels. A single-stage procedure could also be performed in cases where there is tunnel overlap or tunnel widening using a resorbable bioscrew to pack the redundant space in the tunnels, although this method is less well studied in the literature. In a two-stage approach, the first stage includes the debridement of the previous graft, hardware removal and bone packing of the original tunnels, often using autogenous bone from the iliac crest.[226] After the complete healing of the filled tunnels is ensured, often at least 4-6 months after the first stage, the second stage could be performed where new tunnels are drilled and the new graft is inserted.

6.6.2 Outcome after revision ACL reconstruction

Although revision ACL reconstruction has been shown to improve knee function compared with preoperatively, the patient-reported knee function remains inferior after ACL revision compared with primary ACL reconstruction.[277, 278, 283] A meta-analysis reported that 84% of patients are able to return to some kind of sport after revision ACL reconstruction. However, the proportion who return to their preinjury sport level and high-level/competitive sports is considerably lower (52% and 51% respectively).[88] The primary reasons for not returning to sport after ACL revision are the inability to return because of knee-related problems (69%), followed by fear of re-injury (22%) and other reasons (9%).[88] After an ACL revision, 22% have been reported to have an abnormal clinical examination assessment, which can be compared with 8% after primary ACL reconstruction.[85] It has also been shown that ACL revision is associated with a significantly increased risk of residual rotatory laxity compared with a primary ACL reconstruction.[85]

One likely contributing factor shown to correlate with inferior outcome after ACL revision is the high rate of concomitant cartilage injuries found in patients undergoing ACL revision.[163] It is almost twice the rate observed in primary ACL reconstruction, where up to 45% of all patients have at least one concomitant cartilage injury at ACL revision compared with 25-30% at primary ACL reconstruction.[83, 106]

One current limitation in the evidence relating to outcome after revision is, however, that comparative studies have most frequently been performed between separate cohorts of patients after revision and primary ACL reconstruction. As a result, little is known regarding the course between primary and revision surgery in terms of PROs and the development of concomitant injuries for patients who need to undergo both surgeries. Comparing separate cohorts in the quest to understand the difference between primary and revision ACL reconstruction also entails a risk of introducing confounding factors. For example, patients who never undergo an ACL revision have been shown to report superior PROs after primary ACL reconstruction compared with those who require a subsequent ACL revision,[82] which may lead to an overestimation of the difference between primary and revision ACL reconstruction at an individual level.

6.7 RATIONALE FOR THIS THESIS

An ACL rupture occurs in the blink of an eye, but the consequences of once having sustained an ACL injury could remain for a lifetime. Those dreaded milliseconds during which an ACL rupture occurs could jeopardize the dream of becoming an elite athlete, impede choosing a physically demanding occupation and pose a risk of lifelong impairments in knee function. It goes without saying that the ACL has attracted enormous interest in the field of orthopedic sports medicine and today almost 25,000 publications relating to this particular ligament are available in the MEDLINE database. On the one hand, the research has led to new understandings and improved treatment for thousands of patients. On the other hand, it is clear that, despite intensive research, the failure of primary ACL reconstruction remains a problem and far too many patients still experience a second devastating hit – an ACL re-rupture and the need to undergo a revision ACL reconstruction.

An evidence-based approach to counter the high rates of ACL revision surgery, especially among the young and active population, is needed. The identification of factors predisposing to ACL revision is fundamental in this quest, so that it can be acknowledged and targeted in the current ACL treatment regimen. Recently, there has been an increase in the emphasis on the impact of concomitant soft tissue injuries and the risk of ACL revision. Combined ACL and MCL injuries represent a common injury pattern. The current body of evidence clearly shows that the ACL and the MCL share important stabilizing properties and that anteromedial rotatory laxity could be a consequence of ligamentous deficiency. In spite of this, the clinical aspect of this knowledge is scarce in the setting of an ACL reconstruction in terms of how a concomitant MCL injury should be addressed and its potential effects on outcome and the risk of ACL revision.

The establishment of predictors for revision means that modifiable factors could be targeted when it comes to improving treatment and outcome, with the aim of minimizing the risk of necessitating a revision ACL reconstruction. A knowledge of predictors and outcome after revision is also important in the guidance of patients in terms of setting realistic expectations of outcome and enabling patients to make informed lifestyle choices after an ACL injury. Nevertheless, an evidence-based approach to improve the outcome after ACL reconstruction also includes a critical review of the results provided by the intensive research in the field of ACL reconstruction. With the vast amount of literature available in relation to the ACL, which presents both unanimous and contradictory results relative to one another, the pursuit of evidence is not without its challenges. With the arrival of technology enabling the data analysis of large registry databases, the easily accessible information and the high pace of new publications, evidence is closer than ever on the one hand. On the other hand, it has probably never been more important critically to appraise the literature and use it conscientiously. As researchers and clinicians of today, we must ask ourselves the following question: on what premises do we conclude evidence in favor something and how robust is the so-called evidence?

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AIMS

EACH THEME IN THIS THESIS REPRESENTS THREE DISTINCT OVERALL AIMS.

Theme I – To evaluate the evidence and robustness of findings associated with revision ACL reconstruction in the Scandinavian knee ligament registries

Theme II – To assess how a concomitant MCL injury affects the outcome and the risk of revision surgery after ACL reconstruction

Theme III – To compare how revision ACL reconstruction compares with primary ACL reconstruction in terms of outcome and concomitant knee joint injuries

The thesis is divided into the following themes with accompanying studies and specific aims.

THEME I – CURRENT EVIDENCE

Study I: To present an overview of the Scandinavian knee ligament registries regarding factors associated with revision ACL reconstruction

Study II: To test the feasibility of utilizing the fragility index to determine the robustness of findings reported from the Scandinavian knee ligament registries related to revision ACL reconstruction

THEME II – THE IMPACT OF A CONCOMITANT MEDIAL COLLATERAL LIGAMENT INJURY

Study III: To determine whether the risk of revision ACL reconstruction is affected by the presence and type of treatment for a concomitant MCL injury at the time of primary ACL reconstruction and its effect on PROs

Study IV: To study the influence of ACL graft choice on the risk of revision ACL reconstruction and PROs in patients undergoing ACL reconstruction with a concomitant non-surgically treated MCL injury

Study V: To evaluate whether a return to sports activity, tests of muscle function and PROs differ between patients who have undergone ACL reconstruction with a concomitant non-surgically treated MCL injury and a matched cohort of patients who have undergone ACL reconstruction without an MCL injury

THEME III – OUTCOME AFTER REVISION

Study VI: To systematically review factors that affect the PROs in the Scandinavian knee ligament registries

Study VII: To assess the prevalence of concomitant knee injuries and PROs at primary ACL reconstruction compared with revision ACL reconstruction in a cohort limited to patients that have undergone both primary and revision ACL reconstruction. Additionally, to identify predictors of outcome after revision

08

METHODS

The study methodologies applied in this thesis include systematic reviews and registry-based cohort studies. Additionally, they include a systematic evaluation of the robustness of statistically significant results reported from the Scandinavian knee ligament registers by applying the Fragility Index.

8.1 EVIDENCE-BASED MEDICINE

The introduction of the EBM concept is regarded as one of the most important paradigm shifts in the history of medicine.[55] Originally, the EBM concept was developed as part of educating residents on how to perform and interpret scientific evidence in their everyday work at McMaster University, Hamilton, Ontario, Canada.[28] Today, the EBM concept is regarded as a cornerstone for conducting high-quality research and clinical practice. The concept of EBM has been described as "the conscientious, explicit and judicious use of the current best evidence in making decisions about the care of individual patients".[225] Three equally important principles characterize the concept of EBM – the best available evidence, clinical experience and the patient's perspective.

The hierarchy of evidence is important for the purpose of EBM, aiding in categorizing the available literature in levels of evidence. The hierarchy mainly depends on the expected risk of bias and the quality of the study design. Many versions of the hierarchy of evidence are available, although the most frequently used is the one available from the Oxford Centre for Evidence-Based Medicine, which can be accessed from the website www.cebm.net. The hierarchy of evidence system implies that, the higher the level of evidence, the higher the generalizability, reproducibility and applicability of the study results should be.[61] In the version from the Oxford Centre for Evidence-Based Medicine, study designs are ranked on a level I to V scale in descending order of level of evidence. Studies of Level I evidence include randomized controlled trials and systematic reviews based on Level I studies, while Level V evidence includes expert opinions (Figure 9). The hierarchy of evidence not only aids in the interpretation of study quality, but it is also applicable when determining how much weight should be given to the result of one study among others when cumulative evidence of a research question is being sought.

LEVEL 1 - Systematic reviews or Randomized Controlled Trials

LEVEL 2 - Prospective Cohort Studies

LEVEL 3 - Retrospective Cohort Studies and Case-Controll studies

LEVEL 4 - Case series

LEVEL 5 - Mechanism-based Reasoning and Expert Opinions

FIGURE 9
The hierarchy of evidence.

8.1.1 Systematic reviews

Systematic reviews are important in the concept of EBM as they help to determine the best available evidence in a systematic, synthesized manner. This also includes a critical appraisal of the literature, since a systematic review implies that a quality assessment of the evidence should be performed. The most comprehensive database of systematic reviews and synthesized research evidence is the Cochrane Database, provided by the Cochrane Collaboration (www.cochrane.org). The Cochrane Collaboration Handbook describes a systematic review as follows: "A systematic review attempts to collate all the empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question. It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made".[146]

The methodology of performing a systematic review should thus include a systematic literature search where strict, predefined inclusion and exclusion criteria are applied. All studies meeting the eligibility criteria must be included; otherwise there is a risk of selection and reporting bias.[181] The literature should be evaluated objectively and a quality appraisal should be performed. The methodology must be declared in a manner that enables the reproduction of the study. If a systematic review utilizes statistical methods to summarize evidence, this is referred to as a meta-analysis. A meta-analysis offers the advantages of increasing the sample size and may improve the statistical precision. Nevertheless, the pooling of data implies that there is an inevitable risk of heterogeneity. Both methodological heterogeneity and statistical heterogeneity of the included studies could bias the study result of a meta-analysis and should be considered.

To increase quality assessment and enable the transparency of the methodology in systematic reviews, the PRISMA statement has been developed.[173, 196] The first PRISMA checklist was published in 2009[173] and it was recently updated (2020).[196] The PRISMA 2020 checklist includes 27 items that should be fulfilled and reported when conducting a systematic review.[196] Although systematic reviews are regarded as the highest level of evidence, it is important to understand that the level of evidence for a systematic review is dependent on the level of evidence of the included studies. As a result, a systematic review does not generally have a higher level of evidence than the lowest ranked level of the included studies.

8.1.2 Registry studies

Registry studies are a type of cohort study and could be classified as level III evidence, depending on the classification system. Despite a lower level of evidence compared with level I RCTs, registry studies could offer advantages and complement studies with a higher level of evidence. The level I studies remain the gold standard when it comes to determining the efficacy of a treatment and are the most appropriate for estimates of treatment effect.[222] Nevertheless, level I RCTs are conducted under ideal conditions, with strict enrollment criteria, and are often performed at specialized centers in limited geographical areas, which could raise concerns over the generalizability of the results. Moreover, RCTs are many times costly and the ethical aspects of the intervention and patient enrollment sometimes preclude conducting an RCT.

Registry studies offer the advantages of investigating a condition or intervention in the "real world", which could be advantageous for the generalizability of the results. Registry studies are also important in understanding practices and incidences and might detect treatment failures and rare events in large study populations.[111] Large datasets could also allow for the statistical modeling of multiple factors that could influence outcome, i.e. predictors of outcome, by multivariable analyses. On the downside when it comes to large datasets is the fact that they may generate statistically significant findings even though the absolute difference is small. It is therefore important critically to evaluate statistically significant findings in large registry studies based on what is clinically relevant. Other disadvantages of registry studies are that they are unable to prove causality and should only be regarded as hypothesis generating. There is also a risk of confounding factors being introduced in registry data.

8.1.3 Statistical significance and fragility

In most research, comparative analyses are used to determine whether there is any difference between, for example, two interventions. The starting point in these analyses is always that there is no difference between the interventions, also known as the "null hypothesis". From this starting point, a comparative study aims to assess whether or not a null hypothesis of this kind can be refuted. To aid in this process, statistical methods are applied and interpreted. The p-values have come to play a central role in hypothesis testing and establishing evidence in research. Although the concept of p-values should be acknowledged as an important factor in the interpretation of statistical analyses, the use of p-values requires an understanding of the definition and the shortcomings associated with p-values. It is worth noting that the concept of p-values is frequently misunderstood[41, 162] and this could have a disastrous effect on the pursuit of evidence. For example, it is not uncommon to forget that the p-value describes a probability and that obtaining a low p-value, i.e. probability, does not mean that one has found the truth. Nor does a p-value describe a probability estimate of what a true difference might be, something that is better appreciated with confidence intervals. Another common misconception is that finding a non-significant p-value is evidence to conclude a true null hypothesis, which is an incorrect use of the p-value.[41] The p-value describes the probability of obtaining a similar or more extreme result to that observed, on the premise that the null hypothesis is true, i.e. that there is no difference between the factors that are being investigated. It has become generally accepted that a p-value of < 0.05 could be regarded as statistically significant, thereby justifying the refutation of the null hypothesis. Interestingly, one of the main founders of the concept of p-values, Sir Ronald Fisher, never suggested a cut-off based on the p-value to refute a null hypothesis.[67, 162] Instead, he emphasized that an experiment should be repeated until the researcher felt that he or she knew how to perform and interpret the results of the experiment with reasonable certainty.[162]

The fragility index has been developed as a methodology to improve the interpretation of statistically significant results.[263] The fragility index evaluates the robustness of significant findings in comparative analyses between two groups. This is achieved by determining how many individuals in the group with the fewest events would be required to change the outcome from a non-event to an event to change a significant difference between the groups to a non-significant one (i.e. alter the p-value from < 0.05 to ≥ 0.05).[263] In Study II, the fragility index was applied to Scandinavian knee ligament registry studies with a two-group analysis of the outcome of additional ACL reconstruction and residual laxity after primary ACL reconstruction. For example, there are studies reporting a significant increase in the risk of ACL revision in patients undergoing primary ACL reconstruction using HT grafts compared with PT grafts.[79] The fragility index of an analysis of this kind therefore describes how many patients in the PT group would be required to change from not undergoing an ACL revision to undergoing one, in order to change the significant difference between the HT and PT group in the risk of ACL revision to a non-significant difference. As a result, the lower the fragility index, the less robust the statistical significance.

8.2 THE SWEDISH NATIONAL KNEE LIGAMENT REGISTRY

The SNKLR was established in 2005 and, in 2020, the registry included data on more than 50,000 ACL reconstructions.[281] It is not mandatory for healthcare units in Sweden to participate in the registry, but the coverage and the completeness of the registry are high (92.9% and > 90% respectively).[59, 281] The SNKLR can be divided into two separate entities – one surgeon reported and one patient reported. The surgeon uses a web-based protocol (www.aclregister.nu) to enter data related to the injury and surgery. Injury-related data include the activity at the time of injury and details of the injured knee joint structures, including any intra-operatively identified concomitant injuries to other ligaments, menisci or cartilage. Subsequently, surgical variables such as graft choice, graft size, graft fixation and any interventions to concomitant injuries are reported. Additionally, the surgeon registers whether the patient has had any prior ACL reconstruction to either the ipsilateral or contralateral knee. If a patient subsequently undergoes revision ACL reconstruction or a contralateral ACL reconstruction, these are registered according to a similar protocol as separate entries which are linked to a patient's primary ACL reconstruction.[5, 134] The patient-reported part of the registry includes validated PRO questionnaires that are administered to the patients preoperatively and at 1-, 2-, 5- and 10-year follow-ups after the ACL reconstruction. The PROs included in the SNKLR are the KOOS and the EQ-5D. The SNKLR is one of three knee ligament registries in Scandinavia. There are similar registers in Norway and Denmark, established in 2004 and 2005 respectively. In Studies I, II and VI, data from all three Scandinavian knee ligament registries were used.

8.3 PROJECT ACL

Project ACL was initiated in September 2014 and is a rehabilitation outcome registry based in the western part of Sweden. The registry utilizes a web-based platform to register data on patients who have sustained an ACL injury and who decide to participate in regular follow-up assessments. Primarily, physical therapists perform the assessment of the patients and enter data into the registry. Two main categories of outcome measurements are collected – validated tests of lower extremity muscle function and PROs. The outcome evaluations are scheduled according to a predefined protocol to take place preoperatively and at 10-week, 4-, 8-, 12-, 18- and 24-month follow-ups and then yearly up to the 5-year follow-up.[95] The muscle function tests are performed as a battery of hop tests[90] and knee extension and flexion strength.[187] Details of the specific tests and PROs included in Project ACL are given in the section on outcome measurements below. Project ACL comprises data on around 3,000 individuals and includes over 10,000 muscle strength tests and PROs collected on approximately 13,000 occasions. Data from Project ACL were utilized in Study V.

8.4 OUTCOME MEASUREMENTS

The outcome measurements in this thesis include the event of additional ACL reconstruction, defined as undergoing a revision ACL reconstruction and/or a contralateral ACL reconstruction after a primary ACL reconstruction. These events are reported by the surgeon in the SNKLR and linked to the primary ACL reconstruction. Additionally, various PROs, including patient-reported RTS, and tests of muscle function, were used as outcome measurements, which will be further detailed below.

8.4.1 Patient-reported outcomes

The measurement properties of the PROs utilized in this thesis are presented in Table 1.

THE KNEE INJURY AND OSTEOARTHRITIS OUTCOME SCORE

The KOOS is a validated knee-specific questionnaire developed with the aim of assessing patients from knee injury to the development of manifest OA.[220, 221] The KOOS questionnaire comprises 42 items, divided into five separate subscales – pain (9 items), symptoms (7 items), activities of daily living (17 items), function in sport and recreation (5 items) and knee-related quality of life (4 items). Each subscale yields a score ranging from 0 to 100, where 0 represents the worst possible state and 100 indicates no knee impairments. The use of the KOOS for patients with an ACL injury has been criticized for including items that might not target the ACL-injured population, since it was primarily developed for assessments of OA. This means that some of the items might be too "easy" for a young patient with an ACL injury and will thereby produce a ceiling effect. In an attempt to overcome the ceiling effect caused by the ADL subscale (an area where most patients with an ACL injury do not perceive problems), the $KOOS_4$ was developed; in it, the ADL subscale has been omitted.[73] The $KOOS_4$ yields an average score ranging from 0 to 100 for the four remaining KOOS subscales.[73] The KOOS subscales of Sport and recreation and QoL have been reported to be the most responsive, with a minimal important change of 12.1 and 18.3 points respectively.[112]

The use of the PASS further aids in the interpretation of the KOOS.[180] The PASS has been defined as "the highest level of symptom beyond which patients consider themselves well" and has been established by asking the question: "Taking into account all the activity you have during your daily life, your level of pain, and also your activity limitations and participation restrictions, do you consider the current state of your knee satisfactory?".[180] The cut-off values for the KOOS PASS have been determined as follows; Pain ≥ 88.9, Symptoms ≥ 57.1, ADL = 100, Sport and recreation ≥ 75 and QoL ≥ 62.5.[180]

THE EUROPEAN QUALITY OF LIFE-FIVE DIMENSIONS

The EQ-5D is a generic instrument for measuring health status for a variety of medical conditions.[33, 60] Its validity and reliability have been assessed for patients with knee OA,[72] but it has not been validated for patients with ACL injuries. The questionnaire includes five domains – mobility, self-care, usual activities, pain/discomfort and anxiety/

depression. The result for the five domains is summarized to produce an index value, giving a score ranging from -0.594 (worse than death), through 0 (worst possible health status) to 1 (best possible health status).[33] Additionally, a VAS for overall patient perception of health is included, ranging from 0 (worst) to 100 (best).[60]

TEGNER ACTIVITY SCALE

The Tegner activity scale[253] assesses a patient's level of activity in terms of work and sport. The original scale ranges from 0 to 10, where a score of 0 represents such severe knee problems that the patient is unable to perform any type of work. The Tegner activity scale used in Project ACL, which was used in this thesis, is a modified version where the score of 0 has been omitted (Appendix).[94] So, on this scale, a Tegner of 1 represents the least knee-strenuous activity (sedentary work). A score of 10 represents the most knee-strenuous activity, with participation in elite level soccer or rugby. In Study V, a Tegner score of ≥ 6 was defined as knee-strenuous activity.[95]

THE 18-ITEM VERSION OF THE KNEE SELF-EFFICACY SCALE

The K-SES measures a patient's self-efficacy, i.e. the patient-perceived confidence to be able to perform a task at present and in the future, considering their current knee status. The original K-SES consisted of 22 items, 18 items related to the present self-efficacy and 4 items related to future self-efficacy.[255] The original version has been modified to produce a shorter version which includes a total of 18 items (K-SES$_{18}$), of which 14 items relate to the present domain and four items to the future domain.[25] The K-SES$_{18}$ has been proven valid in patients with an ACL injury, with acceptable reliability.[25] In Study V, the K-SES$_{18}$ was utilized. Each item is rated on an 11-point Likert scale, where 0 represents "not at all certain" and 10 means that the patient reports "very certain". The result is presented for the present and future domains separately by calculating a mean score for all the items within each domain, thus yielding a possible mean value ranging from 0 to 10. The higher the score, the more positive the psychological response for self-efficacy can be regarded.[25]

THE ACL-RETURN TO SPORT AFTER INJURY

The ACL-RSI[267] is designed to measure the psychological impact of returning to sport after ACL reconstruction. The scale measures three factors assumed to be important for psychological responses associated with the resumption of sport, namely emotions (5 items), confidence in performance (5 items) and risk appraisal of re-injury (2 items). The ACL-RSI thus consists of 12 items which are ranked on a Likert scale from 0 to 10. The higher the score, the more positive the psychological response.[267] The final score is subsequently transformed into a 0-100 scale, by adding up the total score for all items, multiplying it by 100 and then dividing this score by 120 (total score x 100/120).

TABLE 1. Details of the patient-reported outcome measurements used in this thesis

PRO	Number of items	Min-max score	Test-retest reliability (ICC)
KOOS	42 items	0-100	Pain = 0.85 to 0.93
			Symptoms = 0.83 to 0.95
			ADL = 0.75 to 0.91
			Sport = 0.61 to 0.89
			QoL = 0.83 to 0.95[75]
EQ-5D	5 items	-0.594 - 1	0.70 (95% CI 0.58-0.80)[72]
EQ-VAS	1 item	0-100	0.73 (95% CI 0.61-0.82)[72]
Tegner activity scale	-	1-10*	0.82 (95% CI 0.66-0.89)[31]
K-SES$_{18}$	18 items	0-10	0.92[25]
ACL-RSI (Swedish version)	12 items	0-100	0.89[135]

*Modified version of the Tegner where the 0 has been omitted.

ACL-RSI, Anterior cruciate ligament – return to sport after injury; ICC, Intraclass correlation coefficient; EQ-5D, European quality of life-5 dimensions; EQ-VAS, European quality of life-visual analogue scale; KOOS, Knee injury and osteoarthritis outcome score; K-SES$_{18}$, The 18-item version of the knee self-efficacy scale

8.4.2 Tests of muscle function

The muscle function test battery used in this thesis included the following five tests: isokinetic concentric quadriceps and hamstring strength, the vertical hop, the hop for distance and the side hop. The Biodex System 4 (Biodex Medical Systems, Shirley, New York) was applied for the quadriceps and hamstring strength tests, which were performed according to a standardized protocol.[187] After a standardized 10-minute warm-up procedure on a stationary bike and sub-maximum trials on each test, the tests were performed unilaterally. The injured leg was tested first, followed by the uninjured one. The isokinetic testing was performed with the patient in a seated position and at an angular velocity of 90°/second. Three maximum repetitions (with 40 seconds of rest between each repetition) were performed. The highest peak torque was used for analysis.

The battery of hop tests[90] was performed in the following order: the vertical hop (jump as high as possible), the hop for distance (jump as far as possible) and the side hop (jump sidewise over two lines 40 centimeters apart, as many times as possible for 30 seconds). Two practice trials and three test trials were allowed for the vertical hop and the hop for distance, where the best test trial result was recorded. The distance and height were measured in centimeters, applying the Musclelab™ (Ergotest Innovation AS, Oslo, Norway) to record the vertical hop test which measure the flight time and converting this into height. For the side-hop test, one 30-second trial per leg was allowed and the total number of hops were recorded. Table 2 summarizes the tests of muscle function.[207]

The tests of muscle function were reported as the LSI. The LSI presents the percentage of performance for the injured leg relative to the uninjured leg by dividing the result for the injured leg by the result for the uninjured leg multiplied by 100 (injured leg/uninjured leg X 100).[256]

TABLE 2. Tests of muscle function[207]

	Knee extension	Knee flexion	Vertical hop	Hop for distance	Side hop
Degrees of movement	90°-0°	0°-90°	-	-	-
Practice trials n (% of 1 RM)	10 (50%); 10 (75%); 1-2 (90%)	10 (50%); 10 (75%); 1-2 (90%)	2	2	-
Test trials	3-4	3-4	3	3-5	1
Rest between test trials (seconds)	40	40	20	20	180
Units	Newton meters	Newton meters	Centimeters	Centimeters	Number of hops

n, number; 1RM, one repetition maximum

8.5 THEME I – CURRENT EVIDENCE

STUDY I

Study design

Systematic review

Methods

The PRISMA guidelines were followed.[173] An expert in electronic search methodology at the Sahlgrenska University Hospital library performed the literature searches. A first search was performed on 9 May 2017 and it was updated on 20 April 2018. The PubMed, EMBASE, The Cochrane Library and AMED electronic databases were searched. Search terms were mapped to relevant MeSH terms or subject headings where possible. Additionally, an email was sent to the registry holder of each Scandinavian knee ligament registry with a request to provide a list of publications from the registry. A total of 157 publications were identified by the literature search and one additional publication was provided by a registry holder. All the original publications from any of the Scandinavian knee ligament registries were eligible for inclusion if the data related to any of the following topics: additional ACL reconstruction (defined as revision or contralateral ACL reconstruction following primary reconstruction), patient-reported outcome in relation to additional ACL reconstruction, residual knee laxity following ACL reconstruction or registry comparison with a registry outside Scandinavia. Two authors independently screened all the titles and abstracts, followed by full-text publications for eligibility. A total of 31 publications met the final inclusion criteria, of which 24 related to revision ACL reconstruction and were presented in this thesis (Figure 10).

Data collection and quality assessment were performed independently by two authors. For the quality appraisal, a modified version of the Downs and Black checklist was applied.[56] The modified version of the checklist yielded a maximum of 22 points and is presented in the Appendices. The data synthesis was qualitative. In situations where the studies overlapped, the study with the largest cohort was primarily given the greatest emphasis in the summary and the study with the highest Downs and Black score was considered secondarily.

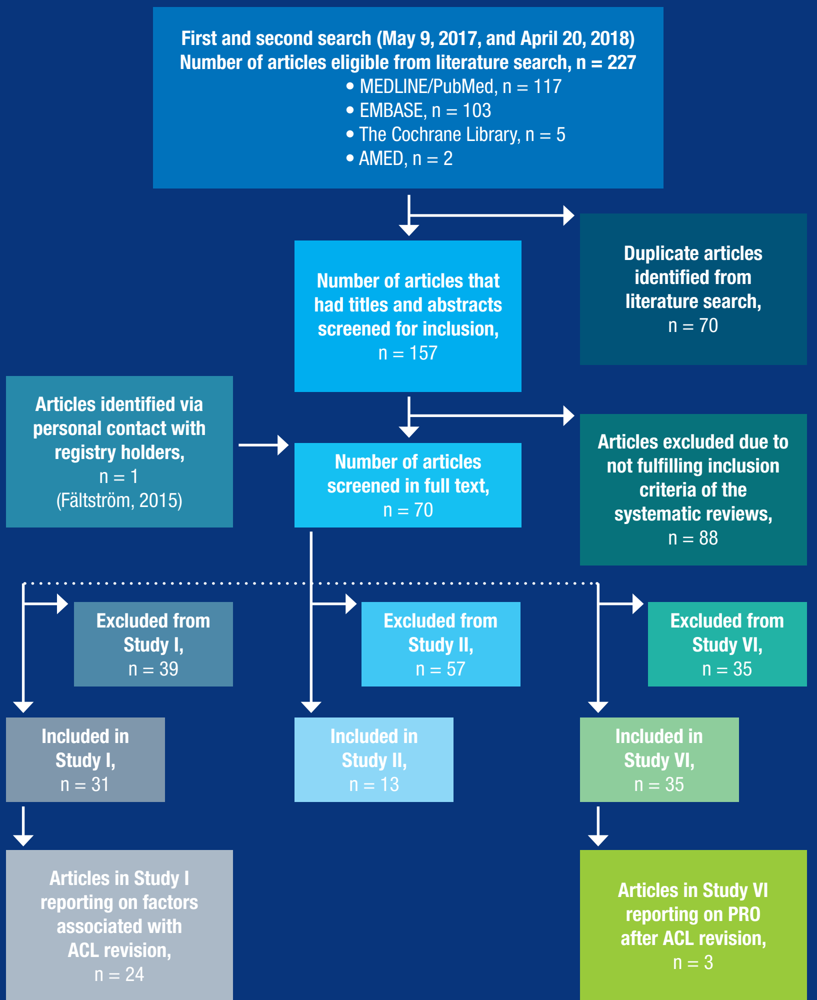

FIGURE 10

Study inclusion process for Studies I, II and VI

STUDY II

Study design

Systematic review

Methods

A similar literature search, quality assessment and data extraction process as presented for Study I were employed for Study II. Eligible studies were those originating from any of the Scandinavian knee ligament registries that reported statistically significant results for any of the following dichotomous outcomes; ACL revision, contralateral ACL reconstruction or presence of residual knee joint laxity. Statistical significance was defined as a p-value of < 0.05 or a 95% CI excluding a null value, with a null hypothesis that there would be no difference between the groups. For analyses with ratio calculations, the 95% CI was required to exclude 1 to be defined as statistically significant. If data needed to calculate the fragility index were missing, e.g. the number/proportion of events or patients in each group, the study was excluded. From a total of 157 studies identified by the literature search, 13 studies were included in Study II, of which 12 reported analyses on the outcome ACL revision (Figure 10).

If a study performed more than one comparative analysis between two groups for the outcome ACL revision, data for each analysis were extracted and reported. For example, the same study may compare the risk of ACL revision between both two age groups and two groups of different graft choice. The results were organized and reported according to the specific predictor studied, i.e. the grouping variable. The methods for calculating the fragility index are presented in the section on Statistical methods in this thesis.

8.6 THEME II – THE IMPACT OF A CONCOMITANT MEDIAL COLLATERAL LIGAMENT INJURY

STUDY III

Study design

Registry-based cohort study

Patients and methods

Data from the SNKLR between 2005 through 2016 were utilized. All primary single-bundle ACL reconstructions with HT or PT autografts in patients over 15 years of age were assessed for eligibility. The exclusion criteria were revision ACL reconstructions, concomitant PCL injury or fracture, nerve or vascular injuries, prior contralateral ACL reconstruction, unknown HT graft diameter, combined MCL and LCL injuries or contralateral MCL or LCL surgery. A total of 19,457 patients met the eligibility criteria and were stratified into groups depending on the treatment of the collateral ligament injury (non-surgical, suture repair or reconstruction) and one group formed a reference group of isolated ACL reconstruction in the absence of any collateral ligament injury. Table 3 presents the demographic data for the study population. The analyses of patients with a concomitant LCL injury, included in the original publication, were not presented in this thesis.

Outcome

The endpoint of ACL revision surgery and the 2-year KOOS were the main outcomes. For the endpoint of ACL revision, the follow-up period started on the date of a patient's primary ACL reconstruction and ended at ACL revision or on December 31, 2016, whichever occurred first.

TABLE 3. Demographic data of the study population in Study III	Isolated ACLR (n=18,490)	ACLR + non-surgically treated MCL (n=657)	ACLR + MCL suture repair (n=52)	ACLR + MCL reconstruction (n=84)
Age at surgery	27.8 (9.8)	30.7 (11.2)***	32.6 (12.2)**	30.3 (11.4)
Patient sex				
Male	10,964 (59.3%)	367 (55.9%)	33 (63.5%)	59 (70.2%)
Cartilage injury				
Yes	5147 (27.8%)	212 (32.3%)*	15 (28.8%)	40 (47.6%)***
Meniscal injury (medial and/or lateral)				
Yes	8290 (44.8%)	302 (46.0%)	26 (50.0%)	50 (59.5%)**
Activity at time of injury				
Soccer	8248 (44.6%)	186 (28.3%)	11 (21.2%)	23 (27.4%)
Other	10,240 (55.4%)	471 (71.7%)***	41 (78.8%)***	61 (72.6%)**

For categorical variables, the number (n) and percentage (%) are presented. For continuous variables, the mean and standard deviation (SD) are presented. The isolated ACL reconstruction group was used as a reference and all the other study groups were compared with the isolated ACL group. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

ACLR, anterior cruciate ligament reconstruction; MCL, medial collateral ligament

STUDY IV

Study design

Registry-based cohort study

Patients and methods

Patients registered in the SNKLR between 2005 through 2017 were assessed for eligibility. Eligible patients were those who had undergone primary ACL reconstruction with either HT or PT autografts and had a concomitant non-surgically treated MCL injury. Only patients > 15 years old with at least a 2-year follow-up were included. Additional exclusion criteria were revision ACL reconstruction, the presence of any other ligamentous injury or surgical intervention on the MCL injury, concomitant fracture, nerve or vascular injury, a history of contralateral ACL reconstruction or contralateral collateral ligament injury and an unknown graft diameter for the HT graft.

A total of 662 patients (mean age 29.7 years, 42.4% females) met the inclusion criteria and were divided into three groups depending on ACL graft choice; 1) The ST group (n = 174), 2) the ST-G group (n = 323) and 3) the PT group (n = 125). (Figure 11). The baseline data for the groups are presented in Table 4.

Outcome

The endpoint of ACL revision and the 1- and 2-year KOOS were the primary outcomes. The date of the primary ACL reconstruction marked the starting point of the follow-up period of the outcome of ACL revision, which ended on the date of ACL revision or on December 31, 2017, whichever occurred first. Additionally, the KOOS PASS at the 1- and 2-year follow-up was compared between the groups.

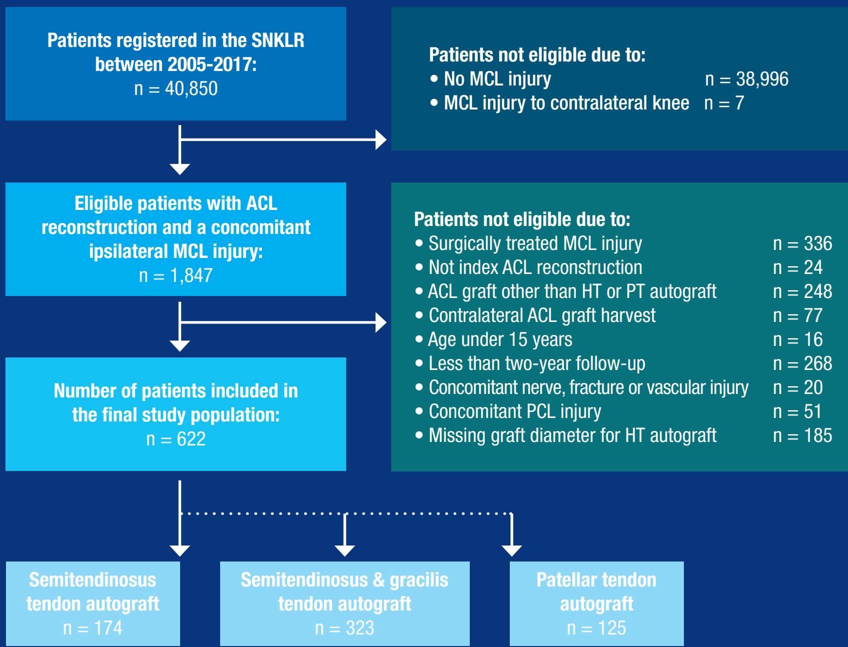

FIGURE 11
Flowchart of inclusion for Study IV

TABLE 4. Demographic data for Study IV

	Total (n = 622)	ST graft (n = 174)	ST+G graft (n = 323	PT graft (n = 125)	p-value
Patient sex					
Female	264 (42.4%)	75 (43.1%)	149 (46.1%)	40 (32.0%)	0.025
Age at ACL reconstruction (years)	29.7 (11.1) 27.0 (15.0; 58.0) n = 622	29.6 (10.9) 28.0 (15.0; 56.0) n = 174	29.7 (11.2) 26.0 (15.0; 58.0) n = 323	29.9 (11.2) 27.0 (15.0; 58.0) n = 125	0.95
Activity at time of injury					
Soccer	191 (30.7%)	53 (30.5%)	108 (33.4%)	30 (24.0%)	
Floorball	39 (6.3%)	6 (3.4%)	22 (6.8%)	11 (8.8%)	
Handball	26 (4.2%)	7 (4.0%)	15 (4.6%)	4 (3.2%)	
Alpine	150 (24.1%)	48 (27.6%)	78 (24.1%)	24 (19.2%)	
Other	216 (34.7%)	60 (34.5%)	100 (31.0%)	56 (44.8%)	0.087
Days from injury to surgery	314.0 (729.9) 165.0 (1.0; 11219.0) n = 598	240.6 (301.7) 130.5 (1.0; 1766.0) n = 168	346.2 (920.8) 172.0 (4.0; 11219.0) n = 313	333.5 (564.9) 206.0 (5.0; 4707.0) n = 117	0.016
ACL graft diameter (millimetres)	8.40 (0.88) 8.00 (6.00; 13.00) n = 578	8.51 (0.87) 8.50 (6.50; 13.00) n = 174	8.11 (0.71) 8.00 (6.00; 10.00) n = 323	9.31 (0.86) 9.00 (7.00; 11.00) n = 81	<.001
Meniscal injury (medial and/or lateral)					
Yes	257 (41.3%)	69 (39.7%)	136 (42.1%)	52 (41.6%)	0.88
Cartilage injury					
Yes	197 (31.7%)	44 (25.3%)	104 (32.2%)	49 (39.2%)	0.036

For categorical variables, n (%) is presented. n=number. For continuous variables, the mean (SD)/median (min; max)/n=is presented.

ACL, anterior cruciate ligament; G, gracilis tendon; PT, patellar tendon; ST, semitendinosus tendon

STUDY V

Study design

Registry-based cohort study

Patients and methods

Patients registered in the SNKLR and Project ACL who had undergone ACL reconstruction and had a concomitant non-surgically treated MCL injury were included if they were ≥ 15 years old at surgery and had available data on the preinjury Tegner[253] and at the one-year follow-up. The exclusion criteria were preinjury Tegner < 6, graft types other than HT or PT autograft, contralateral ACL graft harvest, surgical treatment of MCL injury, double-bundle ACL reconstruction, concomitant other ligament injury, concomitant cartilage injury of the ICRS grades 3-4,[32] concomitant fracture, nerve or blood vessel injury and new ACL injury within one year of the primary ACL reconstruction. Eligible patients were matched to a cohort of patients who had undergone ACL reconstruction without a concomitant MCL injury. For the matching criteria, the presence of a concomitant meniscal injury and patient sex were enforced to be equal, while a maximum difference of five years was allowed for age and a one-unit difference was allowed in the preinjury Tegner activity level. Patients were matched in a 1:3 ratio, which means that one patient with an ACL reconstruction and a concomitant non-surgically treated MCL injury (ACL+MCL group) was matched with three patients undergoing ACL reconstruction without a concomitant MCL injury (ACL group). A total of 30 patients were included in the ACL+MCL group and matched with 90 matched patients in the ACL group. Figure 12 shows the inclusion process. The demographic data are presented in Table 5.

Outcome

The primary outcome was return to knee-strenuous sport at the one-year follow-up, defined as a Tegner of ≥ 6 and referred to as RTS. Additionally, the return to the preinjury level of sport was evaluated, which was defined as reporting the same or a higher Tegner at the one-year follow-up compared with the preinjury Tegner.

Secondary outcome measurements were the KOOS (including $KOOS_4$ and KOOS PASS), the $K\text{-}SES_{18}$, and the ACL-RSI. Muscle function tests included unilateral knee extension strength, knee flexion strength, vertical hop, hop for distance and side hop. All tests of muscle function were reported as the LSI.

FIGURE 12
Flowchart of inclusion for Study V

TABLE 5. Demographic data for the study population in Study V

	Total (n=120)	ACL + MCL (n=30)	ACL (n=90)	p-value
Patient sex				
Female	40 (33.3 %)	10 (33.3 %)	30 (33.3 %)	1.00
Age at ACL reconstruction (years)	26.5 (9.4) 23.7 (15.1; 49.6) (18.7; 31.1) n=120	27.1 (9.6) 23.2 (16; 49.6) (19.2; 33.2) n=30	26.3 (9.4) 24.2 (15.1; 48.4) (18.6; 30.6) n=90	0.71
Time from injury to ACL reconstruction (days)	317.0 (812.0) 133.5 (30; 7451) (85.5; 264.5) n=120	114.6 (78.8) 92 (33; 357) (56; 158) n=30	384.4 (928.0) 154 (30; 7451) (97; 321) n=90	0.0004
ACL graft choice				
Hamstring tendon	101 (84.9%)	22 (73.3%)	79 (88.8%)	
Patellar tendon	18 (15.1%)	8 (26.7%)	10 (11.2%)	0.073
Cartilage Injury				
Yes	9 (7.5%)	2 (6.7%)	7 (7.8%)	1.00
Medial meniscus injury				
Yes	21 (17.5%)	4 (13.3%)	17 (18.9%)	0.70
Lateral meniscus Injury				
Yes	47 (39.2%)	14 (46.7%)	33 (36.7%)	0.45
Pre-injury Tegner Activity Scale				
6	20 (16.7%)	6 (20.0%)	14 (15.6%)	
7	26 (21.7%)	6 (20.0%)	20 (22.2%)	
8	25 (20.8%)	5 (16.7%)	20 (22.2%)	
9	35 (29.2%)	7 (23.3%)	28 (31.1%)	
10	14 (11.7%)	6 (20.0%)	8 (8.9%)	1.00

For categorical variables, n (%) is presented. For continuous variables, the mean (SD)/median (min; max)/ Q1; Q3)/ n= is presented. ACL, anterior cruciate ligament; MCL, medial collateral ligament.

8.7 THEME III – OUTCOME AFTER REVISION

STUDY VI

Study design

Systematic review

Methods

Study VI used the same literature search, review process and data extraction process performed for Study I. For quality appraisal, the modified Downs and Black checklist was applied (Appendix).[56] Studies eligible for inclusion were those presenting data from any of the Scandinavian knee ligament registries on patient-reported outcome or concomitant injuries. The literature search yielded a total of 157 publications, of which 35 met the inclusion criteria for Study VI. The data were synthesized in a qualitative manner and presented under three specific main sections; patient-related factors, surgery-related factors and injury-related factors. Each main section was subsequently organized in sub-headings according to topics identified in the original publications in order to increase the readability of the systematic review. For example, all publications related to the outcome after primary and revision ACL reconstruction were summarized under the sub-heading of "Outcomes after primary and revision ACL reconstruction" in the section on surgery-related factors. For the purpose of Theme III in this thesis, only the results from the systematic review that related to comparisons of outcome between primary and revision ACL reconstruction were presented in this thesis. A total of three publications within the systematic review related to a comparative analysis of this kind. The study inclusion process is presented in Figure 10.

STUDY VII

Study design

Registry-based cohort study

Patients and methods

Patients who had both primary and revision ACL reconstruction registered in the SNKLR between 2005-2017 were assessed for eligibility. Patients aged between 13 to 49 years who received an HT autograft at the primary ACL reconstruction were eligible for inclusion, if they had also reported the KOOS on at least one occasion (preoperative or at one year postoperatively) for both the primary and revision ACL reconstruction. Patients with a concomitant fracture, nerve or vascular injury at either ACL reconstruction were excluded. Likewise, patients who had a contralateral ACL reconstruction or underwent a contralateral ACL reconstruction within two years from the ACL revision surgery were excluded.

The studied variables were stratified into three categories and are presented in Table 6.

A total of 1,014 patients were included in the study. The patient inclusion process is shown in Figure 13 and the baseline demographic data are presented in Table 7.

Outcome

The KOOS and the $KOOS_4$ were used to compare the outcome between primary and revision ACL reconstruction at one year postoperatively. The KOOS subscales of Sport and recreation and QoL, as well as the $KOOS_4$, one year after revision ACL reconstruction, were used as dependent variables, i.e. outcomes, in the analyses of predictors of outcome after ACL revision.

TABLE 6. Studied variables per category in Study VII

Patient demographics	Surgery-related factors	Concomitant injuries
• Patient sex • Age • Activity at injury	• Time from primary ACL reconstruction to revision • Graft type • Graft fixation	• Meniscal injury - Medial/lateral injury - Resection or repair • Cartilage injury - Location - ICRS grade 1-4 • Concomitant ligament injuries - MCL, LCL, PCL, PLC

ACL, anterior cruciate ligament; ICRS, International cartilage repair society; LCL, lateral collateral ligament; MCL, medial collateral ligament; PCL, posterior cruciate ligament; PLC, posterolateral corner

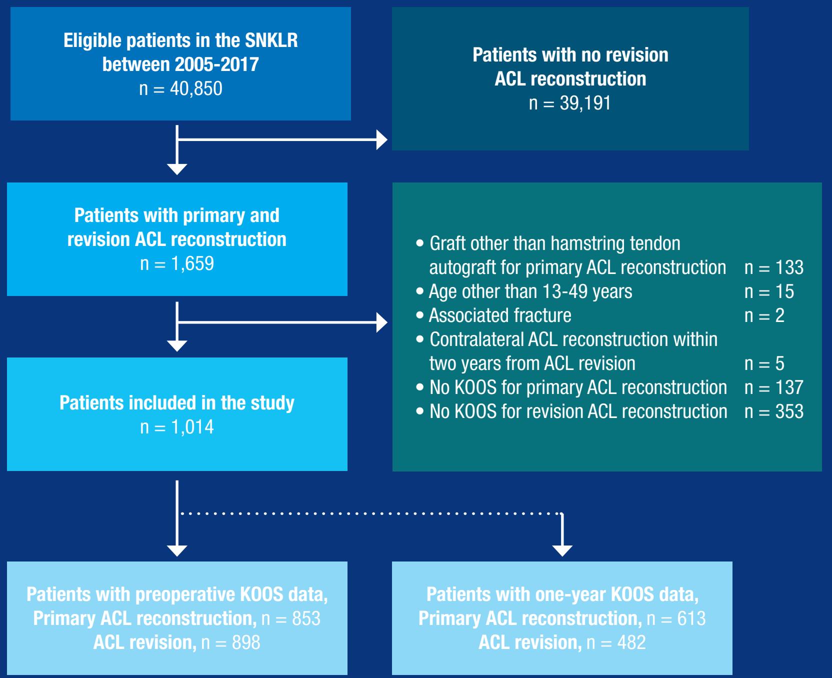

FIGURE 13
Flowchart of inclusion for Study VII

TABLE 7. Baseline demographic data for Study VII

	Primary ACL reconstruction n = 1,014	ACL revision n = 1,014
Patient sex		
Female	494 (48.7%)	494 (48.7%)
Age at ACL reconstruction (years)	21.5 (7.2) 19.0 (13.0; 49.0)	24.2 (7.5) 22.0 (14.0; 53.0)
Time from primary ACL reconstruction to ACL revision (years)		2.7 (2.0) 2.0 (0.2; 12.3)
Activity at time of injury		
Soccer	520 (51.4%)	412 (40.9%)
Floorball	89 (8.8%)	57 (5.7%)
Handball	76 (7.5%)	58 (5.8%)
Alpine	83 (8.2%)	47 (4.7%)
Other	244 (24.1%)	434 (43.1%)
Missing	2	6
ACL graft choice		
Patellar tendon autograft		639 (64.4%)
Hamstring tendon autograft	1,014 (100.0%)	190 (19.1%)
Quadriceps tendon autograft		83 (8.4%)
Allograft		69 (6.9%)
Other		12 (1.2%)
Missing	0	21

For categorical variables, n (%) is presented.
For continuous variables, the mean (SD)/median (min; max) is presented.
ACL, anterior cruciate ligament; n, number

09

STATISTICAL METHODS

The descriptive data were presented similarly across the studies in this thesis. Continuous variables were presented as the mean and standard deviation and/or median and range with the addition of the 1st and 3rd quartiles for selected variables. Categorical variables were presented as counts and proportions. Study I and Study VI did not include any statistical analysis.

STUDY II

The fragility index was calculated according to a previously described method,[263] by using two-by-two tables. First, the statistically significant analyses from the original articles were recalculated by applying a two-sided Fisher's exact test. If the result remained statistically significant, the fragility index was calculated by adding the number of events to the group with the fewest number of events (or lowest risk of event/outcome), while subtracting the same number from the non-events in the group to keep the group sample size constant. This procedure was repeated until the two-sided Fisher's exact test no longer showed a significant difference between the groups ($p \geq 0.05$). The smallest number of patients that were required to change from a non-event to an event to obtain a $p \geq 0.05$ was defined as the fragility index (Figure 14). The mean and median fragility index was calculated for all analyses on the same grouping variable, or predictor, for example, the predictor of "age". Moreover, subgroup analyses for the mean and median fragility index were performed after excluding the analyses that received a fragility index of zero directly when applying Fisher's exact test to the original data. A fragility index of zero thus means that no patients need to change from a non-event to an event for the result to become non-significant when applying Fisher's exact test, which is regarded as a highly fragile significant result. However, since survival analysis is frequently used in studies originating from the Scandinavian knee ligament registries, there is a risk that Fisher's exact test might underestimate the fragility index. The subgroup analyses with the exclusion of analyses with a fragility index of zero represented an attempt to take account of the risk of an underestimation of this kind. All the calculations were performed using Microsoft Excel (Microsoft Corp; Version 1812) and SPSS version 25 (IBM Corp; 2017).

ORIGINAL STUDY RESULT		
	Revision (n =)	No revision (n =)
Group 1	a	b
Group 2	c	d
Fisher's exact test $p < 0.05$		

CALCULATED FRAGILITY		
	Revision (n =)	No revision (n =)
Group 1	a + f	b - f
Group 2	c	d
Fisher's exact test $p \geq 0.05$		

FIGURE 14

Calculation of the fragility index, modified from Walsh et al.[263] Group 1 has the fewest events, the lowest value on "f" that changes the p-value of Fisher's exact test to ≥ 0.05 represents the fragility index.

STUDY III

For comparative analyses between two groups, where the isolated ACL group was set as the reference group, Fisher's exact test was used for dichotomous variables, the chi-square test for non-ordered categorical variables and the Mann-Whitney U test for continuous variables. When unadjusted analyses for comparisons between more than two groups were performed, the Kruskal-Wallis test was used for continuous variables and the chi-square test for non-ordered categorical variables. An ANCOVA analysis was utilized to adjust the comparative analyses of the KOOS for possible confounders in terms of age at surgery, patient sex and cartilage injury. The proportional hazard ratio of ACL reconstruction survival, or ACL revision, was calculated with univariable and adjusted multivariable Cox regression analyses, where the isolated ACL reconstruction group was set as a reference. Patient sex, graft diameter and any additionally identified baseline variables that differed significantly between the groups were tested as potential confounders, i.e. if they correlated with both the predictor and the outcome of the regression model. If so, the Cox regression models were adjusted for the variable. The proportional hazards assumptions were investigated by visually reviewing the log(–log(survival)) versus log(time) curves and by introducing an interaction term between each predictor and the logarithm of time in the study into the model and were found to be fulfilled. The results were reported as HRs, 95% confidence intervals (CI) and p-values. All the statistical tests were two-sided and conducted at the 5% significance level. All statistical analyses were performed using Statistical Analysis System software (SAS/STAT, version 14.2, 2016; SAS Institute Inc., Cary, North Carolina, USA).

STUDY IV

The chi-square exact test was used for non-ordered categorical variables in comparative analyses between the three groups, while the Kruskal-Wallis test was used for continuous variables. Where significant differences were found between the groups, a pairwise analysis with the chi-square test for non-ordered categorical variables, Fisher's exact test for dichotomous variables and the Mann-Whitney U test for continuous variables was performed. The pairwise analyses of the KOOS were adjusted for patient sex and the presence of concomitant cartilage injury using logistic regression with the dichotomized groups as the dependent variable, the KOOS as the independent variable and patient sex and concomitant cartilage injury as confounders. The dichotomized KOOS PASS variables were similarly adjusted in comparison with multiple logistic regression, while the KOOS PASS variables were given as percentages with exact 95% CI. For the study endpoint of ACL revision, Cox regression models were utilized to determine the proportional HR of primary ACL reconstruction survival. The ST-G group was set as a reference in the main analysis. Baseline variables that differed significantly between the groups were tested as potential confounders in the Cox regression models and the models were subsequently adjusted for concomitant cartilage injury. The supremum test showed that the assumption of proportionality was not violated. The results of the Cox regression analyses were reported as unadjusted and adjusted HRs and 95% CIs. All the statistical tests were 2-sided and conducted at the 5% significance level. The statistical analysis was performed using the Statistical Analysis System (SAS/STAT, version 14.2, 2016; SAS Institute Inc., Cary, NC).

STUDY V

A sample-size calculation was made for the main outcome (Tegner ≥ 6 at the one-year follow-up). The results from a previous study were used to estimate the proportion of patients reaching the outcome.[96] It was estimated that 60% of patients in the ACL group and 30% of patients in the ACL+MCL group would report Tegner ≥ 6 one year after ACL reconstruction. To be able to identify a 30% difference between groups with 80% power at an alpha level of 0.05, 28 patients were required to be included in the ACL+MCL group.

A caliper matching procedure was used to ID-match patients with and without a concomitant non-surgically treated MCL injury in a 1:3 ratio. Fisher's exact test (lowest 1-sided p-value multiplied by 2) was used to compare dichotomous variables between groups and the Mantel-Haenszel chi-square exact test was used for ordered categorical variables. Fisher's non-parametric permutation test was used for continuous variables. The CI for dichotomous variables represented the unconditional exact confidence limits. If no exact limits could be computed, the asymptotic Wald confidence limits with continuity correction were calculated instead. The CI for the mean difference between groups was based on Fisher's non-parametric permutation test. All the tests were two-tailed and conducted at the 5% significance level. The statistical analyses were performed using Statistical Analysis System software (SAS/STAT, version 14.2, 2016; SAS Institute Inc., Cary, North Carolina, USA).

STUDY VII

Statistical analyses were performed using the SAS statistical analysis system (SAS/STAT, version 14.2, 2016; SAS Institute Inc., Cary, North Carolina, USA). The sign test was used to analyze the difference in the prevalence, treatment and severity of concomitant injuries from primary to revision ACL reconstruction, i.e. the difference in the proportion of patients with an increase or decrease in a concomitant injury from primary to revision ACL reconstruction was determined. The presence of a concomitant injury or any surgical treatment performed for this at ACL reconstruction was reported as "yes". On the other hand, if no concomitant injury was present or no surgical treatment was performed, this was reported as "no". An increase from primary to revision ACL reconstruction was defined as a patient changing status from "no" at primary reconstruction to "yes" at revision, while a change the other way around was defined as a decrease. With regard to the severity of cartilage injury, this ranged from "no injury or ICRS 0" to ICRS 4 and the increase or decrease was defined as a patient changing one or more levels in either direction from primary to ACL revision surgery. The Wilcoxon signed rank test was used to compare the KOOS between primary and revision ACL reconstruction, preoperatively and at one year postoperatively. The KOOS sport and recreation, KOOS QoL and $KOOS_4$ were set as dependent variables in separate univariable regression models. Table 8 shows the way the independent variables for these analyses were handled. Independent variables that reached a p-value of < 0.10 in the univariable analysis were entered in the forward stepwise multivariable regression model. The results of the regression models were presented with β-coefficients, 95% CI and p-values. All significance tests were two-sided and conducted at the 5% significance level.

TABLE 8. Variables analyzed as predictors of the one-year Knee injury and Osteoarthritis Outcome Score after anterior cruciate ligament revision.[245]

Variable category	Variable
Patient demographics	• Age* (continuous variable per 10 years) • Patient sex (male/female)
Surgery related	• Years from primary ACL reconstruction to ACL revision (continuous variable per year) • Graft type at ACL revision (hamstring tendon, patellar tendon, quadriceps tendon, allograft, other)
Concomitant injuries	
Meniscal injuries	• Any meniscal injury (yes/no)* • Medial meniscus injury (yes/no)* • Lateral meniscus injury (yes/no)* • Surgical treatment of any meniscal injury (yes/no)* • Meniscal resection of any meniscal injury (yes/no)* • Meniscal repair of any meniscal injury (yes/no)*
Cartilage injuries	• Any cartilage injury (yes/no)* • Highest grade on any cartilage injury (ordinal variable – ICRS 0/ICRS 1-2/ICRS 3-4)* • Patella (dichotomized ICRS 0-2/ICRS 3-4)* • Tibial plateaus (dichotomized ICRS 0-2/ICRS 3-4)* • Femoral condyles (dichotomized ICRS 0-2/ICRS 3-4)* • Trochlea (dichotomized ICRS 0-2/ICRS 3-4)*
Ligament injuries	• MCL (yes/no)* • LCL (yes/no)* • PCL (yes/no)* • PLC (yes/no)*

ACL, anterior cruciate ligament; ICRS, International Cartilage Repair Society; LCL, lateral collateral ligament; MCL, medial collateral ligament; PCL, posterior cruciate ligament; PLC, posterolateral corner

*The status of the variable at both primary and revision ACL reconstruction was analyzed. The information in parentheses indicates how the variable was analyzed.

10

ETHICS

Studies III, IV and VII

Ethical approval was obtained from the Regional Ethical Review Board in Stockholm (registration number: 2011/337-31/3).

Study V

Ethical approval was obtained from the Swedish Ethical Review Authority (EPM number: 2020-02501).

Studies I, II and VI

No ethical approval was required since these studies were systematic literature reviews where published data were used exclusively and no new patient data were collected.

Participation in the SNKLR is voluntary for both patients and surgeons and all patients receive written information regarding their participation. All collected data are treated anonymously and only authorized personnel are able to gain access to the data. No written consent is necessary for participation in national databases in Sweden. Similarly, participation in Project ACL is voluntary for all parties (patients, physical therapists and surgeons) and the participants have the right to withdraw from participation at any time without explanation. Prior to inclusion in Project ACL, all patients are given written information about the study and informed consent is obtained if the patient chooses to be included. All the original studies in this thesis were conducted according to the WMA Declaration of Helsinki.

II

RESULTS

11.1 THEME I – CURRENT EVIDENCE

Result Summary

Study I found that the strongest risk factor for revision ACL reconstruction was young age, which was consistently reported. Patient sex did not influence the risk of revision, but the combination of young age, female sex and playing soccer at the time of ACL injury was associated with a higher risk of revision compared with males with the same age and activity. There were inconsistent results with regard to the effect of graft choice, but HT grafts increased the risk of revision compared with PT grafts in three studies, although a larger graft diameter in HT grafts reduced the risk of revision. Patients presenting with a concomitant cartilage injury at the primary ACL reconstruction had a lower risk of revision compared with patients without a cartilage injury.

Study II found that there was high variability in the robustness of statistically significant results related to revision ACL reconstruction in the Scandinavian knee ligament registries. Nearly one third of all analyses had a fragility index of 0, indicating fragile statistical significance. The analyses related to the impact of age on the risk of revision had the highest fragility index overall, while analyses related to most of the surgical predictors for revision overall had a lower fragility index.

Study I

The 24 studies that met the inclusion criteria and reported on factors associated with the risk of revision ACL reconstruction had a Downs and Black score ranging from 9 to 19, with a median score of 16 of a possible 22 points. No study fulfilled item 8 (reporting of adverse events) or item 19 (compliance reliability reported). Apart from these items, there were few studies fulfilling item 12 (ensuring representativeness of the recruited subjects) and item 26 (taking account of the losses to follow-up).

PATIENT-RELATED FACTORS AND REVISION ACL RECONSTRUCTION

- Patient sex did not affect the risk of revision ACL reconstruction in any of the seven studies analyzing the relationship between patient sex and ACL revision. The largest study from the SNKLR presented a crude revision rate of 1.93% and 1.74% for males and females respectively (p = 0.383).[10]

- Young age was consistently associated with an increased risk of revision ACL reconstruction, across the eight studies reporting on this. Patients between 13-15 years of age ran a five times higher risk of undergoing ACL revision compared with the oldest age group (age 36-49 years) (HR 5.3 [95% CI 3.532 to 7.883]).[53] The risk of ACL revision was increased threefold for patients aged ≤ 25 years compared with patients aged ≥ 26 years (95% CI 2.587 to 3.934, p<0.001).[10]

- The BMI was not associated with the risk of ACL revision in the SNKLR.[10] In the NKLR, however, a BMI of < 25 kg/m^2 increased the risk of revision ACL reconstruction (HR 1.7 [95% CI 1.1 to 2.6], p=0.012).[202]

- Four studies reported on the association between activity at the time of primary ACL injury and the risk of revision. Alpine activities had a lower risk of ACL revision compared with soccer (HR 0.81 [95% CI 0.66 to 1.00]), while injury in traffic had an increased risk compared with soccer (HR 1.44 [95% CI 1.12 to 1.87]).[79]

- There was an increased risk of additional ACL reconstruction (both revision and contralateral) when combining young age, female sex and injury sustained during soccer, both compared with the overall study population and compared with males of the same age who played soccer at time of the injury.[5]

Table 9 illustrates the findings of patient-related factors associated with revision ACL reconstruction.

TABLE 9. Patient-related factors and their influence on the risk of revision anterior cruciate ligament reconstruction in Study I				
Factor Investigating studies	Patient sex 7 studies	Age 8 studies	BMI 2 studies	Activity at injury 4 studies
Increased risk		8 studies Younger age	1 study BMI < 25 kg/m^2	3 studies Soccer
Decreased risk				2 studies Alpine activities
No influence	7 studies		1 study	

The risk refers to the risk of revision anterior cruciate ligament reconstruction. The number of studies refer to the number of studies finding an increased risk, decreased risk or no influence for each factor.

BMI, body mass index

SURGERY-RELATED FACTORS AND REVISION ACL RECONSTRUCTION

- Undergoing a primary ACL reconstruction within less than a year from injury increased the risk of ACL revision according to the study with the largest study population.[65] Another study did, however, contradict these findings by reporting that the timing of primary ACL reconstruction did not influence the risk of ACL revision.[9]

- Seven studies reported on the impact of ACL graft choice on the risk of ACL revision, of which three studies found a lower risk with PT autografts compared with HT autografts.[79, 202, 212] In the largest cohort, the use of PT autografts reduced the risk of ACL revision by 37% compared with HT autografts (HR 0.63 [95% CI 0.53 to 0.74]).[79] The largest difference was found in patients aged 15-19 years at the five-year follow-up (revision rate 9.5% [95% CI 8.1 to 10.8] for HT and 3.5% [95% CI 2.1 to 4.8] for PT).[202] Every 0.5 mm increment in HT graft diameter from 7.0 to 10.0 mm reduced the likelihood of ACL revision by 14% (OR 0.86 [95% CI 0.75 to 0.99], p=0.03).[237] Another study found no impact of graft diameter on the risk of revision.[9]

- Five studies reported on the impact of graft fixation. The use of transfemoral HT fixation (Transfix and Rigidfix) resulted in a 30% reduction in the risk of revision compared with the use of Endobutton.[203] Cortical suspensory fixation was associated with an increased risk of ACL revision compared with all other types of fixation (HR 1.24 [95% CI 1.07 to 1.44], p<0.05). An intratunnel fixation technique reduced the risk of revision (HR 0.83 [95% CI 0.73 to 0.95], p<0.05) and the lowest risk of revision was found for femoral/tibial fixation combinations that were used in PT autograft ACL reconstruction.[64] Two of five studies found no impact of graft fixation on the risk of revision.

- Patients who had undergone primary ACL reconstruction using the TP or AM technique ran an increased risk of ACL revision compared with those who had undergone ACL reconstruction with a TT drilling technique in three studies.[53, 213, 246] A non-anatomic TT technique was associated with the lowest risk of ACL revision compared with a TP reference technique (HR 0.694 [95% CI 0.490 to 0.984], p=0.041).[53]

- Concomitant meniscus injury at the time of primary ACL reconstruction did not influence the risk of ACL revision. A concomitant cartilage injury at the time of primary ACL reconstruction reduced the risk of ACL revision compared with the absence of a cartilage injury for patients receiving

HT autografts (1.10% vs 1.86%, RR 0.59 [95% CI 0.41 to 0.84], p=0.004)[9] and two other studies found similar results.[53, 79] One study found no influence of cartilage injury on the risk of ACL revision.[65]

- Four studies reported on the use of single- versus double-bundle ACL reconstruction and the risk of ACL revision. Overall, in all three registries, there was no difference in the risk of ACL revision between HT single- and double-bundle ACL reconstruction, while PT single-bundle ACL reconstruction entailed a lower risk of ACL revision compared with double-bundle (HR 0.62 [95% CI 0.43 to 0.90], p=0.01).[3] In the SNKLR alone, however, double-bundle was associated with a reduced risk of revision compared with HT single-bundle ACL reconstruction (HR 1.00 vs 1.89 [95% CI 1.09 to 3.29], p=0.02).[3] Another study from the SNKLR found similar results, with an increased risk of revision for single-bundle compared with double-bundle ACL reconstruction (HR 1.98 [95% CI 1.12 to 3.51], p=0.019).[246]

Table 10 illustrates the findings of surgery-related factors associated with revision ACL reconstruction.

TABLE 10. Surgery-related factors and their influence on the risk of revision anterior cruciate ligament reconstruction in Study I

Factor Investigating studies	Time to ACLR 2 studies	Graft choice 7 studies	Femoral graft fixation 5 studies	Drilling technique 3 studies	Concomitant Injury 4 studies	Single- versus double-bundle 4 studies
Increased risk	1 study < 1y from injury		2 studies Cortical suspensory	3 studies Transportal > transtibial		1 study SB > DB
Decreased risk		3 studies PT < HT	1 study Transfemoral fixation		3 studies Cartilage	1 study PT SB < DB
No influence	1 study	4 studies	2 studies		4 studies Meniscus 1 study Cartilage	3 studies

The risk refers to the risk of revision anterior cruciate ligament reconstruction. The number of studies refer to the number of studies finding an increased risk, decreased risk or no influence for each factor.

ACLR, anterior cruciate ligament reconstruction; DB, double-bundle ACL reconstruction; HT, hamstring tendon; PT, patellar tendon; SB, single-bundle ACL reconstruction; y, year.

Study II

A total of 56 separate two-group comparative analyses with a dichotomous outcome (ACL revision, contralateral ACL reconstruction or presence of residual laxity) were identified, originating from 13 studies. The comparative two-group analyses were performed for the following grouping variables; age, patient sex, activity at the time of ACL injury, HT versus PT graft, femoral drilling technique, graft fixation, single- versus double-bundle ACL reconstruction, concomitant cartilage injury and country where the ACL reconstruction was performed.

The median sample size for the comparative groups was 5,540 patients (range 92-38,666), with a median sample size difference between the two comparative groups of 5,464.5 patients (range 26-31,930). For all 56 dichotomous analyses, the mean fragility index was 80.6, while the median was 34.5. Seventeen analyses (30.4%) became non-significant directly when applying the two-sided Fisher's exact test, thereby producing a fragility index of 0. A mean fragility index of 115.7 and a median of 87.0 (range 1-1,089) was found when excluding the 17 analyses with a fragility index of 0.

PATIENT-RELATED FACTORS

Age, patient sex and activity were identified as patient-related factors that had been analyzed in one or more two-group comparative analyses with a significant difference. The highest fragility index was found for the analyses of the impact of age, with a mean fragility index of 178.5 and a median of 116. The analyses regarding age consistently showed a higher risk of ACL revision for the younger age group compared with the older one. The mean and median fragility index for the analyses of patient-related factors is shown in Table 11. For further details, please see Table 2 in the published article.[244]

TABLE 11. The fragility index for patient-related factors in Study II

Grouping variable	Number of studies (n =)	Type of dichotomous event (n =)	Overall group sample size (mean/median)	Overall number of events in each group (mean/median)	Mean fragility index	Median fragility index	Number of analyses with an FI of zero (n =)
Age	6	Revision n = 18 CACLR n = 1	7,219 / 5,282	261 / 129	178.5	116.0	0
Patient sex	1	CACLR n = 1	8,841 / 8,841	263 / 263	35*	35*	0
Activity at time of injury	2	Revision n = 5 Revision or CACLR n = 1	10,071 / 9,093	278 / 238	16.0	5.5	2

CACLR, contralateral anterior cruciate ligament reconstruction; FI, fragility index; n, numbers
*Only one analysis for the fragility index, the absolute fragility index for that analysis is presented.

SURGERY-RELATED FACTORS

Surgery-related factors with statistically significant findings were HT versus PT autograft, femoral drilling technique, graft fixation, single- versus double-bundle ACL reconstruction, concomitant cartilage injury and Scandinavian country where the primary ACL reconstruction had been performed. Graft fixation as a grouping variable had the highest number of separate two-group analyses (n = 12), while the country of ACL reconstruction had the lowest (n = 1). The highest fragility index was found for the femoral drilling technique (mean fragility index 48.0, median fragility index 17.0), although three of six analyses of femoral drilling technique had a fragility index of 0. The lowest fragility index was found for the single- versus double-bundle analyses. Three of these analyses became non-significant directly when applying Fisher's exact test (fragility index 0) and the remaining analysis had a fragility index of 2, resulting in a mean fragility index of 0.5 for all four analyses. The mean and median fragility index for the analyses of surgery-related factors is shown in Table 12. For further details, please see Table 3 in the published article.[244]

TABLE 12. The fragility index for surgery-related factors in Study II							
Grouping variable	Number of studies (n =)	Type of dichotomous event (n =)	Overall group sample size (mean/median)	Overall number of events in each group (mean/median)	Mean fragility index	Median fragility index	Number of analyses with an FI of zero (n =)
HT vs. PT	3	Revision n = 3 Residual laxity n = 1	9,659 / 5,645	364 / 254	15.0	10.0	2
Femoral drilling technique	2	Revision n = 4 Residual laxity n = 2	4,374 / 3,493	194 / 165	48.0	17.0	3
Graft fixation	3	Revision n = 12	9,779 / 6,797	300 / 208	37.4	1.0	6
SB vs DB	2	Revision n = 4	5,191 / 2,222	158 / 85	0.5	0.0	3
Concomitant cartilage injury	3	Revision n = 2 CACLR n = 1	13,461 / 11,434	379 / 300	19.7	9.0	1
Country	1	Revision n = 1	20,474 / 20,474	741 / 741	130*	130*	0

CACLR, contralateral anterior cruciate ligament reconstruction; DB, double-bundle, FI, fragility index; HT, hamstring tendon; n, numbers; PT, patellar tendon; SB, single-bundle

*Only one analysis for the fragility index, the absolute FI for that analysis is presented.

11.2 THEME II – THE IMPACT OF A CONCOMITANT MEDIAL COLLATERAL LIGAMENT INJURY

Result summary

Study III found that patients without a concomitant MCL injury ran an approximately 30% lower risk of needing to undergo a revision ACL reconstruction compared with patients who had an MCL injury, regardless of the type of treatment for the MCL injury. When analyzing the risk of revision ACL reconstruction specifically for the type of MCL treatment, non-surgical treatment for an MCL injury resulted in an increased risk of revision, while there was no difference between patients undergoing ACL reconstruction with or without a concomitant MCL injury if the MCL injury was treated surgically. However, patients undergoing ACL reconstruction with surgical treatment to an MCL injury reported a clinically relevant inferior KOOS at the two-year follow-up on the Sport and recreation and QoL subscales, compared with isolated ACL reconstructions in the absence of an MCL injury.

The ACL graft choice did not affect the risk of ACL revision in patients with a concomitant non-surgically treated MCL injury. In Study IV, there was no difference in the risk of ACL revision between ST, ST+G and PT autografts. Nor was there any difference when the ST and the ST+G groups were combined into one HT group, compared with PT autografts. These findings were consistent in subgroup analyses of males and females separately.

Study V found that ACL-reconstructed patients with a concomitant non-surgically treated MCL injury were able to obtain a similar outcome in terms of RTS, tests of muscle function and PROs one year after ACL reconstruction, compared with patients who had undergone an ACL reconstruction without an MCL injury. However, the return to the pre-injury level of sport was low, where only 10% of the patients with a concomitant non-surgically treated MCL injury had returned to their pre-injury level of sport, compared with 26% of the patients without an MCL injury.

Study III

RISK OF ACL REVISION

The crude 2-year revision rate for the isolated ACL group was 1.9% (n = 349) and it had increased to 3.2% (n = 586) at 5 years. For the non-surgically treated MCL group, the 2- and 5-year revision rates were 2.9% (n = 19) and 4.0% (n = 26) respectively. The MCL suture repair and the MCL reconstruction group had no cases with revision surgery within the first 2 years (0.0%), while the revision rates were 3.8% (n = 2) and 1.2% (n = 1) respectively at 5 years. There was no significant difference in the crude revision rate at either the 2- or the 5-year follow-up between the groups.

Patients undergoing ACL reconstruction in the absence of an MCL injury ran a lower risk of ACL revision compared with patients with a concomitant MCL injury (regardless of the type of MCL treatment) (HR = 0.68 [95% CI 0.47–0.98], p = 0.036). When the isolated ACL reconstruction group was compared specifically with each subgroup of MCL treatment, a significantly reduced risk of ACL revision was found for the isolated ACL group compared with the non-surgically treated MCL group in both the unadjusted (HR = 0.69 [95% CI 0.48-0.99], p = 0.045) and adjusted analysis (HR = 0.61 [95% CI 0.41-0.89], p = 0.0097). There was no difference in the risk of revision when the isolated ACL group was compared with the suture repair MCL group (adjusted HR = 1.08 [95% CI 0.15-7.67]) or the MCL reconstruction group (adjusted HR = 2.22 [95% CI 0.31-15.82]).

PATIENT-REPORTED OUTCOME

The 2-year KOOS was significantly lower across the MCL groups compared with the isolated ACL group. All MCL groups reported a significantly lower $KOOS_4$ compared with the isolated ACL group, where the adjusted mean difference was 3.7 (95% CI 1.2-6.3), 9.8 (95% CI 1.3-18.2) and 7.9 (95% CI 0.8-15.0) for the non-surgical MCL group, the MCL suture repair group and the MCL reconstruction group respectively. The KOOS Sport and recreation subscale exhibited the largest differences for the MCL groups compared with the isolated ACL group. The MCL reconstruction group reported a lower score with a mean of 14.1 points (95% CI 4.3–23.9, p = 0.005) compared with the isolated ACL group, the MCL suture repair group reported a lower score with a mean of 13.1 points (95% CI 1.4–24.9, p = 0.028) and the non-surgically treated MCL group reported a lower score with a mean of 5.4 points (95% CI 1.8–9.0], p = 0.003) compared with the isolated ACL reconstruction group on the Sport and recreation subscale. The mean 2-year KOOS is presented in Figure 15.

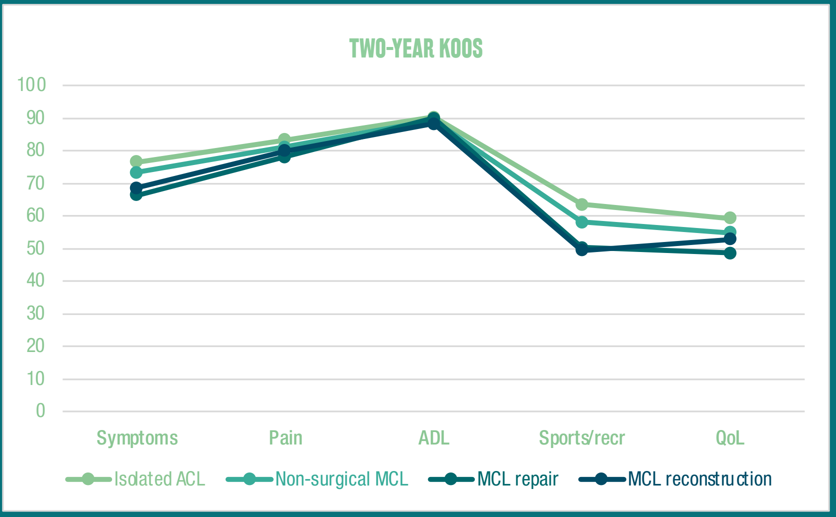

FIGURE 15

The two-year Knee injury and Osteoarthritis Outcome score for each treatment group in Study III. ACL, anterior cruciate ligament; MCL, medial collateral ligament.

Study IV

RISK OF ACL REVISION

The crude revision rates at 2 and 5 years are presented in Table 13. There was no difference in the crude revision rate between the groups. During the entire follow-up period, 39 patients (6.3%) underwent ACL revision surgery (ST group n = 14 [8.0 %], ST-G group n = 19 [5.9%] and PT group n = 6 [4.8%]).

TABLE 13. Crude 2- and 5-year revision rate and surgical intervention on the MCL at revision

	ACL revisions at 2 years, n (%)	ACL revisions at 5 years, n (%)	Surgical MCL treatment at revision, n (%)
Total cohort (n = 622)	21 (3.4%)	30 (4.8%)	6 (15.4%)
ST graft (n = 174)	9 (5.2%)	11 (6.3%)	3 (21.4%)
ST+G graft (n = 323)	10 (3.1%)	15 (4.6%)	2 (10.5%)
PT graft (n = 125)	2 (1.6%)	4 (3.2%)	1 (16.7%)
p-value	0.24	0.48	0.84

For categorical variables, n (%) is presented. n=number

ACL, anterior cruciate ligament; MCL, medial collateral ligament; ST, semitendinosus tendon; G, gracilis tendon; PT, patellar tendon

Using the ST-G group as the reference group, there was no difference in the risk of ACL revision surgery for either the ST group (HR 1.354; 95% CI 0.678-2.702) or the PT group (HR 0.837; 95% CI 0.334-2.100) compared with the ST-G group. Likewise, subgroups analyses of males and females respectively did not reveal any difference between groups in the risk of ACL revision surgery. When the ST-G and ST group were combined into one HT group and compared with the PT group, there was no difference between the groups in the risk of ACL revision (HR 0.745; 95% CI 0.312-1.783) (Table 14).

TABLE 14. Comparison of risk of ACL revision between graft types and subgroup analyses.

				Unadjusted analysis		Adjusted analysis*	
Analyzed population	**Graft choice**	**Number of events**	**Event rate/100 patient years**	**HR**	**95% CI**	**HR**	**95% CI**
Total study cohort (n = 622)	ST+G graft (n = 323)#	19	0.926	-	-	-	-
	PT graft (n = 125)	6	0.619	0.769	0.307 – 1.927	0.837	0.334 – 2.100
	ST graft (n = 174)	14	1.360	1.431	0.717 – 2.854	1.354	0.678 – 2.702
Females¥ (n = 264)	ST+G graft (n = 149)#	7	0.757	-	-		
	PT graft (n = 40)	3	1.018	1.590	0.411 – 6.149		
	ST graft (n = 75)	5	1.132	1.493	0.474 – 4.706		
Males¥ (n = 358)	ST+G graft (n = 174)#	12	1.064	-	-		
	PT graft (n = 85)	3	0.445	0.477	0.135 – 1.692		
	ST graft (n = 99)	9	1.533	1.390	0.585 – 3.300		
Total study cohort (n = 622)	HT graft (n = 497)#	33	1.071	-	-	-	-
	PT graft (n = 125)	6	0.619	0.672	0.281 – 1.604	0.745	0.312 – 1.783

*Adjusted for cartilage injury. #Reference group in the analysis. ¥The number of events in the subgroups of females and males is too small to perform an adjusted analysis.

ACL, anterior cruciate ligament; CI, confidence interval; G, gracilis tendon; HR, hazard ratio; PT, patellar tendon; ST; semitendinosus tendon

PATIENT-REPORTED OUTCOME

For the 1-year KOOS, the only significant difference between the groups was found on the Sport and recreation subscale. The PT group had a significantly lower mean score compared with both the ST group (52.0 [SD 27.5] compared with 64.5 [SD 28.6], p = 0.007) and the ST-G group (52.0 [SD 27.5] compared with 58.8 [SD 27.8], p = 0.032). In the 2-year KOOS, the ST group had a significantly higher score on the Sport and recreation subscale compared with both the ST-G group (68.5 [SD 28.5] compared with 57.4 [SD 27.6], adjusted p = 0.010) and the PT group (68.5 [SD 28.5] compared with 54.1 [SD 30.3], adjusted p = 0.006). Moreover, the ST group reported a significantly higher KOOS QoL compared with the ST-G group (64.2 [SD 24.0] compared with 55.7 [SD 21.9], adjusted p = 0.005) (Table 15).

TABLE 15. Comparison of the Knee injury and Osteoarthritis Outcome Score at the two-year follow-up.											
						ST graft vs ST+G graft		ST graft vs PT graft		ST+G graft vs PT graft	
KOOS sub-scale	Total (n=622)	ST graft (n=174)	ST+G graft (n=323)	PT graft (n=125)	p-value	Unad-justed	Adjust-ed*	Unad-justed	Adjust-ed*	Unad-justed	Adjust-ed*
Pain	82.9 (16.2) 86.1 (11.1; 100.0) n=300	85.9 (16.6) 91.7 (11.1; 100.0) n=85	82.1 (14.4) 86.1 (33.3; 100.0) n=156	80.6 (19.2) 86.1 (22.2; 100.0) n=59	0.016	0.0043	0.086	0.056	0.094	0.86	0.44
Symp-toms	75.5 (18.9) 78.6 (14.3; 100.0) n=300	79.1 (19.2) 82.1 (14.3; 100.0) n=85	73.9 (17.7) 75.0 (35.7; 100.0) n=156	74.6 (21.0) 78.6 (14.3; 100.0) n=59	0.051						
ADL	89.9 (14.7) 97.1 (16.2; 100.0) n=300	91.7 (14.1) 97.1 (33.8; 100.0) n=85	89.9 (14.0) 95.6 (16.2; 100.0) n=156	87.0 (17.1) 95.6 (33.8; 100.0) n=59	0.058						
Sport and recreation	59.9 (28.8) 65.0 (0.0; 100.0) n=299	68.5 (28.5) 75.0 (0.0; 100.0) n=85	57.4 (27.6) 60.0 (0.0; 100.0) n=155	54.1 (30.3) 60.0 (0.0; 100.0) n=59	0.001	0.001	0.010	0.003	0.006	0.53	0.25
QoL	58.2 (23.4) 62.5 (0.0; 100.0) n=299	64.2 (24.0) 68.8 (6.3; 100.0) n=85	55.7 (21.9) 56.3 (6.3; 100.0) n=155	55.9 (24.9) 56.3 (0.0; 100.0) n=59	0.020	0.006	0.005	0.056	0.054	0.87	0.98

For continuous variables, the mean (SD)/median (min; max)/n=is presented.
*) Adjusting for patient sex and cartilage injury using logistic regression

ADL, activities of daily living; G, gracilis tendon; KOOS, Knee injury and Osteoarthritis Outcome Score; ST, semitendinosus tendon; PT, patellar tendon; QoL, quality of life

In the KOOS PASS analyses, there was no difference between the groups in the proportion of patients achieving the 1-year KOOS PASS. The achievement of a 2-year PASS differed significantly between the ST and the ST-G group on the Pain and ADL subscales, where a consistently higher proportion achieved a PASS in the ST group compared with the ST-G group. Additionally, the proportion achieving a PASS on the Sport and recreation subscale was significantly higher for the ST group (55.3%; 95% CI 44.1-66.1%) compared with both the ST-G group (37.4%; 95% CI 29.8-45.5%; p = 0.0014) and the PT group (33.9%; 95% CI 22.1-47.4%; p = 0.009). The 2-year PASS results are presented for each group in Figure 16.

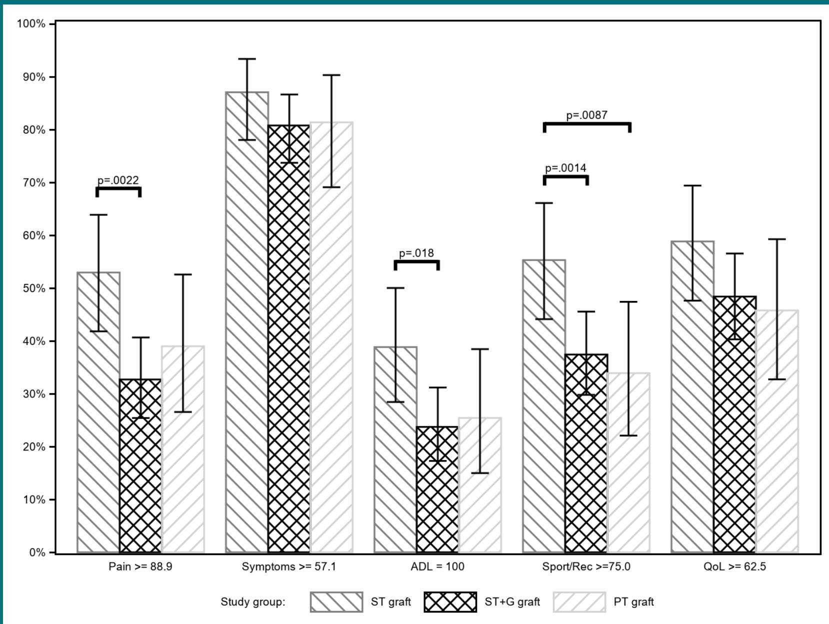

FIGURE 16

The proportion achieving the two-year patient acceptable symptom state for each study group in Study IV.

Study V

RETURN TO SPORT

The RTS rate did not differ between the groups, where 14 patients (46.7%) in the ACL+ MCL group and 44 patients (48.9%) in the ACL group reported that they had returned to knee-strenuous sport at the one-year follow-up (Tegner of ≥6). A lower proportion of patients had returned to their pre-injury level of sport in the ACL+MCL group (n = 3, 10.0%), compared with the ACL group (n = 23, 25.6%). However, this difference was not statistically significant (p = 0.11) (Table 16).

TEST OF MUSCLE FUNCTION

There was no difference between the groups in any of the five muscle function tests. Both groups had a mean LSI of > 90% in four of five tests (quadriceps strength, hamstring strength, single-leg hop for distance and single-leg side hop). In the single-leg vertical hop, both groups had a mean LSI of > 85%. Table 16 presents the results of the tests of muscle function.

TABLE 16. The one-year Tegner activity score and the limb symmetry index for tests of muscle function in Study V

	Total (n=120)	ACL+MCL (n=30)	ACL (n=90)	p-value	Difference between groups Mean (95% CI)
Tegner activity score					
Return to sport (Tegner score ≥ 6)	58 (48.3%)	14 (46.7%)	44 (48.9%)	1.00	-2.2 (-25.1; 20.6)
Return to pre-injury Tegner activity level	26 (21.7%)	3 (10.0%)	23 (25.6%)	0.11	-15.6 (-31.8; 0.7)
Tests of muscle function					
Quadriceps strength LSI (%)	94.0 (8.9) 95.4 (71.9; 123.5) (87.5; 99.3) n=92	92.8 (10.0) 94.6 (71.9; 117.3) (86.6; 100) n=25	94.4 (8.5) 95.6 (72.6; 123.5) (89.3; 99.3) n=67	0.45	-1.6 (-5.7; 2.6)
Hamstring strength LSI (%)	98.6 (11.8) 97.8 (64.5; 128.6) (90.6; 106.8) n=92	99.2 (11.9) 100 (64.5; 122.5) (92.9; 108.3) n=25	98.4 (11.8) 97.3 (72.8; 128.6) (89.5; 105.2) n=67	0.76	0.8 (-4.7; 6.4)
Single-leg vertical hop LSI (%)	85.7 (15.9) 86.3 (41; 123.4) (76.9; 96.1) n=91	85.8 (17.4) 89.1 (46.4; 123.4) (72.2; 96.1) n=23	85.7 (15.6) 86.3 (41; 118) (77; 96) n=68	0.98	0.2 (-7.7; 7.9)
Single-leg hop for distance LSI (%)	94.0 (8.6) 95 (68.6; 111.2) (89.5; 100.7) n=91	96.1 (7.3) 93 (80; 111.2) (90.9; 101.2) n=23	93.3 (9.0) 95.1 (68.6; 111.1) (88.1; 99.7) n=68	0.17	2.9 (-1.1; 7.0)
Single-leg side hop LSI (%)	94.2 (13.7) 93.6 (50; 136.8) (88.5; 102.4) n=86	97.4 (12.6) 94.8 (75; 136.8) (89.5; 105.3) n=23	93.0 (14.0) 93.4 (50; 122.7) (87; 100) n=63	0.18	4.5 (-2.0; 11.2)

ACL, anterior cruciate ligament; CI, confidence interval; LSI, Limb Symmetry Index; MCL, medial collateral ligament
For categorical variables, n (%) is presented. For continuous variables, the mean (SD)/median (min; max)/ Q1; Q3).
Mean differences between groups are calculated as the MCL+ACL group minus the ACL group.

PATIENT-REPORTED OUTCOME

There were no differences between the groups in any of the assessed PROs. The mean ACL-RSI was 59.4 (SD 21.6) and 57.9 (SD 19.4) for the ACL+MCL and the ACL group respectively, p = 0.60. The $KOOS_4$ was 76.0 (SD 16.0) for the ACL+MCL group and 75.7 (SD 13.7) for the ACL group (p = 0.97). With regard to the KOOS PASS, the largest proportion of achievement for both groups was found on the Symptom scale where 90.0% and 94.6% reported a score above the threshold for an acceptable symptom state in the ACL+MCL group and the ACL group respectively (p = 0.75). For the Sport and recreation subscale, the proportion who achieved a PASS in the ACL+MCL group was 55.0%, compared with 58.1% in the ACL group (p = 1.00). The one-year PROs are presented in detail in Table 17.

TABLE 17. Comparison of patient-reported outcomes at the one-year follow-up in Study V					
	Total (n=120)	ACL+MCL (n=30)	ACL (n=90)	p-value	Difference between groups Mean (95% CI)
One-year K-SES$_{18}$					
K-SES$_{18}$ present	8.3 (1.5) 8.7 (2.9; 10.0) (7.5; 9.4) n=119	8.1 (1.7) 8.8 (3.4; 10.0) (7.2; 9.5) n=30	8.3 (1.4) 8.7 (2.9; 10.0) (7.7; 9.4) n=89	0.50	-0.2 (-0.8; 0.4)
K-SES$_{18}$ future	7.3 (1.8) 7.5 (1.0; 10.0) (6.0; 8.8) n=119	7.2 (1.5) 7.2 (3.8; 9.5) (6.0; 8.5) n=30	7.3 (1.9) 8.0 (1.0; 10.0) (6.0; 8.8) n=89	0.83	-0.1 (-0.8; 0.7)
One-year KOOS					
Symptoms	81.7 (14.1) 85.7 (35.7; 100) (75; 92.9) n=94	82.7 (15.3) 85.7 (46.4; 100) (80.4; 94.6) n=20	81.4 (13.8) 85.7 (35.7; 100) (71.4; 92.9) n=74	0.75	1.26 (-5.58; 8.71)
Pain	88.9 (9.9) 91.7 (61.1; 100) (83.3; 97.2) n=94	91.7 (7.8) 91.7 (72.2; 100) (86.1; 97.2) n=20	88.1 (10.3) 91.7 (61.1; 100) (80.6; 97.2) n=74	0.14	3.57 (-1.11; 8.52)
Activities of daily living	96.3 (5.4) 98.5 (70.6; 100) (94.1; 100) n=94	96.9 (3.8) 97.8 (88.2; 100) (96.3; 100) n=20	96.2 (5.8) 98.5 (70.6; 100) (94.1; 100) n=74	0.65	0.727 (-1.765; 3.633)
Sport and recreation	72.2 (21.9) 75 (5; 100) (60; 90) n=94	68.0 (27.9) 80 (5; 100) (52.5; 92.5) n=20	73.4 (20.0) 75 (25; 100) (65; 90) n=74	0.34	-5.38 (-16.15; 6.07)
Quality of life	60.4 (18.7) 62.5 (12.5; 100) (43.8; 75) n=94	61.6 (19.4) 65.6 (25; 93.8) (46.9; 75) n=20	60.1 (18.6) 62.5 (12.5; 100) (43.8; 75) n=74	0.79	1.51 (-7.42; 10.83)
KOOS$_4$	75.8 (14.1) 78.4 (40.6; 98.4) (67.3; 86.4) n=94	76.0 (16.0) 78.4 (40.6; 98.4) (66.4; 87.9) n=20	75.7 (13.7) 78.6 (43.5; 97.9) (67.8; 85.1) n=74	0.97	0.240 (-6.652; 7.370)
One-year KOOS PASS					
Symptoms ≥ 57.1					
Yes	88 (93.6%)	18 (90.0%)	70 (94.6%)	0.75	-4.6 (-21.9; 12.7)
Pain ≥ 88.9					
Yes	50 (53.2%)	12 (60.0%)	38 (51.4%)	0.67	8.6 (-18.8; 36.1)
Activities of daily living = 100					
Yes	42 (44.7%)	8 (40.0%)	34 (45.9%)	0.83	-5.9 (-29.3; 19.7)
Sport and recreation ≥ 75					
Yes	54 (57.4%)	11 (55.0%)	43 (58.1%)	1.00	-3.1 (-30.8; 24.6)
Quality of life ≥ 62.5					
Yes	53 (56.4%)	13 (65.0%)	40 (54.1%)	0.54	10.9 (-16.0; 37.9)
One-year ACL-RSI	57.6 (19.9) 57.5 (16.7; 100) (42.5; 72.5) n=107	59.4 (21.6) 55.8 (25; 95) (40.8; 80) n=27	57.0 (19.4) 57.5 (16.7; 100) (43.3; 70.8) n=80	0.60	2.42 (-6.49; 11.40)

For categorical variables, n (%) is presented. For continuous variables, the mean (SD)/median (min; max)/(Q1; Q3)/ n= is presented. Mean differences between groups are calculated as the MCL+ACL group minus the ACL group.

ACL, anterior cruciate ligament; ACL-RSI, anterior cruciate ligament return to sport after injury; CI, confidence interval; KOOS, Knee injury and Osteoarthritis Outcome Score; K-SES, Knee Self-Efficacy Scale; MCL, medial collateral ligament; PASS, patient acceptable symptom state.

11.3 THEME III – OUTCOME AFTER REVISION

Result summary

Study VI found that three studies from the Scandinavian knee ligament registries had reported PROs after revision ACL reconstruction compared with primary ACL reconstruction. There were consistent findings that patients did significantly less well after an ACL revision, compared with primary ACL reconstruction. The largest level of inferiority was found for the patient-reported outcome for sport and recreational activities, as well as quality of life.

Study VII similarly found an inferior outcome one year after the ACL revision compared with the primary ACL reconstruction, when assessed in the same population of patients who had undergone both primary and revision ACL reconstruction. However, the differences in PROs between the surgeries were smaller compared with what was found in Study VI. The KOOS sport and recreation subscale displayed the greatest inferiority, where the patients reported an approximately 4-point lower score after ACL revision compared with their primary surgery. A PLC injury at ACL revision, a higher severity grade of cartilage injury and higher age at the primary ACL reconstruction predicted a poorer KOOS sport and recreation score after ACL revision. There was a significant decrease in meniscal injuries between primary and revision ACL reconstruction, while the prevalence of cartilage injuries was increased at revision ACL reconstruction. A cartilage injury was present in 18.3% of the cohort at primary ACL reconstruction and in 35.1% at revision ACL reconstruction.

Study VI

Three studies reported the outcome after ACL revision in comparison with primary ACL reconstruction in the Scandinavian knee ligament registries. Two studies originated from the SNKLR[5, 134] and one study from the DKRR.[152] The Downs and Black score ranged from 12 to 15 points of a possible 22. No study took patients lost to follow-up into account (Item 26), nor did any study determine the representativeness of the study population (Item 12). Only one study adjusted for potential confounding factors (Item 25). To summarize, all three studies reported a significantly poorer outcome after ACL revision compared with primary ACL reconstruction.

One study from the SNKLR by Kvist et al.[134] included patients undergoing surgery between 2005 and 2012 and comprised 22,059 primary reconstructions and 1,431 ACL revisions.[134] The ACL revision cases reported a significantly lower KOOS compared with primary ACL reconstruction cases on all follow-up occasions, across all KOOS subscales. The differences between the groups varied between 5 and 19 points ($p < 0.01$). The largest difference of 19 points was seen on the KOOS sport and recreation subscale at the 5-year follow-up. Similarly, the EQ-5D index was significantly lower for the ACL revision cases at all follow-ups (with differences between 0.067 and 0.101, $p < .001$) and EQ-5D VAS (with differences between 6 and 7, $p < .001$).[134] Figure 17 presents the KOOS data reported in the study by Kvist et al.[134]

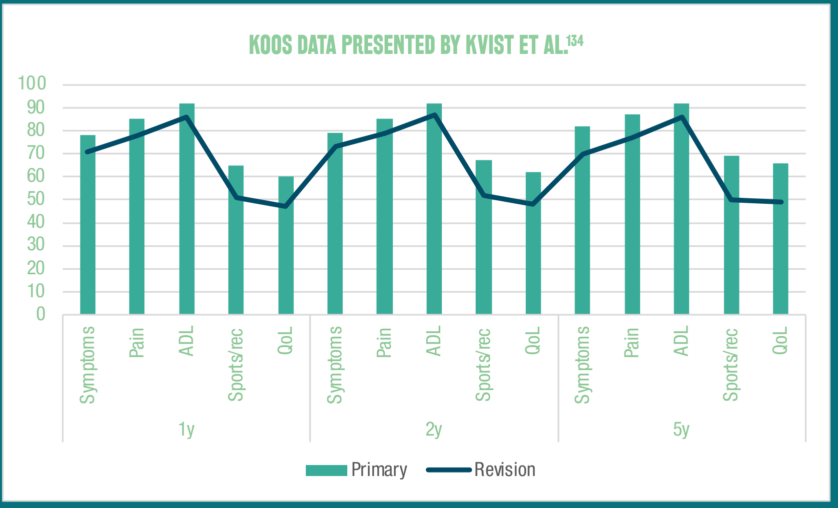

FIGURE 17

Data presented by Kvist et al.[134] on the KOOS at the one- to five-year follow-up after primary and revision ACL reconstruction. The staples represent the mean KOOS score at primary ACL reconstruction and the line represents the mean score at revision ACL reconstruction

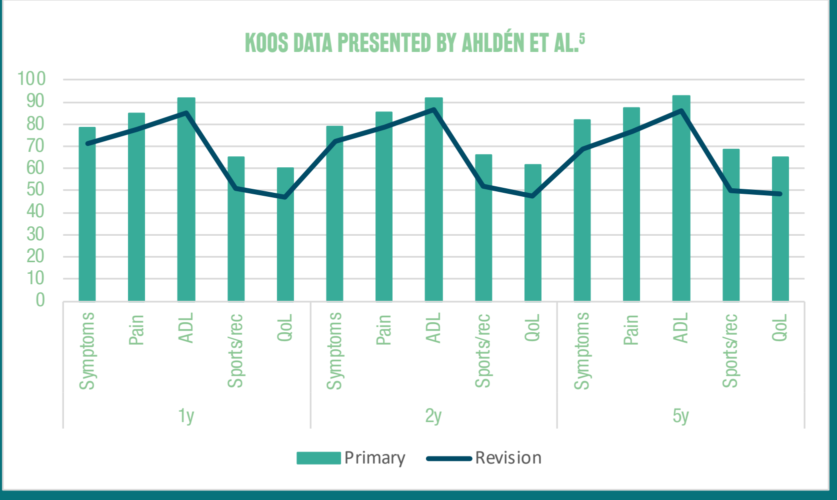

FIGURE 18

Data presented by Ahldén et al.[5] on the KOOS at the one- to five-year follow-up after primary and revision ACL reconstruction. The staples represent the mean KOOS score at primary ACL reconstruction and the line represents the mean score at revision ACL reconstruction.

Another study from the SNKLR by Ahldén et al.[5] comprised patients undergoing primary and revision ACL reconstruction between 2005 and 2010.[5] A total of 16,351 patients were included. A significantly lower KOOS was found after ACL revision compared with primary ACL reconstruction across all subscales on all follow-up occasions ($p < 0.001$). Figure 18 presents the KOOS data for primary and revision ACL reconstruction reported by Ahldén et al.[5] There was a significant improvement on all KOOS subscales at the 1- and 2-year follow-up compared with the preoperative score for patients undergoing ACL revision ($p < 0.05$), except for the Symptom subscale at 2 years ($p = 0.07$). However, at the 5-year follow-up, only the KOOS sport and recreation and the QoL subscale remained significantly improved compared with the preoperative KOOS score ($p < 0.002$).[5]

One study by Lind et al.[152] originated from the DKRR and comprised patients undergoing primary and revision ACL reconstruction between 2005 and 2010.[152] The study cohort comprised 12,193 primary ACL reconstructions and 1,099 ACL revisions. The one-year KOOS was significantly lower after ACL revision compared with primary ACL reconstruction ($p < 0.001$). Figure 19 presents the KOOS data reported by Lind et al.[152] Similarly, the Tegner score at the one-year follow-up was lower after ACL revision compared with primary ACL reconstruction (median 4 [range 3-5] compared with 5 [range 4-6], $p < 0.05$). One year after ACL revision, 38% reported a KOOS QoL of < 40, which was defined by the authors as subjective failure. The subjective failure rate after primary ACL reconstruction was 20%.[152]

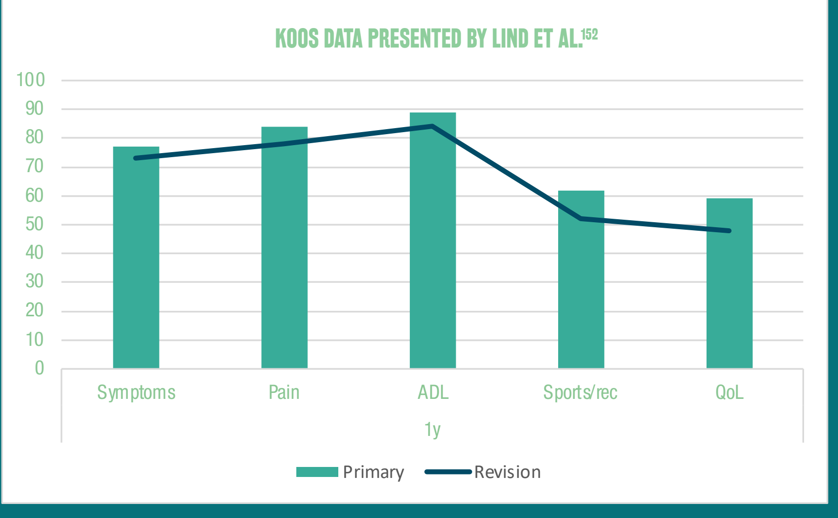

FIGURE 19

Data presented by Lind et al.[152] on the mean KOOS at one-year follow-up after primary and revision ACL reconstruction. The staples represent the mean KOOS score at primary ACL reconstruction and the line represents the mean score at revision ACL reconstruction.

CONCOMITANT INJURIES

At primary ACL reconstruction, 43.0% of the patients presented with a meniscal injury compared with 33.7% at revision ACL reconstruction. There was a significant decrease in meniscal injuries between primary and revision ACL reconstruction, as 27.3% of the cohort had a meniscal injury at primary ACL reconstruction that was not present at revision, while 18.0% presented with a new meniscal injury at the ACL revision ($p < 0.001$). For medial meniscal injuries, there was no change over time from primary to revision ACL reconstruction in prevalence or the number of patients treated with medial meniscal resection. However, 4.0% of the patients underwent medial meniscal repair at primary ACL reconstruction compared with 6.2% at revision ACL reconstruction, representing a significant increase in medial meniscal repair at revision ACL reconstruction ($p = 0.032$). For lateral meniscal injuries, there was a significant decrease between primary and revision ACL reconstruction ($p < 0.001$). At primary ACL reconstruction, 27.8% had a lateral meniscal injury and 18.9% had a lateral meniscal injury at revision. There was a significant decrease in lateral meniscus resection at revision compared with primary surgery ($p = 0.003$), however, there was no difference in lateral meniscal repair ($p = 1.00$). The proportion of patients with meniscal injuries and meniscal procedures at primary and revision ACL reconstruction is presented in Figure 20.

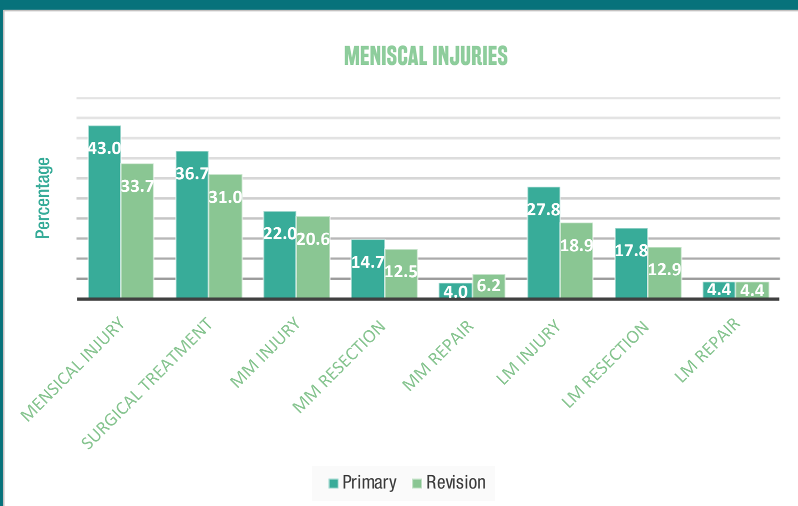

FIGURE 20

The proportion of patients with meniscal injuries and treatment of such, at primary and revision ACL reconstruction respectively. MM, medial meniscus; LM, lateral meniscus.

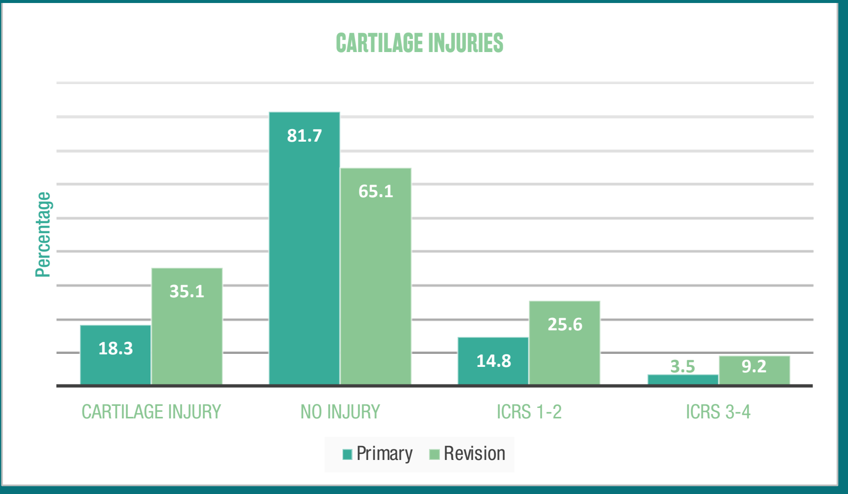

FIGURE 21

The proportion of patients with cartilage injuries at primary and revision ACL reconstruction respectively, and the severity grading according to the ICRS.

A new cartilage injury, not present at the primary ACL reconstruction, was identified in 23.0% of the cohort at the revision ACL reconstruction. This represented a significant increase in cartilage injuries from primary to revision ACL reconstruction ($p < 0.001$). A cartilage injury was present in 18.3% of the cohort at primary ACL reconstruction and in 35.1% at revision ACL reconstruction. Similarly, there was an increase in the severity of cartilage injuries overall at revision ACL reconstruction compared with primary ACL reconstruction, where 26.1% of the cohort increased at least one step in the ICRS grade (ICRS 0 / ICRS 1-2 / ICRS 3-4) ($p < 0.001$). The proportion of patients with cartilage injuries and within each ICRS grouping at primary and revision ACL reconstruction is presented in Figure 21.

Concomitant PLC injuries increased significantly between primary and ACL revision (0.3% at primary ACL reconstruction compared with 1.6% at ACL revision, $p = 0.002$), while MCL injuries decreased significantly (3.3% at primary ACL reconstruction compared with 1.2% at ACL revision, $p = 0.003$).

PATIENT-REPORTED OUTCOME

Preoperatively, patients reported a significantly higher KOOS prior to the ACL revision compared with the primary ACL reconstruction on the KOOS subscales of Pain, Symptoms and Sport and recreation. The largest difference preoperatively was found on the Sport and recreation subscale, where the patients reported a mean of 3.7 (SD 30.7) points higher prior to the ACL revision surgery compared with the primary ACL reconstruction ($p = 0.002$). The preoperative $KOOS_4$ was significantly higher for the revision ACL reconstruction compared with the primary ACL reconstruction (mean 56.8 [SD 20.4] compared with 55.3 [SD 17.7], $p = 0.012$).

The one-year postoperative KOOS was significantly lower after ACL revision compared with after the primary ACL reconstruction on all subscales, including the $KOOS_4$, except for the QoL subscale. The largest difference was seen on the Sport and recreation subscale (mean 56.0 [SD 31.0] after primary ACL reconstruction compared with 51.9 [SD 30.3] after revision ACL reconstruction, $p = 0.002$).

In terms of the change from preoperatively to one year postoperatively, the patients improved significantly less at the revision ACL reconstruction on the majority of the KOOS subscales. For the $KOOS_4$, the improvement was a mean of 4.6 points [SD 32.0] lower at revision ACL reconstruction compared with the primary ACL reconstruction (p = 0.028). The KOOS subscale with the largest difference in improvement between the occasions was the Sport and recreation subscale, where the patients reported a mean of 7.1 [SD 46.9] points less improvement after ACL revision compared with primary ACL reconstruction (p = 0.024). Table 18 presents the KOOS data from Study VII.

TABLE 18. The Knee injury and Osteoarthritis Outcome Score for primary and revision ACL reconstruction.[245]

	Primary ACL reconstruction (n = 1,014)	ACL revision (n = 1,014)	Change from primary ACL reconstruction to revision	p-value
Preoperative KOOS				
Pain	75.2 (17.9) 77.8 (0.0; 100.0) n=853	76.1 (19.2) 80.6 (11.1; 100.0) n=898	1.3 (18.8) 0.0 (-83.3; 66.7) n=754	0.017
Symptoms	69.7 (18.3) 71.4 (3.6; 100.0) n=852	70.9 (19.3) 71.4 (10.7; 100.0) n=898	1.7 (20.7) 0.0 (-75.0; 67.9) n=753	0.032
ADL	84.9 (16.7) 91.2 (0.0; 100.0) n=853	85.0 (17.5) 92.7 (2.9; 100.0) n=897	0.2 (17.5) 0.000 (-94.1; 61.8) n=753	0.37
Sport and recreation	42.2 (28.0) 40.0 (0.0; 100.0) n=853	45.4 (29.9) 45.0 (0.0; 100.0) n=898	3.7 (30.7) 0.0 (-75.0; 100.0) n=754	0.002
QoL	34.3 (19.7) 31.3 (0.0; 100.0) n=853	34.9 (24.0) 31.3 (0.0; 100.0) n=898	1.4 (25.0) 0.0 (-81.3; 100.0) n=754	0.86
$KOOS_4$	55.3 (17.7) 55.7 (0.9; 100.0) n=853	56.8 (20.4) 56.5 (7.9; 100.0) n=898	2.0 (19.7) 1.9 (-59.4; 61.5) n=754	0.012
One-year postoperative KOOS				
Pain	79.9 (18.7) 86.1 (5.6; 100.0) n=613	78.2 (20.6) 84.7 (5.6; 100.0) n=482	-3.1 (20.1) -2.8 (-63.9; 91.7) n=303	0.003
Symptoms	72.8 (19.6) 75.0 (14.3; 100.0) n=612	71.1 (21.1) 75.0 (3.6; 100.0) n=482	-2.8 (20.1) 0.0 (-64.3; 60.7) n=302	0.014
ADL	88.0 (16.3) 94.1 (11.8; 100.0) n=612	86.6 (18.3) 94.1 (2.9; 100.0) n=482	-2.6 (16.1) 0.0 (-61.8; 57.4) n=302	0.006
Sport and recreation	56.0 (31.0) 60.0 (0.0; 100.0) n=613	51.9 (30.3) 52.5 (0.0; 100.0) n=482	-5.2 (32.2) -5.0 (-95.0; 100.0) n=303	0.002
QoL	46.8 (28.2) 43.8 (0.0; 100.0) n=613	45.8 (26.2) 43.8 (0.0; 100.0) n=482	-1.8 (29.3) 0.0 (-81.3; 93.8) n=303	0.17
$KOOS_4$	63.8 (22.2) 66.9 (7.9; 100.0) n=613	61.7 (22.4) 64.6 (3.7; 100.0) n=482	-3.2 (22.3) -3.2 (-59.8; 62.3) n=303	0.01
KOOS change preoperatively to one-year follow-up				
Pain	5.8 (17.6) 5.6 (-55.6; 66.7) n=452	2.8 (19.7) 2.8 (-75.0; 72.2) n=366	-3.2 (28.2) -2.8 (-77.8; 94.5) n=201	0.033
Symptoms	4.3 (19.6) 3.6 (-78.6; 60.7) n=451	0.6 (20.6) 0.0 (-89.3; 89.3) n=366	-4.5 (.) . (-82.1; 121.4) n=200	0.011
ADL	3.7 (15.9) 1.5 (-55.9; 61.8) n=451	2.1 (15.6) 0.0 (-54.4; 55.9) n=365	-0.6 (22.7) -1.5 (-57.4; 97.1) n=200	0.088
Sport and recreation	16.4 (31.3) 15.0 (-85.0; 100.0) n=452	8.1 (32.7) 5.0 (-100.0; 100.0) n=366	-7.1 (46.9) -10.0 (-115.0; 130.0)n=201	0.024
QoL	15.6 (28.4) 12.5 (-100.0; 87.5) n=452	12.1 (29.9) 12.5 (-100.0; 93.8) n=366	-3.8 (44.5) -6.3 (-137.5; 125.0) n=201	0.26
$KOOS_4$	10.5 (20.6) 11.3 (-71.8; 69.9) n=452	5.9 (22.5) 5.9 (-91.1; 71.4) n=366	-4.6 (32.00) -4.2 (-79.2; 99.3) n=201	0.028

The mean (SD)/median (min; max)/n = is presented.

ADL, activities of daily living; KOOS, Knee injury and Osteoarthritis Outcome Score; n, numbers; QoL, quality of life

PREDICTORS OF OUTCOME AFTER REVISION ACL RECONSTRUCTION

For the KOOS Sport and recreation subscale one year after ACL revision, the multivariable model identified the following independent predictors of outcome: a PLC injury (β = -29.20 [95% CI -50.71; -6.69], p = 0.011) at the time of ACL revision, higher ICRS of any cartilage injury (β = -4.55 [95% CI -8.67; -0.44], p = 0.030) and higher age at primary ACL reconstruction. Specifically, every one-step increment in ICRS category (ICRS 0, ICRS 1-2, ICRS 3-4) predicted a 4.55 points lower score for KOOS sport and recreation, while every 10-year increment in age at primary ACL reconstruction predicted a 4.69-point lower score (β = -4.69 [95% CI -8.38; -1.01], p = 0.013). The multivariable model had an adjusted R^2 of 0.041 (Figure 22).

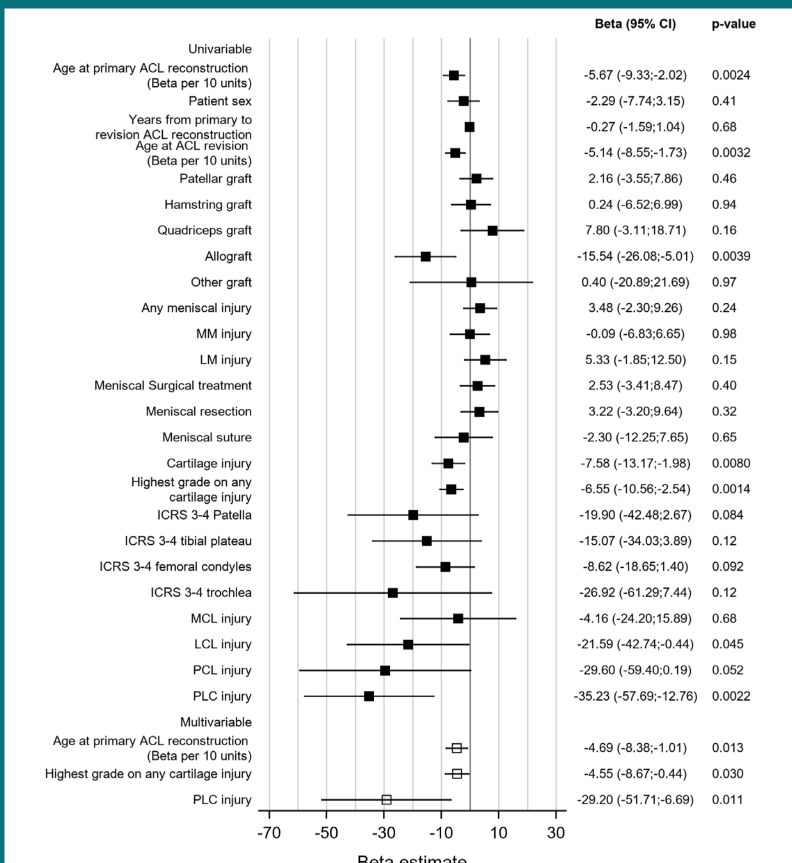

FIGURE 22

Univariable and multivariable linear regression models of the KOOS sport and recreation one year after ACL revision. LCL, lateral collateral ligament; LM, lateral meniscus; MCL, medial collateral ligament, MM, medial meniscus; PCL, posterior cruciate ligament, PLC, posterolateral corner

For the KOOS QoL subscale one year after ACL revision, the multivariable model identified the following independent predictors: a concomitant PLC injury (β = -25.21 [95% CI -44.77; -5.65], p = 0.012) at the time of ACL revision and the use of allograft for ACL revision (β = -12.69 [95% CI -21.84; -3.55], p = 0.0066), both thus predicting a poorer KOOS QoL score. The multivariable model had an adjusted R^2 of 0.030 (Figure 23).

For the $KOOS_4$ one year after ACL revision, the multivariable model identified the following independent predictors: the use of allografts for ACL revision (β = -11.40 [95% CI -19.24; -3.57], p = 0.0044) and a PLC injury at the time of ACL revision (β = -24.20 [95% CI -40.96; -7.43], p = 0.0048). The multivariable model had an adjusted R^2 of 0.036 (Figure 24).

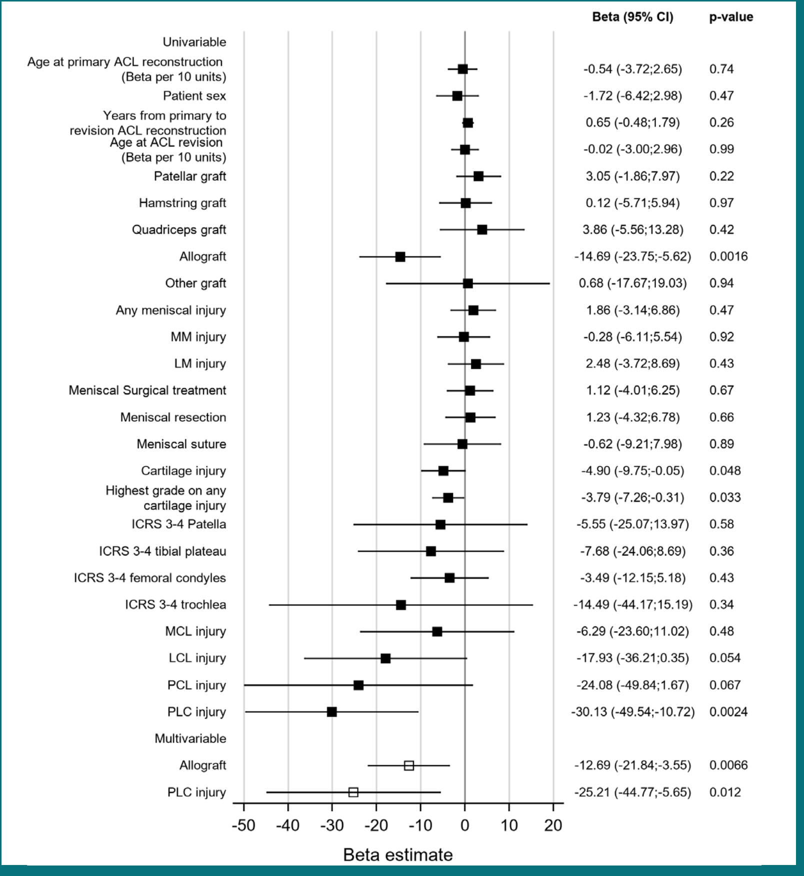

FIGURE 23

Univariable and multivariable linear regression models of the KOOS Quality of Life one year after ACL revision. LCL, lateral collateral ligament; LM, lateral meniscus; MCL, medial collateral ligament, MM, medial meniscus; PCL, posterior cruciate ligament, PLC, posterolateral corner

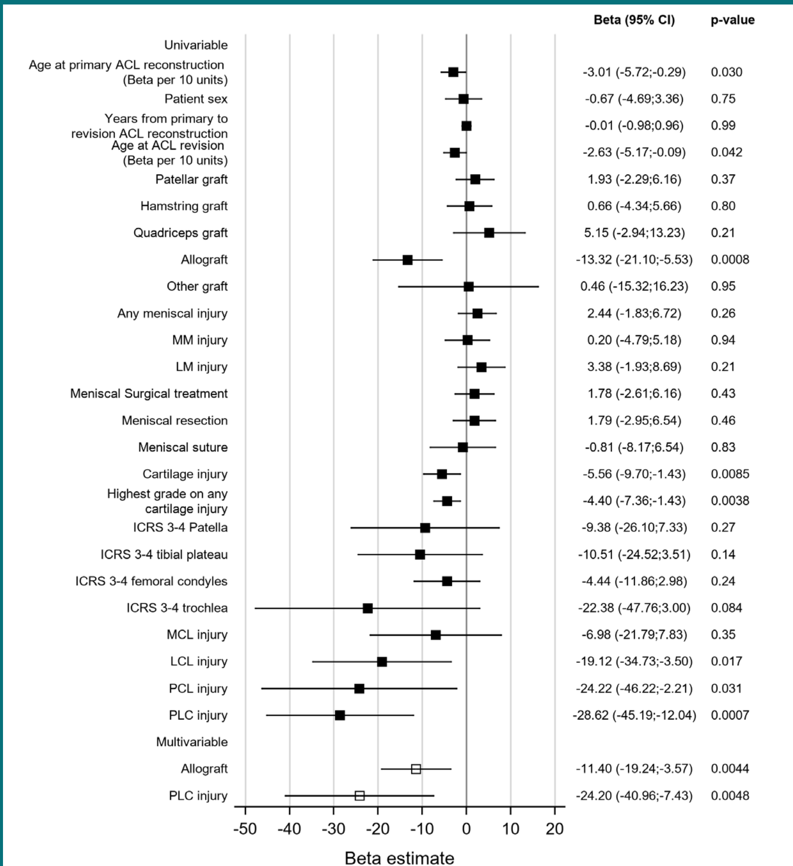

FIGURE 24

Univariable and multivariable linear regression models of the $KOOS_4$ one year after ACL revision. LCL, lateral collateral ligament; LM, lateral meniscus; MCL, medial collateral ligament, MM, medial meniscus; PCL, posterior cruciate ligament, PLC, posterolateral corner

12

DISCUSSION

12.1 THEME ONE – CURRENT EVIDENCE

The Scandinavian knee ligament registries have now been established for over 15 years and have generated numerous publications on the risk factors for revision ACL reconstruction, with both concordant and conflicting results. The aim of theme one was critically to evaluate the evidence provided by the Scandinavian knee ligament registries on risk factors for ACL revision, including an evaluation of the robustness of statistically significant results.

Patient-related factors

The patient-related factors found significantly to influence the risk of ACL revision was age and activity at the time of injury, while patient sex did not affect the risk of revision and there were conflicting results with regard to the impact of BMI.

PATIENT SEX

There is evidence to support the fact that females run a higher risk of sustaining an ACL injury compared with males.[175, 210, 243] However, in agreement with the findings from the Scandinavian knee ligament registries, the literature does not support any major difference between the sexes in the risk of revision or graft failure.[199] More recent studies from the registries have confirmed previous findings of no difference in revision between the sexes.[58, 238] Females might, however, run an increased risk of residual laxity, report inferior PROs and return to sport to a lesser degree than males after ACL reconstruction.[247] Factors that have been proposed to increase the risk of ACL injury in females include hormonal factors, less muscle strength, increased joint laxity and poorer neuromuscular control, especially in puberty.[103, 239] It is somewhat contradictory that females appear to run an increased risk of sustaining a primary ACL injury but not a traumatic re-rupture according to the literature. On a worldwide population level, it is possible that there are circumstances leading to differences in lifestyle choices and the activity level after primary ACL reconstruction between the sexes, where females perhaps tend not to expose themselves to the risk of re-injury to the same extent as males. One study included in Study I reported that young female soccer players ran an increased risk of revision compared with male soccer players of the same age, as well as compared with the total study population.[5] This led to the interpretation that, in certain subgroups of patients, females appear especially vulnerable to re-injury or graft failure. On the other hand, a recent study with a larger cohort of adolescent soccer players from both the SNKLR and NKLR found a 50% increase in the risk of revision for both female and male soccer players compared with the general population, thus indicating no difference between the sexes.[238] Additionally, a recent meta-analysis of patients participating, or aiming to participate, in knee-strenuous activity found that females and males were equally likely to sustain a second ACL injury, with a pooled risk of ipsilateral re-injury of 12% for males and 11% for females.[199] If anything, females were found to experience a slight reduction in the risk of ipsilateral re-injury compared with males (risk difference=–3.4%).[199] It should, however, be mentioned that the majority of the patients in the aforementioned meta-analysis were over 18 years old and, as a result, a deeper understanding of potential sex differences at pediatric and early pubertal age is warranted in future research.

AGE

With regard to age, it was consistently reported that younger age increases the risk of revision according to Study I. An approximate 5-fold increase in the risk of revision was observed for the youngest population compared with the oldest.[53, 79] Conclusively in the literature, young age is one of the strongest risk factors for revision.[118, 265, 268, 271] Younger patients are generally more active, place higher demands on their knees and are likely eager to return to previous sport participation. In particular, patients who return to pivoting sports at a young age run a substantial risk of sustaining a new ACL injury, with a possible 40 times higher risk of new ACL injury compared with their uninjured peers.[271] Older patients might run a lower risk of revision due to less exposure to activities with a risk of re-injury and it is also possible that some adapt their lifestyle and choose not to undergo a revision despite experiencing a graft failure or re-injury. The endpoint of revision surgery might also be influenced by selection and indication bias towards the young population with regard to the performance of revision surgery.

ACTIVITY

In addition to the finding that soccer is a risk factor for revision, the registries revealed that alpine activities reduced the risk of revision. This is supported by a recent study with combined data from the SNKLR and NKLR, which found an approximately 50% increase in the risk of revision for young female and male soccer players, while downhill skiing reduced the risk of revision by nearly 70% compared with other activities for females but not for males.[238] Recent data from the NKLR alone reported that alpine skiers had a significantly lower crude revision rate than handball and soccer players, although no difference between the three activities was found in the adjusted analysis of risk of revision.[58] Nevertheless, to draw appropriate conclusions on the impact of activity on the risk of revision, more information than the registries currently offer is needed. The registries are limited by the fact that data on the level of sports participation and RTS are not included. Additionally, although the registered activity at the time of primary ACL injury has commonly been used as a proxy for the principal activity of the patient, its correlation with the etiology of the ACL revision surgery remains unknown. Interestingly, the activity at the time of primary ACL injury has always been used as the variable of interest for the risk of revision in available registry studies, while no study has used the activity registered as causing the ACL revision surgery as a factor in a risk analysis. A future analysis of the activity at the time of injury for both the primary and the revision ACL reconstruction would be of value.

Surgery- and injury-related factors

Surgical predictors of ACL revision reported by several registry studies were graft choice, the drilling technique, the fixation method and single- versus double-bundle ACL reconstruction. Additionally, time to ACL reconstruction and a concomitant cartilage injury may be factors that affect the risk of revision.

GRAFT CHOICE

While some Scandinavian knee ligament registry studies found no difference in the risk of revision between HT and PT autografts, it must be acknowledged that three studies, including the largest studied cohort, found a lower risk with the use of PT autografts. A vast number of studies have compared the outcome after PT and HT grafts and likewise reported conflicting results with small or no differences between the graft types.[99, 174, 227, 282] There are, however, indications that the use of PT may result in a slightly lower risk of graft rupture and revision compared with HT[227] and that PT may be superior when it comes to restoring knee joint stability.[174, 282]

The conflicting results necessitate consideration of other factors potentially affecting the comparison between HT and PT autografts. The PT is a more homogeneous graft compared with the HT, since the harvested tendons of the ST and gracilis are patient specific to a greater extent than the PT and could be constructed in various ways. Increased HT diameter was reported to reduce the risk of revision in Study I[237] and a recent study even found that HT grafts with a diameter of > 9 mm entailed a lower risk of revision compared with PT grafts.[236] For this reason, comparative analyses of HT with other graft choices should preferably be performed with respect to the graft diameter. The move from PT as the gold standard in Scandinavia to greater use of the HT in the most recent time period also means that a comparison of the two is a comparison of ACL reconstructions performed during different time periods, which might influence the result.

The reasons for the difference between HT and PT autografts found by registry studies could also be biased by indication, a variable not known in the registries. Because of the bone harvest associated with the PT, the use of the PT is avoided in a growing individual and it is possible that the younger high-risk individuals more frequently receive HT. However, even after adjustment for age, Gifstad et al.[79] found an increased risk of revision with HT compared with PT. With regard to activity, a recent meta-analysis showed that the RTS rate is higher for PT compared with HT, with a similar return to preinjury rate and re-rupture rates.[49] A high rate of RTS with the PT, without increasing the risk of re-rupture, has led some surgeons to advocate the PT, especially for active patients. A study from the NKLR including patients who sustained their ACL injury during soccer, handball or alpine skiing reported that HT autografts resulted in a 1.8 times higher risk of revision compared with PT autografts, which rose to a factor of 2.8 in the age group ≤ 18 years. This led the authors to conclude that, among young, active patients, the PT should be used rather than the HT.[58]

Taken together, there are pros and cons with each graft choice. If sufficient HT graft diameter could be ensured, there appears not to be any increased risk of revision according to the Scandinavian knee ligament registries. However, graft choice should be individualized and it is possible that the PT is more suitable in active patients depending on their hamstring strength and in patients with excessive joint laxity.[124]

DRILLING TECHNIQUE

The use of TP, or AM drilling, increased the risk of revision compared with TT drilling, according to the registry studies. During the last decade, there has been an overall transition from the TT technique to the TP/AM technique because of the facilitation of an anatomic tunnel placement with the latter. The surgical learning curve during this transitional period could be one explanation of the observed increase in revision risk with the TP/AM technique. A recent study from the DKRR supports this interpretation of the early results relating to drilling technique from the registries, by reporting that the AM drilling technique did not entail an increased risk of revision compared with TT when specifically analyzing ACL reconstructions performed during the most recent time period.[63] Although graft placement within the native ACL footprint could be accomplished with the TT, it often results in a more vertical graft due to the higher placement of the femoral tunnel in the footprint.[24, 185] This could in turn be the reason for recent cumulative evidence of superior PROs, clinical examination and knee joint stability with the TP/AM compared with the TT technique.[46, 176] Additionally, no difference in the risk of re-injury or revision has been reported between the techniques when pooling data from level-one and level-two studies.[46, 160]

GRAFT FIXATION

While some studies found no association between fixation method and ACL revision, others reported that cortical suspensory femoral fixations exhibited an increased risk of revision compared with transfemoral fixation (or cross-pin fixation).[64, 203, 204] The evaluation of the impact of graft fixation method is a complex area, since these analyses are especially at risk of confounding factors, in particular in registry data. For example, within each type of fixation, there are several manufacturers, some fixation devices are associated with certain arthroscopic techniques and some have been predominantly used during certain time periods.[64, 203] It should also be remembered that no causality between a fixation method and a subsequent revision can be proven. The main function of the fixation is to secure the graft during the early phase of incorporation, which has been reported to be during the first six postoperative weeks for the PT graft[197] and 12 weeks for the HT graft.[81] Attributing a graft failure occurring years after the primary ACL reconstruction to the fixation method without further evaluation could therefore be discussed. Moreover, an isolated analysis of either the impact of the femoral or tibial fixation is a simplification, since sufficient fixation at both locations is equally important and there is no way of knowing whether a graft failure due to inappropriate graft fixation has occurred at the femoral or the tibial insertion using current registry data. Each graft fixation has its advantages and disadvantages and this is still an area of controversy in the literature, where there is insufficient evidence to support one method over another. When broadening the perspective to include other types of literature, there is to date no firm evidence that one graft fixation technique is superior to any other.[107, 110, 115, 264]

SINGLE- VERSUS DOUBLE-BUNDLE

According to the Scandinavian knee ligament registries, the choice between single- and double-bundle ACL reconstruction appears not to majorly affect the risk of revision at group level. Data from the SNKLR alone have indicated a slight decrease in the risk of ACL revision with the use of double-bundle ACL reconstruction compared with single-bundle ACL reconstruction.[3, 246] However, it is important to take account of the fact that the sample size is small for the double-bundle group in the registries, which limits the analyses. The current evidence on single- versus double-bundle ACL reconstruction shows that a satisfactory outcome can be achieved using both techniques, without any evident difference in the risk of revision at population level.[113, 167, 257] There have, however, been reports of the superior restoration of rotational stability when using double-bundle compared with single-bundle ACL reconstruction[229] and, in patients with large knee joints and severe laxity, the double-bundle ACL reconstruction technique could still be considered to be in line with the concept of individualizing the ACL reconstruction.[261] However, an anatomically placed single-bundle ACL reconstruction and sufficient graft size are probably the most important factors in patients with an average-size ACL insertion site, rather than the number of bundles.[251]

CONCOMITANT KNEE JOINT INJURIES

Impaired knee function and pain might impede the resumption of knee-strenuous activities after ACL reconstruction, which could be a plausible explanation for the reduced risk of revision with cartilage injuries found in the Scandinavian knee ligament registries. In other words, with a plausibly larger proportion of patients who are unable to resume risk activities in the cartilage-injured population, the risk of traumatic re-rupture decreases and thereby the risk of ACL revision. Another hypothesis is that patients with knee impairments and pain after the primary ACL reconstruction are less motivated to undergo revision surgery, even though it might be indicated, which could lead to an underestimation of the true graft failure rate for this group. Meniscal injuries are similarly known to be a risk factor for impaired knee joint health and the development of OA.[39, 194] It would therefore be reasonable to apply similar reasoning with regard to activity modification and reduced risk of re-rupture even for meniscally injured patients. However, to date, the registries have not found any indication that a concomitant meniscal injury affects the risk of ACL revision. Notably, little interest has as yet focused on the impact of concomitant injuries other than cartilage and meniscal injuries in the registries. Nor has the effect of different combinations, severity grades and the treatment of concomitant injuries on the risk of revision been satisfactorily investigated. This is an important area for future investigation.

The fragility index

Study II found that age was by far the most robust risk factor for an ACL revision. Notably, there was a large overall variability in the fragility index, both between different types of predictors and within analyses of the same predictor. Nearly one third of the significant findings presented in the registries had a fragility index of zero, which indicates high statistical fragility.

One interesting evaluation is to relate the fragility index for each significant predictor in the Scandinavian knee ligament registries to the total number of events (i.e. ACL revisions) in the analyses for that specific predictor. For example, the mean fragility index for age was 178.5. As a result, a mean of 178.5 patients in the group with fewest revisions (older group) would be required to change from not undergoing a revision to undergoing a revision to change the result to non-significant. The mean number of revisions for all the significant analyses of age was 261. So, the overall proportion of patients required to change outcome in relation to the actual numbers of event would be around 70% (178.5/261 = 0.683). This could be set in relation to the activity at the time of injury, for example, where the mean fragility index of 16.0 patients represents approximately 6% of the total number of revisions in those analyses. As a result, the statistical fragility of activity at the time of injury as a risk factor for revision is considerably higher than that of age.

For the comparison of HT and PT autografts, the mean fragility index was 15. A recent study evaluated the fragility index for outcomes with HT versus PT autografts in RCTs and comparative studies and found a median fragility index of 2.[57] As a result, only 2 patients with a reversed outcome in current level I and II studies would change significant results to non-significant with HT versus PT autografts for ACL reconstruction.[57] Additionally, it should be noted that the number of patients lost to follow-up was higher than the fragility index in 76% of the outcome analyses,[57] meaning that the unknown outcome for these patients could have had a considerable impact. In line with these findings, a noteworthy low fragility index of 2 has been reported in 48 RCTs of sports medicine and arthroscopic surgery.[123] For comparative analyses of hip arthroscopy, a fragility index of 3.5 has been reported.[198] The conclusions in current studies of the fragility index in the field of sports medicine have therefore been unanimous; the evidence is not as statistically stable as might previously have been thought and sole reliance on p-values should be avoided. Additionally, including the reporting of the fragility index in studies has been encouraged.[57, 123, 198]

The almost glorified status of p-values among researchers of today requires consideration. A p-value of < 0.05 is no absolute truth. The fragility index does not, however, show the whole truth either. First, the fragility index is still based on the arbitrary cut-off of $p < 0.05$ as statistical significance, which means that 5% of the results could still be due to chance. Interestingly, if the threshold of statistical significance were to be lowered from $p < 0.05$ to $p < 0.005$ in recent RCTs in orthopedic sports medicine, only around 40% of statistically significant results at a level of $p < 0.05$ would remain significant.[62] In fact, fewer than 20% of the primary outcomes in those RCTs would be considered significant if the threshold of significance was lowered to $p < 0.005$.[62] Second, the fragility index is not without its limitations and criticism of applying it in time-to-event analyses has been raised, even though it has been applied in these analyses in multiple previous studies.[11, 57, 123, 198] The majority of the analyses of ACL revision provided by registry studies are time-to-event analyses, which are, in addition, frequently adjusted for confounding factors. The use of Fisher's exact test to recalculate the p-value for the fragility index does not take account of either the time to event or any potential adjustments for confounders. This means that that the application of the fragility index in Study II should be regarded as a gross measurement of robustness and that the large proportion of analyses with a fragility index of 0 should be interpreted carefully, in the knowledge that Fisher's exact test might not be the most appropriate test to determine significance in these analyses. In Study II, the fragility index rose considerably when excluding the analyses with a fragility index of 0. One interesting observation in Study II was, however, that the fragility index was generally higher than previously reported for RCTs in sports medicine,[57, 123, 198] which exemplifies the strength of the large datasets provided by the registries. Third, however, another factor with an impact on statistical robustness is the patients lost to follow-up. When using revision as an endpoint, it is not known how many patients never have an event of this kind registered, despite graft failure, if a decision is made not to proceed to revision surgery. The area in which the registries are most vulnerable to loss to follow-up, however, is the PROs. The overall mean compliance in national arthroscopy registries with PROs at two years has been reported to range between 40% and 61%,[259] which is worrying.

Study II represents the first aim to evaluate the statistical robustness of findings presented in the Scandinavian knee ligament registries and could be regarded as a rough interpretation of the robustness. The high variability of the fragility index warrants attention. In one way, it raises the question of whether some of the reported predictors of revision in particular are not as statistically stable as previously thought, despite large datasets. In another way, the overall robustness was higher than that reported many times for RCTs in similar fields of research.[57, 123, 198] The feasibility of performing fragility index analyses of registry data must be further evaluated and research to find the most suitable methodology for reporting statistical robustness in registry studies is warranted to enable its reporting and appreciation when drawing conclusions.

12.2 THEME II – THE IMPACT OF A CONCOMITANT MEDIAL COLLATERAL LIGAMENT INJURY

Theme II in this thesis explored how a concomitant MCL injury affects outcome after ACL reconstruction. In Study III, data from the SNKLR showed that a concomitant MCL injury increases the risk of ACL revision, in particular if the MCL injury is treated non-surgically. Among ACL-reconstructed patients with a non-surgically treated MCL injury, the graft choice between HT and PT tendons does not appear to affect the risk of revision according to the findings in Study IV. Only 10% of patients with a concomitant MCL injury had returned to their preinjury activity level one year after ACL reconstruction, which can be compared with 26% of patients with an isolated ACL injury in Study V. However, there were no significant differences between the groups in RTS, PROs or tests of muscle function.

Risk of revision

Until recently, combined MCL and ACL injuries have not attracted much intention in the literature. The MCL has even been referred to as the “neglected ligament” in this context.[273] This is noteworthy considering that the concept of the “unhappy triad” was described half a century ago[193] and shortly thereafter Slocum and Larson described an anteromedial rotatory laxity pattern caused by combined ACL and MCL injuries.[233] The publication by Slocum and Larson in 1968 stated: “Although long recognized as a clinical entity, rotatory instability has too often been overlooked by inexperienced surgeons because standard testing methods stress valgus rocking and anteroposterior joint laxity rather than rotatory instability.”[233] These words are probably as relevant today as they were then. Whether overlooked laxity caused by the MCL injury was the reason for the increased risk of ACL revision in patients with a concomitant non-surgically treated MCL in Study III remains unknown, since the SNKLR does not include data on laxity. It is, however, a plausible hypothesis that, for some patients where the MCL injury has not healed satisfactorily with non-surgical treatment, a persisting unaddressed anteromedial laxity pattern places strain on the newly reconstructed ACL graft and predisposes to graft failure. In theory, excessive anteromedial laxity caused by MCL insufficiency could also involve an increased risk of traumatic ACL re-rupture by predisposing excessive knee abduction when valgus-directed forces are applied to the knee joint, a common ACL injury mechanism that places a high level of strain on the ACL.[21]

The knowledge of the role played by secondary stabilizers in the rotatory stability of the knee joint has evolved over the years and a great deal of interest has recently focused on the anterolateral structures of the knee joint.[77] Early data indicate that lateral extra-articular tenodesis in conjunction with ACL reconstruction could lower the risk of graft failure and improve stability and might be indicated in high-risk patients.[77, 78] In the same manner, it seems logical that, if a concomitant MCL injury and clinically relevant anteromedial rotatory laxity are not detected and addressed, the risk of re-injury or ACL graft failure could increase. This is supported by evidence of increased forces on the ACL in the MCL-deficient knee.[22, 288] In line with the findings in Study III, an almost 2-fold increase in the risk of ACL revision was recently reported among patients under 20 years of age with a concomitant MCL injury.[147] Additionally, one third of the patients fulfilling the combination of female sex, age between 10 and 14 years, meniscal injury and a concomitant MCL injury could be expected to necessitate a revision ACL reconstruction.[147] A concomitant grade II MCL injury has also been reported to increase the odds of postoperative laxity after ACL reconstruction by a factor of 13.6.[7] Increased medial-side laxity in isolation after the non-surgical treatment of a concomitant MCL injury may not always cause any functional impairment after ACL reconstruction.[93, 285] However, an almost 17 times increase in the risk of residual laxity after a revision ACL reconstruction has been found in patients displaying medial-side laxity prior to the ACL revision surgery.[8] This highlights the importance of diagnosing and addressing medial-side laxity if it represents a clinically relevant problem, but also that the risk of residual laxity is high after a revision ACL reconstruction in patients with medial-side laxity. It has further been reported that ACL revision surgeries are not uncommonly associated with overlooked concomitant injuries at the primary ACL reconstruction.[8, 192] Since the literature suggests that medial-side laxity could play a more important role in ACL graft failure than previously thought, every attempt must be made to detect medial-side laxity and address it if needed.

The surgically treated MCL groups displayed no difference in the risk of revision compared with isolated ACL reconstructions in Study III. Recent findings suggest that a surgical medial-side stabilizing procedure at the time of the ACL revision surgery could reduce the odds of postoperative laxity in patients with preoperative medial-side laxity 13 times.[8] Although these findings indicate a positive effect of surgical MCL intervention, not all patients need or should receive surgical treatment for a concomitant MCL injury, which involves both greater surgical trauma and longer convalescence compared with non-surgical MCL treatment.[92] The clinical decision-making regarding the surgical and non-surgical treatment of a concomitant MCL injury is aggravated by the fact that there is no consensus on how much medial-side laxity should be regarded as acceptable. A medial compartment gap of more than 3.2 mm compared with the healthy knee has been reported as being indicative of a grade III MCL injury,[140] for which the need for surgical intervention in particular should be carefully evaluated. The quest is first to be able to identify patients that require surgical treatment of the MCL and to establish evidence-based surgical techniques for this. For many patients, a period of non-surgical treatment with bracing to enable the healing of the MCL prior to the ACL reconstruction is an appropriate treatment. However, there is a need for further research to determine how laxity should be evaluated, interpreted and addressed if the MCL deficiency persists at the time of ACL reconstruction.

Graft choice

The graft choice of an HT or PT autograft was found not to influence the risk of revision ACL reconstruction in patients with a concomitant non-surgically treated MCL injury, according to Study IV. Concerns have been raised that harvesting the medial hamstring in the MCL-injured knee could compromise medial-side stability even further and should therefore be avoided in patients with a concomitant MCL injury.[100, 131] Independently of whether the HT was compared with the PT as a single group, or in subgroups of ST alone or combined ST and gracilis, the risk of revision was not affected in Study IV. Previous biomechanical studies have created an MCL injury, either complete[100] or partial,[131] and found that preserving the medial hamstrings for valgus stability in such a situation is of crucial importance. The clinical data in Study IV might, however, not be comparable to situations of this kind since the majority of the patients would likely have experienced the healing of the MCL, at least to some extent, during the mean period of 314 days to ACL reconstruction in the study cohort. Moreover, it should be remembered that cadaveric studies might report laxity that is not always clinically relevant and further clinical studies of ACL graft choice in patients with a concomitant MCL injury are needed to elucidate this.

Patient-reported outcome

Study III found that patients undergoing surgical treatment of a concomitant MCL injury reported inferior PROs compared with patients undergoing ACL reconstruction in the absence of an MCL injury. Similar results were recently reported from the DKRR, where the reconstruction of a concomitant MCL injury resulted in inferior PROs compared with isolated ACL reconstruction.[151] However, combined ACL and MCL reconstruction improved PROs compared with preoperatively,[151] which was also observed in Study III. Specifically, the surgically treated MCL groups reported a 13- to 14-point reduction in function in KOOS sport and recreation compared with the isolated ACL reconstruction group in Study III, which can be regarded as clinically relevant.[151] The inferior outcome in patients receiving surgical treatment for a concomitant MCL injury is likely a function of a more severe injury, where patients should perhaps not expect to achieve a similar function in sport compared with isolated ACL injuries. In fact, the patient-reported impairment in sport for the surgically treated MCL groups could have reduced their risk of revision, as found in Study III. It is possible that a larger proportion of these groups were not able to return to knee-strenuous activity, thereby reducing the risk of ACL re-injury.

Among patients undergoing non-surgical treatment of a concomitant MCL injury, neither Study III nor Study V found any clinically important differences in PROs compared with patients undergoing ACL reconstruction in the absence of an MCL injury. In Study IV, the proportion of patients achieving a PASS was considerably low, regardless of graft choice. On the Sport and recreation subscale, the overall proportion achieving a PASS at the two-year follow-up was 41.8%. Although Study V included a substantially smaller cohort, the proportion of patients achieving a KOOS PASS was higher on the majority of the subscales already at the one-year follow-up compared with Study IV. Moreover, the knee-related self-efficacy was comparable between patients with and without a concomitant MCL injury. So, according to the PRO measurements used in the current thesis, patients undergoing ACL reconstruction with a concomitant non-surgically treated MCL injury do not appear to fare less well than patients without a concomitant MCL injury in the short-term perspective.

Test of muscle function and return to sport

In Study V, a mean LSI of > 90% was found in the majority of the muscle function tests for the non-surgically treated MCL group, which did not differ from patients undergoing ACL reconstruction in the absence of an MCL injury. In one way, these findings are positive in that they show that a more severe injury pattern with a concomitant MCL injury does not need to delay the achievement of symmetric muscle function. On the other hand, the achievement of an LSI of > 90% is a commonly used criterion in the decision-making relating to RTS,[156] which requires consideration in relation to the possible correlation between a concomitant MCL injury and an increased risk of revision. Since the muscle function tests and the PROs did not differ from those of patients without an MCL injury, the findings in Study V may indicate that other factors are especially important to consider in the decision-making relating to RTS in patients with a concomitant MCL injury. Unknown factors in Study V, such as laxity, functional instability, neuromuscular control and the process of progression to RTS, could be even more important to consider in patients with a concomitant MCL injury compared with isolated ACL injuries to minimize the risk of ACL re-injury under the hypothesis that some medial-side deficiency may still exist.

Patients with the absence of a concomitant MCL injury have previously been reported to have 7-times higher odds of RTS within one year of ACL reconstruction, compared with patients who have a concomitant MCL injury.[96] Study V found no difference between patients with and without an MCL injury in terms of return to knee-strenuous activity, where slightly fewer than 50% in both groups had returned after one year. However, only 10% of the patients with a concomitant MCL injury had returned to their preinjury level of sport at one year compared with 26% in the ACL-reconstructed group without an MCL injury, which represents a considerable difference, although it did not reach statistical significance. The reason for this discrepancy in the return to the preinjury level of sport remains unknown and necessitates further research, preferably with a larger study population, since it is possible that Study V was underpowered to show any difference between the groups for this outcome. The 10% rate of return to their preinjury level of sport for patients with a non-surgically treated MCL injury is substantially lower than that previously reported among ACL-reconstructed patients in general, where 81% of ACL-reconstructed patients return to some kind of sports at a mean follow-up of 40 months, while 65% return to their preinjury level of sport within this time frame.[16] Moreover, psychological readiness to RTS has recently attracted more attention in the literature and an ACL-RSI of < 56 points has been reported as a negative predictor of return to preinjury level of sport.[17] Considering that both groups in Study V reported a mean ACL-RSI above 56 points, there is reason to believe that the prognosis for RTS is still good with time.

The relatively low rate of RTS at the one-year follow-up in Study V could also be an indication of a careful rehabilitation process, implementing a successive progression to sports activities and also taking consideration of concomitant injuries and the biological healing process, for example.[170] Although there is evidence to support a criterion-based approach in the decision-making relating to the timing of RTS,[89, 136] where the achievement of symmetric muscle function should be evaluated, for example,[156] the pure time-based aspect should not be neglected.[170] With a 51% decrease in the risk of re-injury with every month RTS is delayed up to 9 months postoperatively[89] and the time needed for biological healing,[184] careful consideration must also be paid to not allowing the patient to RTS too early, despite good functional outcomes. It has even been proposed that a two-year delay to RTS after ACL reconstruction might be necessary,[184] probably largely due to the data indicating that a re-injury commonly occurs early after RTS.[89, 136, 200] Taken together, the low proportion of RTS in Study V could thus also be set in the positive light of patience with RTS.

12.3 THEME III – OUTCOME AFTER REVISION

The comparison of outcome between primary and revision ACL reconstruction has not attracted much interest in the Scandinavian knee ligament registries. Only three studies, all published during the early era of the registries, have compared the outcome after primary and revision ACL reconstruction and they found unanimously that patients do less well after a revision ACL reconstruction.[5, 134, 152] This is not surprising and is in line with the literature.[13, 85, 277, 283] The inferiority on the KOOS after revision compared with primary ACL reconstruction ranged between 5 and 19 points, according to the Scandinavian knee ligament registries. The Scandinavian knee ligament registries are, however, limited by relying on only the KOOS and EQ-5D as outcome measurements to understand the outcome after revision. Many of the concluded differences between primary and revision ACL reconstruction did not exceed the minimal important change for the KOOS.[112] The generally small difference in the KOOS between primary and revision ACL reconstruction found in Study VI raises the question of whether there are few meaningful differences between primary and revision surgery, or whether the outcome measurements are not able to discriminate differences that are actually important. Concerns have been raised with regard to the capability of the KOOS to capture relevant outcome for patients after ACL reconstruction, since it includes three original subscales (Pain, Symptoms and ADL) from the WOMAC, which was intended to evaluate hip and knee OA.[27, 44] A recent study found that the KOOS was inadequately developed to target patients with an ACL injury and that the ADL and Pain subscales are irrelevant for patients with an ACL injury, which could have serious consequences for the responsiveness of the KOOS.[97] However, the Sport and recreation and the QoL subscales have been reported as the most responsive subscales, with a minimal important change of 12.1 and 18.3 points respectively.[112]

There may also be several individual factors that affect the outcome after ACL revision and one limitation of several of the current studies comparing primary and revision ACL reconstruction is that two independent patient groups have commonly been compared, i.e. there is little knowledge of the course between primary and revision surgery at individual level. The KOOS score has, for example, been shown to be influenced by patient sex and age[4, 54, 134] and there might also be a selection towards which patients comply with the questionnaires.[216] Moreover, patients who never need to undergo revision surgery have been shown to report a superior KOOS compared with those who require a revision.[82] Study VII in this thesis was an attempt to re-analyze the outcome between primary and revision ACL reconstruction with the aim of minimizing the potential impact of confounding factors by only including patients who had undergone both primary and revision ACL reconstruction. In this manner, each patient functioned as its own "control" and this also enabled analyses of the course of concomitant injuries for primary to revision ACL reconstruction in the same study cohort.

Implications for activity

In Study VI, the differences between primary and revision ACL reconstruction exceeded the minimal important change on the Sport and recreation subscale on all follow-up occasions, apart from the one-year follow-up by Lind et al.[152] These findings suggest that there is good reason to believe that the prognosis for activity resumption and RTS is poorer after a revision ACL reconstruction compared with the primary reconstruction. Meta-analyses of the literature have revealed a similar proportion of return to any sport after primary and revision ACL reconstruction, 81% and 84% respectively.[16, 88] However, revision ACL reconstruction is associated with a lower proportion of return to preinjury level compared with primary ACL reconstruction, where only 52% have been reported to resume their sporting activity at preinjury level after revision compared with 65% after primary ACL reconstruction.[16, 88] As a result, the prognosis for maintaining an active lifestyle is probably also good after revision surgery, although it is possible that patients are forced to adapt their physical demands and give up an athletic career after revision surgery to a greater extent than after primary ACL reconstruction.

Knee-related problems have been reported as the primary reason for not returning to sport after revision ACL reconstruction, accounting for 69% of cases that do not return.[88] This is not surprising, since revision ACL reconstruction is associated many times with repeated knee joint trauma and the increased prevalence of concomitant intra-articular injuries[171, 280, 283] and is in itself a more complicated procedure with a higher complication rate compared with primary ACL reconstruction.[166] Moreover, revision ACL reconstruction is associated with a 4-fold increase in the risk of residual rotatory laxity compared with primary reconstruction and a 2-fold increase in the risk of abnormal knee function as classified by the IKDC clinical examination.[85] For this reason, a revision ACL reconstruction should not be expected to yield an outcome similar to that of a primary ACL reconstruction, which should be taken into account in the clinical setting so that both the patient and the clinician have realistic expectations in the decision-making relating to proceeding to a revision ACL reconstruction.

Concomitant injuries

In agreement with previous literature,[280] there was a significant increase in cartilage injuries between primary and revision ACL reconstruction. Considering the relatively short mean time between primary and revision ACL reconstruction of 2.7 years, it is notable that more than one in four patients who did not have a cartilage injury at primary surgery had developed one at revision surgery in Study VII. This raises concerns about the course of knee joint health in patients who need to undergo revision and the risk of future OA. Pooling data has revealed that 55% of patients who have undergone revision have radiographic signs of OA at a mean follow-up of 4.5 years, which represents a two-fold increase in risk compared with primary ACL reconstruction, where 25% have radiographic evidence of OA.[85] There is no doubt that the integrity of the cartilage and the development of OA are connected and it is therefore not surprising that the degree of cartilage injury is a predictor of poorer outcome after ACL revision[163] and also a lower rate of return to preinjury activity level.[266] Although a concomitant cartilage injury was a predictor of poorer one-year KOOS sport and recreation in Study VII, it had little absolute effect on the KOOS score, which questions the clinical relevance. It is possible that the short follow-up in Study VII obscures the effects of cartilage injury, which might first yield clinical symptoms in a mid- to long-term perspective. Knowledge that the prevalence of cartilage injuries is high while the PROs remain fair early after a revision ACL reconstruction could, however, have important clinical implications. It must be set in relation to the risk of future deterioration of intra-articular knee joint health and thus be considered in lifestyle choices and expectations of outcome.

Patient-reported outcome

While the one-year KOOS was significantly inferior after revision compared with primary ACL reconstruction in Study VII, the differences were smaller than those previously reported in the Scandinavian knee ligament registries.[5, 134, 152] When analyzing the same cohort for primary and revision ACL reconstruction, there appears not to be any clinically relevant difference at one year postoperatively. The largest difference was found on the Sport and recreation subscale, where patients reported a mean of 5 points lower after the revision compared with primary ACL reconstruction. This is a substantially smaller difference than previously reported from the registries, ranging between 10 to 14 points lower for the revision group at one year in previous studies.[5, 134, 152] If only the mean score one year after the revision surgery is considered, there was a similar sport and recreation score in Study VII compared with previous registry studies.[5, 134, 152] Instead, the smaller difference between primary and revision ACL reconstruction in Study VII was due to a lower one-year KOOS sport and recreation after the primary ACL reconstruction among the patients who later proceeded to revision surgery. On the one hand, this could be interpreted in a positive manner, suggesting that patients who undergo a revision ACL reconstruction do not necessarily do less well after a revision compared with a primary ACL reconstruction. On the other hand, it is possible to speculate that the lower one-year KOOS related to the primary reconstruction reflected a failed primary ACL reconstruction for at least some of the patients who later required a revision. Based on this theory, it is therefore somewhat worrying that the outcome was not improved after the ACL revision but deteriorated still further.

The smaller differences between primary and revision ACL reconstruction found in Study VII do in fact raise new questions with the emphasis on understanding the outcome after revision. To date, there is a large discrepancy relating to the amount of research related to primary compared with revision ACL reconstruction. Although the aim is to minimize the number of ACL revisions required following improved primary treatment, the realistic prognosis is that the number of ACL revisions will increase with the increasing performance of primary ACL reconstructions worldwide, especially among the young population.[102, 179, 188, 287] In order to understand the patient perspective after revision in greater depth and the reason for the inferior outcome after ACL revision, outcome measurements other than those contained in the Scandinavian knee ligament registries are needed. Moreover, there is a lack of long-term evaluations after ACL revision,[86] which are important to further evaluate in order to understand the course of knee joint health and function from a long-term perspective.

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LIMITATIONS

13.1 OVERALL RESEARCH METHODOLOGY

The foundation of this thesis is registry data, which involves several inherent methodological limitations. Registry data should be regarded as hypothesis generating since registry data are unable to prove a causal effect. Moreover, registry data are subject to several sources of bias. With regard to possible sources of bias in the SNKLR, the data are collected prospectively rather than retrospectively in order to minimize the risk of recall bias.

The entry of data by surgeons and patients could, however, be influenced by manual entry errors and to some extent also by recall bias. Attrition bias caused by non-participating units and surgeons must also be considered, although the completeness and compliance of participating units in Sweden is high. Nevertheless, patient compliance with the administered PRO questionnaires is problematic. With a response rate between 50-70%, registry data are subject to potential attrition as well as selection bias in this regard. Selection bias might also be present with regard to the choice of treatment interventions, since no data on indications for treatment are kept in the SNKLR. The fact that multiple surgeons report to the SNKLR means that there is a risk of reporting bias for the investigated variables, as well as different subjective assessments and treatments with regard to concomitant injuries, for example. It could also be claimed that the registry data are subject to detection bias, in terms of including only a limited set of outcome measurements in the context of outcome after ACL injury. The outcome of ACL revision does not take account of failed primary ACL reconstructions that do not proceed to ACL revision, which means that the true failure rate might be underestimated. Other types of outcome measurement to detect failure or adverse events, such as laxity measurements, radiologic data and range of motion data, are not included in the SNKLR. The PROs included in the SNKLR may also fail to capture relevant outcomes for ACL-injured patients, which creates a severe limitation in terms of understanding the patient perspective after ACL injury and may lead to misleading conclusions. There are also several unknown, potentially confounding, variables that should be mentioned. Patient compliance with the recommendations from surgeons and physical therapists is a possible confounding factor that is always present, since no information about the pre- or postoperative rehabilitation is kept in the SNKLR. Nor is the activity level or RTS detected, which are crucial aspects to consider in a large proportion of the ACL-injured population. There are also surgical details that are currently not kept in the SNKLR, such as the drilling technique and variables to determine the degree of anatomic ACL reconstruction. Although the NKLR and DKRR differ slightly from the SNKLR, the majority of the aforementioned limitations could also be applied to these registries. However, the DKRR offers the advantage of including laxity data, as well as information on the drilling technique.

In the same way, Project ACL includes the inherent limitations of registry data. In Project ACL, it should also be mentioned that several outcome assessors are involved in the strength and hop tests. Although standardized and validated tests are used, there could be intra- and inter-observer differences in the outcome assessment. With regard to the patients included in Project ACL, there could also be a selection bias towards patients who are motivated to undergo this type of regular follow-up and testing. Nevertheless, the loss to follow-up in both muscle function tests and PROs represents a limitation of Project ACL.

13.2 STUDY-SPECIFIC LIMITATIONS

In addition to the limitations described in the previous section, which applies to all the studies included in this thesis, there are some additional specific study limitations.

Study I and Study VI

The systematic reviews of the Scandinavian knee ligament registries are limited by the fact that no validated and standardized quality assessment tool for registry studies exists. The modified version of the Downs and Black checklist was determined as the most appropriate method for the quality appraisal of included studies, although it should be remembered that the checklist is primarily aimed at determining the reporting quality of a study and no threshold values for defining quality have been determined for the Downs and Black checklist. In Study I, the median Downs and Black score of 16 points of a possible 22 indicates that the studies had fair reporting quality. Nevertheless, the conclusion-making regarding predictors of revision ACL reconstruction is limited by the fact that studies with a higher level of evidence than registry studies were not included. The same thing applies to Study VI, where the studies included in this thesis had a Downs and Black score ranging from 12 to 15 points.

When it comes to interpreting study results from multiple registry studies, there is a potential risk of drawing conclusions on overlapping cohorts, i.e. using the same patient data multiple times. The frequent publication from the Scandinavian knee ligament registries creates a potential risk of multiple significance and, on the other hand, a risk of assigning too much importance to a single significant result among several non-significant ones. A bias could also have been introduced by the decision to use a qualitative method of data synthesis, since a potential bias in the result presentation according to the original publication could have been directly retransmitted to the systematic reviews.

Study II

In Study II, several of the predictors were analyzed in only one or two studies originally, which makes them highly susceptible to any bias in the original studies. Moreover, many of the fragility index calculations for a specific predictor were based on few original analyses and in some cases only a single analysis. The fewer original analyses per predictor, the more sensitive the fragility index analyses could be to outliers. Moreover, the feasibility of applying the fragility index to registry studies is limited by the susceptibility of confounding factors in registry studies, which in the original publications had commonly been dealt with by statistical adjustments. The calculation of the fragility index is made independently of any adjustments for confounding factors, which represents one of the most important limitations when applying the fragility index to these data. Additionally, the fragility index is calculated independently of whether an analysis originally applied a time-to-event analysis, which means that the fragility index should be interpreted with care for time-to-event analyses and with the understanding that it may become a rougher measurement in these analyses. A fragility index of zero in analyses could be due to the fact that Fisher's exact test was not the most appropriate test to evaluate differences between groups. The fragility index could also be affected by group size, the number of events and the patients lost to follow-up, which should be considered in terms of the variable sample sizes in the included studies and the unknown impact of patients lost to follow-up for ACL revision such as outcome, i.e. failures that did not proceed to a revision.

Study III and Study IV

The most important limitations in Studies III and IV were the unspecified grade of the MCL injury, the degree of laxity and the unknown surgical technique and indications for the surgical treatment of an MCL injury. The relatively few patients with a concomitant MCL injury in the SNKLR also unfortunately raise a real suspicion that a concomitant MCL injury that is primarily treated non-surgically and regarded as healed at the time of the ACL reconstruction is not always registered, which means that there is a risk of introducing reporting and attrition bias in the data. The absence of laxity data and information about the grading of a concomitant MCL injury obstructs the drawing of conclusions about the specific consequences of the concomitant MCL injury and knowledge of these factors would also be required to assess the outcome of the specific MCL intervention that was chosen. The course between the time of injury and the ACL reconstruction remains unknown, which involves several important aspects of the concomitant MCL injury, such as whether an initial period of bracing was used and on what indications the MCL treatment was based at the time of ACL reconstruction. Moreover, the MCL groups were found to be relatively small with few events in each group, which increases the risk of a type II error.

Study V

Strict inclusion and exclusion criteria were applied in Study V in order to set the matching criteria for the groups. This did, however, result in relatively small study groups. Although the a-priori power analysis showed that the study should have been sufficiently powered for the primary outcome, the secondary outcome measurements used in this study might have been underpowered. The power analysis was also calculated according to limited evidence relating to the expected difference between the groups and it is possible that an overly large difference between the groups was estimated in the power calculation. There were also patients lost to follow-up in the secondary outcome measurements, which further limited the sample size and could have affected the study result. It must be remembered that the primary outcome of RTS was assessed using patient-reported information according to the Tegner, which includes limitations in terms of not providing specific information on the exact sport, the frequency of participation or the performance in sport. It should also be mentioned that the preinjury Tegner is reported by the patients after the ACL injury has occurred, i.e. retrospectively. The use of the LSI for the test of muscle function and hop tests was limited by not taking preinjury capacity into consideration, since no such data were available. The preinjury capacity of the LSI would have been of value to consider, since it is possible to achieve a symmetric muscle function after ACL reconstruction, despite not having regained preinjury capacity. The absence of laxity data further limits conclusion-making in the study, especially in relation to the patients with a concomitant MCL injury. The generalizability of the results could also be questioned since the setting was limited to one center and fewer females were included in the study compared with males.

Study VII

The missing data on the KOOS probably represent the greatest limitation in Study VII. Available KOOS data were required on at least one occasion (preoperatively or one year postoperatively) for both the primary and the revision ACL reconstruction for inclusion. Despite this criterion for inclusion, there were unfortunately many patients that did not have complete data for the corresponding follow-up occasions at both the primary and revision ACL reconstruction – for example, complete one-year follow-up data for both the primary and revision ACL reconstruction. To enable strict comparisons of the same patients on both occasions, the comparative analyses of the KOOS therefore consisted of considerably smaller groups than the total study population. Moreover, the predictive univariable and multivariable regression models all had low R^2 values, which means that the models poorly explained the variance in the KOOS one year after ACL revision based on the included variables. There could be several reasons for this. A larger study population might be necessary, or a more responsive outcome measurement than the KOOS. It is also possible that factors other than the studied predictors are more important to explain the outcome after ACL revision, factors other than those kept in the SNKLR. With regard to the analyses of concomitant injuries, these were highly dependent on the reporting by the surgeons, which means that the subjective assessment of several participating surgeons in this matter poses a risk of bias. The short-term follow-up of only one year in this study is also a limiting factor.

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CONCLUSIONS

Study I

Younger age at primary ACL reconstruction was the strongest risk factor for ACL revision. The risk was further increased if young age, female sex and playing soccer were combined. However, patient sex alone did not influence the risk of ACL revision. The use of PT grafts reduced the risk of ACL revision compared with HT grafts, but an increased graft diameter for HT grafts reduced the risk of ACL revision. The transportal drilling technique was associated with an increased risk of ACL revision compared with the transtibial technique. A concomitant cartilage injury at primary ACL reconstruction was associated with a reduced risk of ACL revision.

Study II

The robustness of results related to revision ACL reconstruction in the Scandinavian knee ligament registries was highly variable when evaluated by the fragility index. Almost one third of the analyses had a fragility index of zero, likely indicating that the evidence provided by these analyses is fragile. Further research is encouraged to find the most appropriate metric for robustness in registry studies.

Study III

Patients with a concomitant MCL injury treated non-surgically at the time of ACL reconstruction might run an increased risk of future ACL revision surgery compared with patients without an MCL injury. The surgical treatment of the MCL injury did not, however, increase the risk of revision, although patients receiving surgical treatment for a concomitant MCL injury reported a poorer patient-reported outcome at the 2-year follow-up.

Study IV

The choice of a HT or PT autograft for ACL reconstruction in patients with a concomitant non-surgically treated MCL injury did not affect the risk of revision ACL reconstruction. Nor was the risk of revision affected by the use of the ST alone or the use of the combined ST and gracilis tendon. However, patients receiving a combined ST and gracilis tendon autograft reported poorer PROs at the 2-year follow-up compared with patients receiving an ST alone.

Study V

The RTS, recovery of muscle strength and PROs at the one-year follow-up did not differ between patients who had undergone ACL reconstruction with a concomitant non-surgically treated MCL injury, compared with patients without a concomitant MCL injury. However, only 10% of the patients with a concomitant MCL injury had returned to their pre-injury level of sport at one year, which warrants further investigation to characterize the impact of a concomitant MCL injury in the ACL-reconstructed knee.

Study VI

A revision ACL reconstruction improved the patient's subjective knee function compared with preoperatively. However, a revision ACL reconstruction resulted in significantly inferior PROs compared with a primary reconstruction at all follow-ups between one and five years postoperatively. Nearly 40% of patients undergoing revision ACL reconstruction reported a KOOS QoL of < 40 points at the one-year follow-up, which can be regarded as a subjective failure.

Study VII

In a cohort limited to patients who have undergone both primary and revision ACL reconstruction, the patient perception of outcome was slightly inferior after ACL revision compared with the primary ACL reconstruction. Concomitant cartilage injuries increased at revision ACL reconstruction compared with the primary ACL reconstruction. Clinically relevant predictors of a significantly inferior KOOS one year after revision ACL reconstruction were the use of allografts and a concomitant PLC injury at the time of revision ACL reconstruction.

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FUTURE PERSPECTIVES

The future will involve new methods of using registry data that enable the patient-specific and real-time use of data for the prediction of outcome, namely the use of artificial intelligence and machine learning as a standard of care in clinical practice. The large amount of data in registries is the perfect candidate for applying new technology for algorithm-based decision-making and prognosis.

Today, research has informed us about the most important predictors of outcome after ACL reconstruction in multiple publications and through multiple methods of statistical analyses. However, in the next phase of improving the care of ACL-injured patients, there will be systems of artificial intelligence that could instantly summarize and understand data to provide the optimal treatment algorithm for an individual patient. What if we in future could enter patient-, injury- and surgery-specific factors into an artificial neural network circuit that could provide a prediction of outcome in a moment, based on the data of hundreds of thousands of patients? This might be a reality sooner than we think. Using machine learning models, we could more closely understand the impact of single risk factors, as well as the combination of several. This could take the pursuit of individualizing ACL reconstruction to a completely new level by targeting modifiable factors related to, for example, the patient or the surgical technique from a mathematical perspective of probabilities, and help to tailor the treatment accordingly to optimize the premises of outcome.

The use of new technology could also be used to improve the diagnosis and understanding of the knee joint through artificial biomechanical models. The knee joint is complex and, despite intensive research, we have not yet fully understood the impact of concomitant injuries or the synergistic effects of stabilizing structures of the knee joint. With the aid of new technology, this research could move forward rapidly in simulated models of kinematics and biomechanics and more reliably create decision bases for surgical treatment than the methods of today. In the example of combined ACL and MCL injuries, we must further understand which patients require surgical treatment for their MCL injury. In a biomechanical model using machine learning, this may be accomplished not only by focusing on the MCL injury per se but also by incorporating patient-specific risk factors, anatomic factors, radiological findings and objectively assessed laxity data, to mention just a few. We might further be able to get closer to the optimal surgical technique by simulating different techniques in mathematical models of artificial intelligence rather than in cadaveric studies.

Nonetheless, the conduct of high-quality clinical research will always remain a priority to test new hypotheses in the "real world" and we must continue to develop methodology to conduct and interpret clinical research wisely. The conduct of registry-based RCTs is an interesting aspect in terms of utilizing the large datasets provided by registries while adding part of the strength provided by RCTs. Registry-based RCTs have been successfully implemented in other fields, but they are yet to be implemented in knee ligament registries. There is also a need to further establish relevant outcome measurements to be used in ACL-injured patients and to seek consensus on what relevant outcome measurements should be assessed for the more homogeneous interpretation of study results.

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APPENDICES

KOOS
Frågeformulär för knäpatienter

DATUM: ________________ PERSONNUMMER: _________________

NAMN: ____

INSTRUKTIONER: Detta formulär innehåller frågor om hur Du ser på ditt knä. Informationen ska hjälpa till att följa hur Du mår och fungerar i ditt dagliga liv.
Besvara frågorna genom att kryssa för det alternativ Du tycker stämmer bäst in på dig (ett alternativ för varje fråga). Om Du är osäker, kryssa ändå för det alternativ som känns riktigast.

Symptom
Tänk på de **symptom** Du haft från ditt knä under den **senaste veckan** när Du besvarar dessa frågor.

S1. Har knät varit svullet?

Aldrig	Sällan	Ibland	Ofta	Alltid
☐	☐	☐	☐	☐

S2. Har Du känt att det maler i knät eller hör Du klickande eller andra ljud från knät?

Aldrig	Sällan	Ibland	Ofta	Alltid
☐	☐	☐	☐	☐

S3. Har knät hakat upp sig eller låst sig?

Aldrig	Sällan	Ibland	Ofta	Alltid
☐	☐	☐	☐	☐

S4. Har Du kunnat sträcka knät helt?

Alltid	Ofta	Ibland	Sällan	Aldrig
☐	☐	☐	☐	☐

S5. Har Du kunnat böja knät helt?

Alltid	Ofta	Ibland	Sällan	Aldrig
☐	☐	☐	☐	☐

Stelhet
Följande frågor rör **ledstelhet**. Ledstelhet innebär svårighet att komma igång eller ökat motstånd då Du böjer eller sträcker i knät. Markera graden av ledstelhet Du har upplevt i ditt knä den **senaste veckan**.

S6. Hur stelt har ditt knä varit när Du just har vaknat på morgonen?

Inte alls	Något	Måttligt	Mycket	Extremt
☐	☐	☐	☐	☐

S7. Hur stelt har ditt knä varit efter att Du har suttit eller legat och vilat **senare under dagen**?

Inte alls	Något	Måttligt	Mycket	Extremt
☐	☐	☐	☐	☐

Smärta

P1. Hur ofta har Du ont i knät?

Aldrig	Varje månad	Varje vecka	Varje dag	Alltid
☐	☐	☐	☐	☐

Vilken grad av smärta har Du känt i ditt knä den **senaste veckan** under följande aktiviteter?

P2. Snurra/vrida på belastat knä

Ingen	Lätt	Måttlig	Svår	Mycket svår
☐	☐	☐	☐	☐

P3. Sträcka knät helt

Ingen	Lätt	Måttlig	Svår	Mycket svår
☐	☐	☐	☐	☐

P4. Böja knät helt

Ingen	Lätt	Måttlig	Svår	Mycket svår
☐	☐	☐	☐	☐

P5.Gå på jämnt underlag

Ingen	Lätt	Måttlig	Svår	Mycket svår
☐	☐	☐	☐	☐

P6. Gå upp eller ner för trappor

Ingen	Lätt	Måttlig	Svår	Mycket svår
☐	☐	☐	☐	☐

P7. Under natten i sängläge (smärta som stör sömnen)

Ingen	Lätt	Måttlig	Svår	Mycket svår
☐	☐	☐	☐	☐

P8. Sittande eller liggande

Ingen	Lätt	Måttlig	Svår	Mycket svår
☐	☐	☐	☐	☐

P9. Stående

Ingen	Lätt	Måttlig	Svår	Mycket svår
☐	☐	☐	☐	☐

Funktion, dagliga livet

Följande frågor rör Din fysiska förmåga. **Ange graden av svårighet Du upplevt den senaste veckan vid följande aktiviteter på grund av dina knäbesvär.**

A1. Gå nerför trappor

Ingen	Lätt	Måttlig	Stor	Mycket stor
☐	☐	☐	☐	☐

A2. Gå uppför trappor

Ingen	Lätt	Måttlig	Stor	Mycket stor
☐	☐	☐	☐	☐

A3. Resa dig upp från sittande

Ingen	Lätt	Måttlig	Stor	Mycket stor
☐	☐	☐	☐	☐

Ange graden av **svårighet** Du upplevt med varje aktivitet den **senaste veckan**.

A4. Stå stilla

Ingen	Lätt	Måttlig	Stor	Mycket stor
☐	☐	☐	☐	☐

A5. Böja Dig, t ex för att plocka upp ett föremål från golvet

Ingen	Lätt	Måttlig	Stor	Mycket stor
☐	☐	☐	☐	☐

A6. Gå på jämnt underlag

Ingen	Lätt	Måttlig	Stor	Mycket stor
☐	☐	☐	☐	☐

A7. Stiga i/ur bil

Ingen	Lätt	Måttlig	Stor	Mycket stor
☐	☐	☐	☐	☐

A8. Handla/göra inköp

Ingen	Lätt	Måttlig	Stor	Mycket stor
☐	☐	☐	☐	☐

A9. Ta på strumpor

Ingen	Lätt	Måttlig	Stor	Mycket stor
☐	☐	☐	☐	☐

A10. Stiga ur sängen

Ingen	Lätt	Måttlig	Stor	Mycket stor
☐	☐	☐	☐	☐

A11. Ta av strumpor

Ingen	Lätt	Måttlig	Stor	Mycket stor
☐	☐	☐	☐	☐

A12. Ligga i sängen (vända dig, hålla knät i samma läge under lång tid)

Ingen	Lätt	Måttlig	Stor	Mycket stor
☐	☐	☐	☐	☐

A13. Stiga i och ur badkar/dusch

Ingen	Lätt	Måttlig	Stor	Mycket stor
☐	☐	☐	☐	☐

A14. Sitta

Ingen	Lätt	Måttlig	Stor	Mycket stor
☐	☐	☐	☐	☐

A15. Sätta dig och resa dig från toalettstol

Ingen	Lätt	Måttlig	Stor	Mycket stor
☐	☐	☐	☐	☐

A16. Utföra tungt hushållsarbete (snöskottning, golvtvätt, dammsugning etc)

Ingen	Lätt	Måttlig	Stor	Mycket stor
☐	☐	☐	☐	☐

A17. Utföra lätt hushållsarbete (matlagning, damning etc)

Ingen	Lätt	Måttlig	Stor	Mycket stor
☐	☐	☐	☐	☐

Funktion, fritid och idrott
Följande frågor rör Din fysiska förmåga. **Ange graden av svårighet Du upplevt den senaste veckan vid följande aktiviteter på grund av dina knäbesvär.**

SP1. Sitta på huk

Ingen	Lätt	Måttlig	Stor	Mycket stor
☐	☐	☐	☐	☐

SP2. Springa

Ingen	Lätt	Måttlig	Stor	Mycket stor
☐	☐	☐	☐	☐

SP3. Hoppa

Ingen	Lätt	Måttlig	Stor	Mycket stor
☐	☐	☐	☐	☐

SP4. Vrida/snurra på belastat knä

Ingen	Lätt	Måttlig	Stor	Mycket stor
☐	☐	☐	☐	☐

SP5. Ligga på knä

Ingen	Lätt	Måttlig	Stor	Mycket stor
☐	☐	☐	☐	☐

Livskvalité

Q1. Hur ofta gör sig Ditt knä påmint?

Aldrig	Varje månad	Varje vecka	Varje dag	Alltid
☐	☐	☐	☐	☐

Q2. Har Du förändrat Ditt sätt att leva för att undvika att påfresta knät?

Inte alls	Något	Måttligt	I stor utsträckning	Totalt
☐	☐	☐	☐	☐

Q3. I hur stor utsträckning kan Du lita på Ditt knä?

Helt och hållet	I stor utsträckning	Måttligt	Till viss del	Inte alls
☐	☐	☐	☐	☐

Q4. Hur stora problem har Du med knät generellt sett?

Inga	Små	Måttliga	Stora	Mycket stora
☐	☐	☐	☐	☐

Tack för att Du tagit dig tid att besvara samtliga frågor!

Information om KOOS kan erhållas från:
Professor Ewa Roos, Syddansk Universitet, Odense
Epost: eroos@health.sdu.dk

PROJEKT KORSBAND

EQ-5D

Hälsoenkät

Svensk version
(Swedish version)

Markera, genom att klicka i ett alternativ i varje nedanstående grupp vilket påstående som bäst beskriver Ditt hälsotillstånd i dag.

1. Rörlighet

Jag går utan svårigheter ○
Jag kan gå men med viss svårighet ○
Jag är sängliggande ○

2. Hygien

Jag behöver ingen hjälp med min dagliga hygien, mat eller påklädning ○
Jag har vissa problem att tvätta eller klä mig själv ○
Jag kan inte tvätta eller klä mig själv ○

3. Huvudsakliga aktiviteter
(t ex arbete, studier, hushållssysslor, familje- och fritidsaktiviteter)

Jag klarar av mina huvudsakliga aktiviteter ○
Jag har vissa problem med att klara av mina huvudsakliga aktiviteter ○
Jag klarar inte av mina huvudsakliga aktiviteter ○

4. Smärtor/besvär

Jag har varken smärtor eller besvär ○
Jag har måttliga smärtor eller besvär ○
Jag har svåra smärtor eller besvär ○

5. Oro/nedstämdhet

Jag är inte orolig eller nedstämd ○
Jag är orolig eller nedstämd i viss utsträckning ○
Jag är i högsta grad orolig eller nedstämd ○

PROJEKT KORSBAND

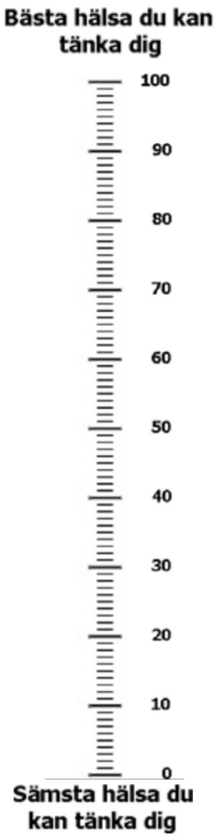
Tillbaka

Vi vill veta hur bra din hälsa är IDAG.

Den här skalan är numrerad från 0 till 100.
100 är den <u>bästa</u> hälsa du kan tänka dig.
0 är den <u>sämsta</u> hälsa du kan tänka dig.

Klicka på skalan för att visa hur din hälsa är IDAG.

DIN HÄLSA IDAG



PROJEKT KORSBAND

K-SES - Tilltro till din förmåga - A & B

Om formuläret ser konstigt ut så tryck här för en simplare version.

Frågeformulär om:

hur säker du är på din förmåga att klara av olika aktiviteter **just nu**
och
hur säker du känner dig på hur ditt knä skall fungera **i framtiden**

Vi vill ta reda ***på hur säker du är på din förmåga*** att ***just nu*** klara av:
A. Vissa dagliga aktiviteter
B. Vissa fritids-, motions- och idrottsaktiviteter
C. Vissa fysiska aktiviteter
Vi vill också ta reda på hur säker du känner dig ***just nu*** på hur ditt knä skall fungera i framtiden.
D. Din knäfunktion i framtiden

Du skall endast svara på ***din upplevelse*** av ***hur säker du är på din förmåga att*** klara av de olika aktiviteterna och inte på hur bra du faktiskt klarar av det.

A. Dagliga aktiviteter

Markera rutan för den siffra som bäst beskriver ***hur säker du är på din förmåga*** att kunna utföra aktiviteten ***just nu*** oavsett smärta/besvär.

Hur säker är du på att:	**0 = inte alls säker**									**10 = mycket säker**	
gå i skogen	0	1	2	3	4	5	6	7	8	9	10
gå nedför backar/trappor	0	1	2	3	4	5	6	7	8	9	10
springa för att hinna med tex en buss	0	1	2	3	4	5	6	7	8	9	10
arbeta i trädgården	0	1	2	3	4	5	6	7	8	9	10
städa	0	1	2	3	4	5	6	7	8	9	10

B. Fritids-, motions- och idrottsaktiviteter

Markera rutan för den siffra som bäst beskriver ***hur säker du är på din förmåga*** att kunna utföra aktiviteten ***just nu*** oavsett smärta/besvär.

Hur säker är du på att:	**0 = inte alls säker**									**10 = mycket säker**	
cykla längre sträckor	0	1	2	3	4	5	6	7	8	9	10
åka längdskidor	0	1	2	3	4	5	6	7	8	9	10
simma	0	1	2	3	4	5	6	7	8	9	10
dansa	0	1	2	3	4	5	6	7	8	9	10
fjällvandra	0	1	2	3	4	5	6	7	8	9	10

PROJEKT KORSBAND

K-SES - Tilltro till din förmåga - C & D

Om formuläret ser konstigt ut så tryck här för en simplare version.

Du skall endast svara på ***din upplevelse*** av ***hur säker du är på din förmåga att*** klara av de olika aktiviteterna och inte på hur bra du faktiskt klarar av det.

C. Fysiska aktiviteter

Markera rutan för den siffra som bäst beskriver ***hur säker du är på din förmåga*** att kunna utföra aktiviteten ***just nu*** oavsett smärta/besvär.

Hur säker är du på att:	0 = inte alls säker									10 = mycket säker
att sitta på huk	0	1	2	3	4	5	6	7	8	9	10
att hoppa i sidled från ett ben till det andra	0	1	2	3	4	5	6	7	8	9	10
att göra enbenshopp på det skadade benet	0	1	2	3	4	5	6	7	8	9	10
att göra snabba vändningar	0	1	2	3	4	5	6	7	8	9	10

D. Din knäfunktion i framtiden

Markera rutan för den siffra som bäst beskriver just nu ***hur säker du är på din förmåga*** i framtiden.

Hur säker är du på att:	0 = inte alls säker									10 = mycket säker
du blir bra i ditt knä	0	1	2	3	4	5	6	7	8	9	10
du skall kunna återgå till den fysiska aktivitetsnivå du hade före skadan?	0	1	2	3	4	5	6	7	8	9	10
du inte får nya skador i ditt knä?	0	1	2	3	4	5	6	7	8	9	10
ditt knä blir bättre än före operation (för dig som är opererad)	0	1	2	3	4	5	6	7	8	9	10

GÖTEBORGS UNIVERSITET
Institutionen för Neurovetenskap och Fysiologi

Sahlgrenska Universitetssjukhuset

SVENSKA KORSBANDSREGISTRET

PROJEKT KORSBAND

Tegner - Fysisk aktivitet

Före skada

Klicka på den **högsta** nivå när det gäller ansträngning/påfrestning på ditt knä, som du ansåg dig vara på i samband med arbete, motionsidrott eller aktiv idrott **före din knäskada**.

Finns inte din idrott eller ditt arbete med på skalan så försök värdera och likställ det emot något av alternativen.

Motionsidrott – idrott "bara för skojs skull" **Aktiv idrott** – Regelbunden tävling och träning

10	**Aktiv idrott**	Akrobatik, Am fotboll, Brottning, Fotboll på högsta elitnivå, Konståkning, Rugby
9	**Motionsidrott**	Akrobatik, Am fotboll, Brottning, Konståkning, Rugby
	Aktiv idrott	Fotboll, Ishockey, Puckelpist
8	**Motionsidrott**	Puckelpist
	Aktiv idrott	Backhoppning, Basketboll, Budo, Handboll, Innebandy, Längdhopp, Squash, Trestegshopp
7	**Motionsidrott**	Backhoppning, Basketboll, Budo, Fotboll, Handboll, Innebandy, Ishockey, Längdhopp, Squash, Tresteg
	Aktiv idrott	Badminton, Höjdhopp, Stavhopp, Tennis, Utförsåkning, Volleyball
6	**Motionsidrott**	Badminton, Höjdhopp, Ishockey, Stavhopp, Tennis, Utförsåkning, Volleyball
	Aktiv idrott	Bandy, Baseball, Hinderlöpning, Häcklöpning, Orientering, Telemark skiing, Snowboard
5	**Arbete**	Tung verkstad, Brandman, Militär, Skogsarbetare
	Motionsidrott	Bandy, Baseball, Orientering, Telemark, Snowboard
	Aktiv idrott	Boxning, Brännboll, Diskus, Fallskärmshopp, Fäktning, Gymping, Kulstötning, Längdskidor, Motorcross, Motionsspårlöpning, Slägga, Speedway, Spjut, Tyngdlyftning, Vattenskidor
4	**Arbete**	Bonde, Polis, Hamnarbetare, Plåtslagare, Murare, Byggarbetare
	Motionsidrott	Boxning, Brännboll, Diskus, Fäktning, Gymping, Kulstötning, Längdskidor, Motorcross, Motionsspårlöpning, Slägga, Speedway, Spjut, Tyngdlyftning, Vattenskidor
	Aktiv idrott	Bordtennis, Dans, Löpning på plant underlag, Vattenpolo, Windsurfing
3	**Arbete**	Jägmästare, Lätt verkstadsarbete, Lastbilschaufför, Målare, Trädgårdsarbetare, Renhållningsarbetare, Skådespelare, Snickare, Sotare, Städerska, Vägarbetare
	Skogspromenader	
	Motionsidrott	Bordtennis, Dans, Löpning på plant underlag, Vattenpolo, Windsurfing
	Aktiv idrott	Bodybuilding, Bowling, Curling, Cykel, Golf , Segling, Simning, Ridning
2	**Arbete**	Affärsbiträde, Bilreparatör, Biträde, Förskollärare, Militär, Nattvakt, Servitör, Sjuksköterska
	Gång på ojämt underlag	
	Motionsidrott	Bodybuilding, Bowling, Curling, Cykel, Golf, Segling, Simning, Ridning
1	**Arbete**	Busschaufför, Flygare, Frisör, Kock, Kontor, Läkare, Lärare, Sekreterare
	Gång på plant underlag	
	Idrott	Bridge, Bågskytte, Kanot, Schack, Skytte

Nästa

Tegner Y, Lysholm J. Rating systems in the evaluation of knee ligament injuries. Clin Orthop Relat Res. 1985(198):43-49

Ser formuläret konstigt ut? tryck här För en enklare version.

PROJEKT KORSBAND

Återgång till idrott efter främre korsbandsskada

Instruktioner: Vänligen svara på följande frågor med tanke på den huvudsakliga idrottsaktivitet du utövade innan skadan. Besvara varje fråga genom att markera med ett kryss i den ruta som beskriver, hur du upplever situationen just nu i relation till de två ytterligheterna.

Är du säker på att du kan utöva din idrottsaktivitet på samma nivå som tidigare?

Inte alls säker	1	2	3	4	5	6	7	8	9	10	Helt säker

Tror du det är sannolikt att du skadar ditt knä igen genom att delta i din idrottsaktivitet?

Extremt sannolikt	1	2	3	4	5	6	7	8	9	10	Inte alls sannolikt

Är du orolig för att utöva din idrottsaktivitet?

Extremt orolig	1	2	3	4	5	6	7	8	9	10	Inte alls orolig

Är du säker på att ditt knä inte kommer att ge vika vid utövandet av din idrottsaktivitet?

Inte alls säker	1	2	3	4	5	6	7	8	9	10	Helt säker

Är du säker på att du kan utöva din idrottsaktivitet utan att bekymra dig för ditt knä?

Inte alls säker	1	2	3	4	5	6	7	8	9	10	Helt säker

Upplever du att det är frustrerande att behöva ta hänsyn till ditt knä med avseende på din idrottsaktivitet?

Extremt frustrerande	1	2	3	4	5	6	7	8	9	10	Inte alls frustrerande

Är du rädd för att skada ditt knä igen vid utövandet av din idrottsaktivitet?

Extremt rädd	1	2	3	4	5	6	7	8	9	10	Inte alls rädd

Är du säker på att ditt knä klarar att bibehålla kontroll under belastning?

Inte alls säker	1	2	3	4	5	6	7	8	9	10	Helt säker

Är du rädd att du, av en olyckshändelse, skadar ditt knä vid utövandet av din idrottsaktivitet?

Extremt rädd	1	2	3	4	5	6	7	8	9	10	Inte alls rädd

Har tankar på att vara tvungen att genomgå operation och rehabilitering igen, hindrat dig från att utöva din idrottsaktivitet?

Alltid	1	2	3	4	5	6	7	8	9	10	Aldrig

Är du säker på din förmåga att kunna prestera bra i din idrottsaktivitet?

Inte alls säker	1	2	3	4	5	6	7	8	9	10	Helt säker

Känner du dig avspänd inför att utöva din idrottsaktivitet?

Inte alls avspänd	1	2	3	4	5	6	7	8	9	10	Helt avspänd

THE MODIFIED VERSION OF THE DOWNS AND BLACK CHECKLIST[56] USED IN STUDIES I, II AND VI	
Included Items	
Item 1	Is the hypothesis/aim/objective of the study clearly described?
Item 2	Are the main outcomes to be measured clearly described in the Introduction or Methods section?
Item 3	Are the characteristics of the patients included in the study clearly described?
Item 4	Are the interventions of interest clearly described?
Item 5	Are the distributions of principal confounders in each group of subjects to be compared clearly described?
Item 6	Are the main findings of the study clearly described?
Item 7	Does the study provide estimates of the random variability in the data for the main outcomes?
Item 8	Have all important adverse events that may be a consequence of the intervention been reported?
Item 9	Have the characteristics of patients lost to follow-up been described?
Item 10	Have actual probability values been reported (e.g. 0.035 rather than < 0.05) for the main outcomes except where the probability value is less than 0.001?
Item 11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
Item 12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?
Item 13	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?
Item 16	If any of the results of the study were based on “data dredging”, was this made clear?
Item 17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?
Item 18	Were the statistical tests used to assess the main outcomes appropriate?
Item 19	Was compliance with the intervention/s reliable?
Item 20	Were the main outcome measures used accurate (valid and reliable)?
Item 22	Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?
Item 25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?
Item 26	Were losses of patients to follow-up taken into account?
Excluded Items	
Item 14	Was an attempt made to blind study subjects to the intervention they have received?
Item 15	Was an attempt made to blind those measuring the main outcomes of the intervention?
Item 21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?
Item 23	Were study subjects randomised to intervention groups?
Item 24	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?
Item 27	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?