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# O knee, where art thou?

Patient-reported outcomes and physical performance  
in individuals with acute knee injury

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VALA FLOSADOTTIR

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O knee, where art thou?



# O knee, where art thou?

Patient-reported outcomes and physical performance in  
individuals with acute knee injury

Vala Flosadottir



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DOCTORAL DISSERTATION


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To be defended at the Health Sciences Centre, Lund on April 20<sup>th</sup> 2018 at 09.00.

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*To my family*

“Embrace the journey”

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# Abstract

Knee injuries are severe and common injuries in young and physically active individuals. Knee injury treatment, non-surgical and surgical, is aimed at improving patient-reported outcomes (PROs), reducing symptoms and restoring physical function. Physical performance tests and patient-reported outcome measures (PROMs) are often used in the evaluation of outcome after knee injury treatment. For this purpose, it is critical that the PROMs that are used demonstrate adequate measurement properties. Furthermore, it is important to identify modifiable factors that may be associated with improved outcome after knee injury. The first aim of this thesis is to investigate and present the measurement properties, specifically the responsiveness, of knee-specific and generic PROMs, in individuals undergoing knee injury rehabilitation. The second aim of this thesis is to investigate the associations between lower extremity physical performance and self-reported activity participation, knee function and knee self-efficacy in individuals after anterior cruciate ligament (ACL) injury or ACL reconstruction (ACLR).

Two methodological studies (I and II) were performed to assess the cross-cultural validity of the Swedish version of the Activity Rating Scale (ARS) for disorders of the knee (n=100) and to assess the responsiveness of the Knee injury and Osteoarthritis Outcome Score (KOOS), the Tegner Activity Scale (TAS), the Activity Rating Scale (ARS) for disorders of the knee, and the Knee Self-Efficacy Scale (K-SES) (n=76), respectively. Two cohort studies (III and IV) were conducted to assess the associations between single-leg hop performance, lower extremity muscle strength and postural orientation, respectively, and the KOOS, the TAS, the ARS (n=54) and the K-SES (n=89).

The results of this thesis show that the Swedish version of the ARS has good reliability and validity in the settings of and after knee injury rehabilitation. The results also indicate that the ARS, the K-SES, the KOOS, and the Physical Component Summary of the 36-Item Short-Form Health Survey have good responsiveness in young adults undergoing rehabilitation for a knee injury.

Furthermore, the results of this thesis demonstrate that worse single-leg physical performance, in particular performance in the vertical hop tests and the side hop tests and postural orientation, correlated moderately with lower future self-reported activity participation and worse future knee function after ACL injury/ACLR. Also, worse



symmetry between legs in the single-leg hop test and in knee flexion muscle strength correlated moderately with lower future knee self-efficacy after ACL injury /ACLR. In addition, treatment strategy, in terms of exercise therapy only, or in combination with early or delayed ACLR, after ACL injury did not appear to have an impact on future knee self-efficacy.

# Populärvetenskaplig sammanfattning

Knäskador är vanligt förekommande bland unga och fysiskt aktiva individer. En skada på ligament, menisker eller brosk i knäet kan leda till att leden blir instabil samt att rörelsemönstret och belastningen i själva leden förändras. Dessutom ökar risken för en tidig artrosutveckling i knäleden. Behandlingen av en knäskada går ut på att optimera självskattade variabler (t.ex. livskvalitet, upplevd knäfunktion och aktivitetsnivå), samt att återställa den fysiska funktionen och minimera knä-relaterade symptom. Därför utvärderas behandling efter knäskada ofta med hjälp av självskattningsinstrument och funktionella test, t.ex. hopp- och styrketest, som mäter den fysiska prestationsförmågan.

På senare tid har användning av självskattningsinstrument ökat och antalet instrument som används i bedömningen av behandling av knäskada har efter hand blivit större. Instrument som ofta används för självskattning i dessa sammanhang är Knee Injury and Osteoarthritis Outcome Score (KOOS) för upplevd knäfunktion, Activity Rating Scale for disorders of the knee (ARS) och Tegners aktivitets skala (TAS) för fysisk aktivitetsnivå samt Knee Self-Efficacy Scale (K-SES) för upplevd tilltro till knäet. För självskattning av allmän fysisk och mental hälsa används ofta Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36). Individer som råkar ut för en knäskada har oftast höga förväntningar på att de ska återhämta sig till fullo efter behandling samt att de ska kunna återgå till tidigare aktivitetsnivå eller idrott. Trots rehabilitering efter en knäskada, med eller utan kirurgisk behandling, kan dock inte alltid ett lyckat resultat uppnås.

Det är viktigt att de instrument som används för utvärdering av behandling är relevanta för de individer som drabbas av en knäskada och att dessa instrument uppvisar goda mätegenskaper, dvs. god validitet, tillförlitlighet samt känslighet för förändring inom det område de är avsedda för att mäta. Ökad kunskap om mätegenskaperna kan underlätta för fysioterapeuter, läkare och forskare att välja lämpliga instrument för utvärdering av behandling efter knäskada. God fysisk prestationsförmåga efter främre korsbandsskada har visats sig vara prediktiv för bättre upplevd knäfunktion, återgång till idrott och minskad risk för artros i knäleden. Syftet med studierna i den här avhandlingen var att undersöka och jämföra mätegenskaperna, särskilt känsligheten för förändring, hos ARS, KOOS, TAS, K-SES och SF-36. Dessutom, var syftet att undersöka vilka faktorer av fysisk prestationsförmåga som kan ha samband med bättre självskattad knäfunktion, aktivitetsnivå och tilltro till knäet efter främre korsbandsskada.

Vi genomförde två metodstudier, där vi i den ena översatte och utvärderade mätenskaperna hos den svenska versionen av the Activity Rating Scale for the disorders of the knee (ARS). I den andra metodstudien undersökte vi känsligheten för förändring i fem självskattningsinstrument, som används för bedömning av upplevd knäfunktion, aktivitetsnivå, tilltro till knäet och allmän hälsa. I dessa studier ingick individer som var i rehabilitering för en knäskada. I två longitudinella studier undersökte vi betydelsen av fysisk prestationsförmåga för framtida upplevd knäfunktion, aktivitetsnivå och tilltro till knäet efter främre korsbandsskada. Dessutom undersökte vi betydelsen av olika behandlingsstrategier av främre korsbandsskada för framtida tilltro till knäet.

Resultaten i avhandlingen visar att den svenska versionen av ARS är valid och tillförlitlig, samt att den kan användas för att upptäcka förändring i aktivitetsnivå under och efter rehabilitering av en knäskada. Vidare visar resultaten att KOOS, K-SES och SF-36 är lämpliga instrument som kan användas för att upptäcka förändring i självskattad funktion i idrotts- och fritidsaktiviteter, knä-relaterad livskvalitet, tilltro till nuvarande knäfunktion respektive allmän fysisk hälsa hos individer som har genomgått rehabilitering för en knäskada.

Nedsatt fysisk prestationsförmåga, speciellt i vertikalhopp och sidohopp utförda på ett ben, samt förmågan att stabilisera de olika kroppsdelarna i relation till varandra och omgivningen, verkar ha ett tydligt samband med lägre aktivitetsnivå och självskattad knäfunktion efter en främre korsbandsskada. Dessutom verkar en större skillnad i resultat mellan skadat och oskadat ben i enbenslängdhopp samt fram- och baklårsstyrka ha ett klart samband med tilltro till knäet efter främre korsbandsskada. När det gäller främre korsbandsskada verkar behandlingsstrategin, dvs. rehabilitering bestående av strukturerad träning, eller rehabilitering i kombination med tidig eller senarelagd kirurgisk behandling, inte påverka den upplevda tilltron till knäet. Dessa resultat understryker betydelsen av målinriktade övningar i rehabiliteringen av en främre korsbandsskada för att förbättra den fysiska prestationsförmågan, framför allt i hopp- och styrketest.

# Definitions and abbreviations

## Definitions

<b>Exercise therapy</b>	A regimen or plan of physical activities designed and prescribed for specific therapeutic goals. Its purpose is to restore normal musculoskeletal function or to reduce pain caused by diseases or injuries.
<b>Measurement properties</b>	Features of a measurement instrument that reflect the quality of the measurement instrument
<b>Patient-reported outcome</b>	A measurement or a response that comes directly from the patient without any interpretation by anyone else.
<b>Rehabilitation</b>	A treatment by a physical therapist that includes exercise therapy and other physical therapy modalities.

## Abbreviations

ACL	Anterior cruciate ligament
ACLR	Anterior cruciate ligament reconstruction
ACL-D	Treated with exercise therapy only
ACL-R	Treated with exercise therapy and early reconstruction
ACL-X	Treated with exercise therapy and optional delayed reconstruction
ADL	Activities of daily living
ARS	Activity Rating Scale for disorders of the knee
BMI	Body Mass Index
COSMIN	COnsensus-based Standards for the selection of health Measurement INstruments
ES	Effect size
GRC	Global Rating of Change
ICC	Intraclass Correlation Coefficient
IQR	Inter Quartile Range
KOOS	Knee injury and Osteoarthritis Outcome Score
- Pain	Symptoms of pain, subscale in KOOS
- Symptoms	Other symptoms than pain, subscale in KOOS
- ADL	Activities of daily life, subscale in KOOS
- Sport/Rec	Function in sport and recreation, subscale in KOOS
- QOL	Knee-related quality of life, subscale in KOOS
KOOS <sub>4</sub>	Mean score of KOOS subscales Pain, Symptoms, Sport/Rec and QoL
K-SES	Knee Self-Efficacy Scale
- Present	Perception present knee-related capability, subscore in K-SES
- Future	Perception about RTS and fear of reinjury, subscore in K-SES
LCL	Lateral collateral ligament
LOA	Limits of agreement
MCL	Medial collateral ligament

OA	Osteoarthritis
PCL	Posterior cruciate ligament
PROs	Patient-reported outcomes
PROMs	Patient-reported Outcome Measures
RCT	Randomized Controlled Trial
SD	Standard deviation
SDC	Smallest detectable change
SEM	Standard error of measurement
SF-36	Medical Outcomes Study 36-Item Short-Form Health Survey
- PF	Physical functioning, subscale in SF-36
- RP	Role physical, subscale in SF-36
- BP	Bodily pain, subscale in SF-36
- GH	General health, subscale in SF-36
- VT	Vitality, subscale in SF-36
- SF	Social functioning, subscale in SF-36
- RE	Role emotional, subscale in SF-36
- MH	Mental health, subscale in SF-36
- PCS	Physical component summary, subscore in SF-36
- MCS	Mental component summary, subscore in SF-36
RTS	Return to sports
SGPALS	Modernized Saltin-Grimby Physical Activity Level Scale
SRM	Standardized response mean
TAS	Tegner Activity Score
VAS Pain	Visual Analogue Scale for Pain





# List of studies

This thesis is based on the following studies, which will be referred to by their Roman numerals in the text.

- I. Flosadottir V, Roos EM, Ageberg E. Cross-cultural translation and measurement properties of the Swedish version of the Activity Rating Scale (ARS) for disorders of the knee. *Orthop J Sports Med.* 2017 Sep 25;5(9):2325967117729361. doi: 10.1177/2325967117729361.
- II. Flosadottir V, Roos EM, Ageberg E. Responsiveness of knee-specific and generic patient-reported outcome measures in people undergoing rehabilitation for a knee injury. In manuscript.
- III. Flosadottir V, Roos EM, Ageberg E. Muscle function is associated with future patient-reported outcomes in young adults with ACL injury. *BMJ Open Sport & Exercise Medicine*, 2016 Oct 10;2(1):e000154
- IV. Flosadottir V, Frobell RB, Roos EM, Ageberg E. Impact of treatment strategy and physical performance on future knee-related self-efficacy in individuals with ACL injury. *BMC Musculoskelet Disord.* 2018 Feb 13;19(1):50. doi: 10.1186/s12891-018-1973-2.



# Introduction

## Knee injury

### Epidemiology

Acute injury affecting the knee joint, including injuries to ligaments, menisci and/or cartilage, isolated or in combination, are most frequent among physically active young adults and middle-aged individuals (1). These injuries are a major risk factor for the development of early onset knee osteoarthritis (OA) (2-4). The injury mechanism often includes pivoting and twisting movements and sudden changes of directions, typically as seen in sports such as soccer, handball, floorball, down-hill skiing and basketball (5, 6). The anatomical location of the knee results in enormous weight bearing forces acting on the joint during exercise and physical activities. Therefore, it may not be surprising that knee is one of the most common injured joint (7), and that knee injuries account for up to 48% of all injuries in soccer, handball, basketball and floorball (8).

Injury to the anterior cruciate ligament (ACL) is the most common knee ligament injury among athletes and the estimated incidence is around 80 injuries per 100 000 person-years (9, 10). In Sweden, this corresponds to approximately 6000 ACL injuries per year, and around 250 000 injuries per year in the United States (5). Injury to the ACL is commonly associated with injuries to the menisci, joint cartilage or other ligaments (11, 12). Gender wise, female athletes have 1.5 times increased risk of ACL compared to male athletes (13). Meniscal injury, another common knee injury, has an estimated incidence of 60-70 injuries per 100 000 person-years (6, 14). Articular cartilage lesions are relatively frequent in the knee, and based on studies of knee arthroscopies, the prevalence is estimated at around 60% in young to middle-aged individuals (6, 15). These injuries; ligament, meniscus and cartilage, often occur in combination (6, 16). At least 50% of all ACL injuries are associated with meniscus injuries (11) and around 70% of articular cartilage injuries are associated with either ACL or meniscus injuries (6). The incidence of dislocation of the patella, most commonly seen in adolescents, is estimated at 43 injuries per 100 000 person-years (17).

## Anatomy and biomechanics

The different structures in the knee joint each have a specific purpose for joint function and health. The menisci act as load transmitters, shock absorbers and stabilizers in the knee joint (18-22). The joint cartilage has a fundamental role in varying load bearing, which reduces the pressure on subchondral bone, and in minimizing friction through range of motion and functional activities (16). The ACL plays an important role in the knee joint by providing stability in the anterior-posterior translational and internal-external rotational direction (23, 24). An injury to these structures causes mechanical joint instability (25), changed kinematics and joint loading (26, 27), reduced muscle strength (28, 29) and worse balance (30). These physical impairments increase the risk of secondary injuries (31), and in the long-term, may lead to early onset knee osteoarthritis (11, 14, 27, 32, 33) and increased risk of total knee replacement (34). Subsequently, all these consequences and unsuccessful outcomes after ACL injury can result in direct and indirect costs for the individual, as for the society (35).

The knee joint is dependent on both dynamic and passive stability, which is provided by muscles and ligaments, respectively (25, 36). After a ligament injury, patients often experience reduced control of the knee joint in weight bearing activities (i.e. giving way events), referred to as functional instability (37). The functional joint instability caused by a ligament injury may be replaced with dynamic stability through adequate rehabilitation, including structured exercise therapy (38-42). It is suggested that optimal knee and muscle function after knee injury is first regained at approximately 2 years after injury (43-47).

## Treatment

The treatment after a knee injury is aimed at improving patient-reported outcomes (PROs), reducing symptoms and restoring physical function. Individualized exercise therapy, with or without the addition of a surgery, is considered the main choice of treatment for knee ligament, meniscal and cartilage injury, and, typically includes exercises aimed at increasing functional stability and lower extremity strength, restoring range of knee joint motion, sensorimotor function (balance, coordination and proprioception), and minimizing joint effusion and pain (14, 45, 48-52). Surgery may be considered in cases of frequent activity participation and significant knee instability (10, 53-56), or mechanical interference of joint movements (14) despite completed exercise therapy.

The treatment of an ACL injury, surgical or non-surgical, should include individualized exercise therapy and all progress should be based on clinical milestones rather than a specific timeline (57). It is still debated whether a surgical or a non-surgical treatment is the best approach in the long term (35, 58-60). A surgical reconstruction of the ACL

may offer the prospect of better anatomical reconstruction, improved mechanical stability during recovery and over time, as well as return to preinjury level sports participation (61-65). However, not all patients experience normal knee function or return to preinjury sports after ACL reconstruction (ACLR) (66, 67). Furthermore, the outcomes up to 5 years after ACL injury, in terms of PROs and physical function, do not appear to differ between surgical or non-surgical treatment (40, 61, 68-71). Therefore, a non-surgical approach may be advocated as the primary choice of treatment for ACL injury (40, 41, 71-73). In addition, recent findings suggest that it is favorable to start exercise therapy before considering ACL reconstruction, especially for young and physically active individuals with acute ACL injury and associated meniscus injury, and for individuals that report severe knee-related pain, symptoms and impaired knee function early after injury (74). Therefore, it could be speculated that the best approach for treating an ACL injury lies in optimizing exercise therapy treatment. However, if lower perceived knee function, joint instability, lower extremity strength deficits, and movement asymmetries still persists after structured exercise therapy treatment, and if the intent is to return to high-demanding work or physical activity including pivoting and cutting movements, an ACLR may be considered (56). This period of structured exercise therapy before ACLR has been shown to be associated with better outcomes, in terms of improved self-reported knee function and increased lower extremity muscle strength (75, 76).

There have been great advances in the treatment of ACL injuries during the last decades (77-79), and recently an evidence statement for the rehabilitation after ACLR was published (80). In addition, an international consensus statement for the prevention, diagnosis and treatment of paediatric ACL injury has been established (81). Yet, there are no evidence-based guidelines available for the optimal selection of non-surgical or surgical treatment strategies for patients with acute ACL injury. In a global perspective, there is an apparent difference in the management of ACL injuries, specifically in the trends and incidence of ACLR. This may be illustrated by the majority of the patients in the United States undergo surgical reconstruction after ACL injury (12, 63), compared to only one in every three patients in Sweden (10). Consequently, patients need uniform guidance based on high-quality evidence in their decision-making regarding treatment options following a knee injury.

## Outcomes after knee injury

Assessment of treatment outcome is critical in the clinical practice. The information regarding the outcome during or after treatment can be used to make decisions about the choice or progress of treatment, and to evaluate the treatment effect. Evaluation of outcome after knee injury treatment includes generic and knee-specific PROMs and



tests of clinical measures, such as physical performance, joint range of motion and joint stability (50, 82-84). It is important to evaluate the effect and process of the treatment using measures that are meaningful and relevant to the patient (85, 86). For individuals with a knee injury, measures of knee function, symptoms, quality of life, physical activity level and return to sports and psychological factors are often used in treatment evaluation (68, 84, 85, 87-89).

### **Patient-reported outcomes measures**

PROMs constitute the recommended main outcome in clinical trials (90) and according to international consensus, PROMs should be the primary outcome in the evaluation of outcome after knee injury (84). Generic PROMs, such as Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), allow for comparisons across different medical conditions, yet, important aspects may not be noticed for specific populations (91). Therefore, the development of PROMs should include condition-specific patient involvement and be validated in the population of interest (92). There are several knee-specific PROMs commonly used to evaluate outcome after knee injury treatment, including the Knee Injury and Osteoarthritis Outcome Score (KOOS), the Tegner Activity Scale (TAS), the Activity Rating Scale for disorders of the knee (ARS), and the Anterior Cruciate Ligament Return to Sport after Injury scale (ACL-RSI) (84, 85). These knee-specific PROMs measure the patient's perception on how the knee injury affects their daily life, body structure and function, quality of life, activity, participation as well as contextual factors.

In the short- and the long-term, knee injuries can result in serious concerns and consequences for the individual (11). Despite knee injury treatment, non-surgical or surgical, impairments often persist in terms of worse patient-reported outcomes (3, 17, 40, 41). Impairments in knee-specific PROs compared to pre-injury levels and population norms have been reported for quality of life (68), knee function (93), knee-related pain (3, 6), and physical activity participation (94). In individuals with ACL injury, generic PROs have also been shown to be impaired, in terms of worse general health (86) and increased depression (95) compared to normative values.

Pre-injury, present, and desired physical activity levels are often assessed both for clinical and research purposes in individuals with knee injury. In addition, return to physical activity participation at a pre-injury, or at a modified activity level, is commonly used to evaluate success in knee injury treatment (84, 85, 87, 96, 97). It has been shown that individuals with ACL injury have high expectations of good recovery of knee function and return to sports (RTS) (65, 98). However, these expectations may never be accomplished, as many patients do not return to their pre-injury level sports participation despite completed rehabilitation and good self-reported knee function. Around 82% return to some type of physical activity participation after ACL injury or

reconstruction, and only 39-55% return to competitive sports despite completed rehabilitation (67, 89). Physical activity participation in terms of intensity and type is often assessed with the Tegner Activity Scale (TAS) and the Activity Rating Scale for disorders of the knee (ARS) is used to assess the frequency of activity participation (85). The ARS has been recommended to evaluate progression and outcome after ACLR rehabilitation (80). Until now, a validated version of the ARS has not been published in Swedish.

It has been shown that sport injuries can be accompanied with negative psychological responses, such as sadness, fear of reinjury, and loss of confidence and identity (99) and that these responses can affect the outcome after injury (100). In recent years, there has been increased focus on psychological factors and their association to recovery and RTS after ACL injury (101-104). Knee-related self-efficacy, defined as the perception of one's capability to perform knee-related activities, is one psychological factor that has shown to be important for outcome after ACL injury (105). Knee-related self-efficacy has been reported to be low soon after ACL injury or ACLR but appears to increase during the process of rehabilitation (106, 107). However, factors, such as physical performance or treatment strategies (surgical or non-surgical), that may affect future knee-related self-efficacy after ACL injury need further investigation. The Knee Self-Efficacy Scale (K-SES) has been recommended to be included in the evaluation of psychological changes during and after ACLR rehabilitation (80).

## **Measures of physical performance**

Knee function is reliant on numerous biomechanical factors and conditions (25). Therefore, it may be speculated that no single factor, in terms of physical performance, can be used to determine knee function after knee injury. Tests of single leg hop performance and lower extremity muscle strength are often used to assess physical outcome and knee function after knee injury (108). The advantage of these tests is that they may be used to determine progress during rehabilitation, discharge from rehabilitation and a safe return to sports (109). Often, the performance of the non-injured leg is used as control for the performance of the injured leg, by calculating the Limb Symmetry Index ( $LSI = \text{injured leg}/\text{non-injured} \times 100$ ) (110). However, this method may raise some concerns as altered movement patterns and strength deficits have been reported not only for the injured leg but also for the non-injured leg after ACL injury (111-113). Therefore, deficits in performance may be underestimated when using the LSI. Despite this, LSI is frequently used and a 90% symmetry between legs ( $LSI \geq 90\%$ ) in several physical performance tests has been suggested as criteria for a successful outcome and return to sports (84, 114, 115).

Single-leg hop tests, assessing maximum hop performance or endurance, are commonly used and are designed to reflect the demands of a high level of physical activity (109,

116). The single leg hop for distance is the most commonly used hop performance test after ACL injury (110). In addition, tests of lower extremity muscle strength, assessing knee extension and flexion strength, are recommended in outcome evaluation after knee injury (31, 110, 117, 118). Assessment of postural orientation, defined as the ability to stabilize joints in relation to each other and to the environment (119), may also be used to complement strength and hop assessment after knee injury (120). Extensive test batteries, which include hop tests, strength test and assessment of postural orientation, can preferably be used to quantify knee-related performance in patients after ACL injury or ACLR (80).

### **Patient-reported outcomes or physical performance?**

The use of PROMs and physical performance tests to evaluate recovery and progress during and after rehabilitation after ACL injury has shown that these measures also appear to be predictive of several outcomes after ACL injury. The associations between physical performance and knee-specific PROs in individuals with ACL injury have been investigated to a certain extent.

PROMs assessing psychological factors, in terms of fear of reinjury, reduced self-efficacy and reduced motivation, have been shown to be associated with lower rate of return to sports after ACL injury (88, 102, 121, 122). High pre-operative knee-related self-efficacy seems to be predictive of better single-leg hop performance at 1 year after ACLR (105). Furthermore, worse score in the SF-36 Bodily pain prior to ACLR seems to be a predictor for worse self-reported knee function at 2 years after ACLR (76). Low physical activity participation at 2 years after ACLR has been reported to be associated with an increased risk of painful knee at 6 years (123).

Physical performance tests can provide valuable information about self-reported knee function, knee-related quality of life, treatment strategies, reinjury and knee OA development after ACL injury. The LSI for the single leg hop test for distance at 2.5 months and the LSI for the triple-leg crossover and the 6-meter timed hop at 6 months, respectively, have been shown to be predictive of self-reported knee function at 1 year after ACL injury or ACLR (124, 125). Lower LSI in the single leg hop and the triple hop for distance at 1 year after ACLR was associated with lower rates of return to preinjury level sports at 2 years (103). Also, a LSI of < 90% in the single leg hop for distance at 1 year was found to be associated with knee OA development at 10 after ACLR (126). Worse performance in the one leg rise test after completed rehabilitation following ACL injury or ACLR has been reported to be associated with worse self-reported knee function at 2 and 5 years (70). A failure to achieve LSI  $\geq$  90% in any single-leg hop or lower extremity muscle strength test, included in a battery of discharge tests, has been shown to be associated with higher risk of reinjury up to 2 years after ACLR (31, 127).

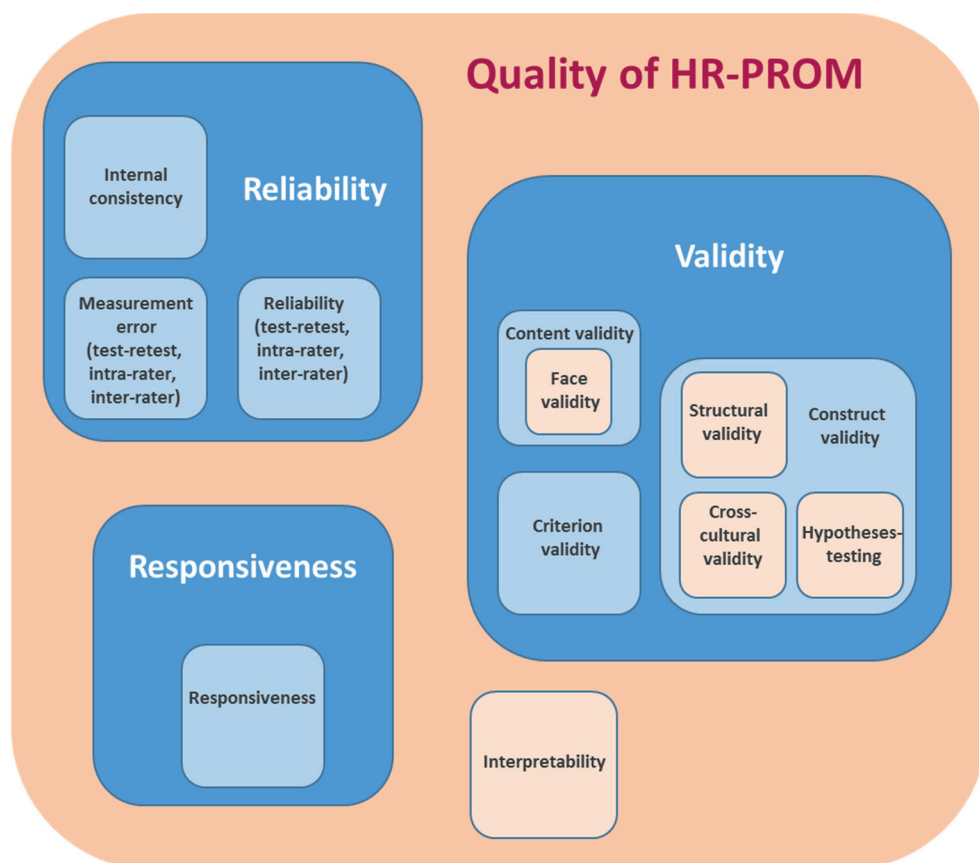
The moderate correlations previously reported between measures of physical performance and PROMs after ACL injury suggest that while these measures share some similarities, the information they gather is not the same (128-130) (70, 103, 124, 125, 129). Therefore, PROMs and measures of physical performance are obvious in complementing, rather than replacing each other.

## Measurement properties of outcome measures

Over the past 20 years, there has been a considerable growth in the number of PROMs designed to evaluate outcome after knee injury. The process of choosing the appropriate PROM to accurately evaluate changes after treatment needs to include information about the construct to be measured, the target population and the measurement properties of the specific PROM (131). This is fundamental to enable correct investigation and comparison of different elements and options of treatment.

In recent years, the effectiveness of different treatment strategies for knee injuries, such as ACL and meniscus tears, have been investigated and compared in a number of randomized clinical trials (29, 40, 41, 132-134). PROMs are extremely important in the evaluation and interpretation of these trials. There is a need for a consistency in the PROMs that are used to enable comparisons between trials and to find the most appropriate PROM for each population. In this context, the measurement properties of the PROMs are critical.

The concepts of measurement properties, i.e. what they represent and how they should be assessed, have been defined in different and inconsistent manner (135, 136). These varieties of definitions and terms have led to different methods for assessing measurement properties of PROMs. The results of a study of measurement properties is dependent on the methods that are used. Therefore, it is important to use one definition in addition to an accompanying method in the assessment of measurement properties. In the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) study, an international consensus was reached on the taxonomy, the terminology and the measurement properties of health-related PROMs (Figure 1) (92). These consensus-based recommendations can be used as guidelines to evaluate and develop the measurement properties of PROMs.



**Figure 1.** The COSMIN taxonomy of relationships between measurement properties. COSMIN, Consensus-based Standards for the selection of health Measurement INstruments; HR-PROM, health-related patient-reported outcome measure. Adapted from Mokkink et al 2010.

According to the COSMIN guidelines, there are three basic domains of measurement properties, including validity, reliability and responsiveness (Table 1). These domains are commonly assessed to provide evidence for the measurement properties of a PROM. Validation studies investigate whether the underlying construct of interest is properly assessed. Reliability studies probe into the stability of repeated measurements and the error or the “noise” of the measurements. Responsiveness studies investigate the longitudinal validity of the instrument and confirm that the instrument can detect changes over time in the construct of interest. (92) The three domains of measurement properties each include subcategories, which are further defined in Table 1.

**Table 1. COSMIN definitions of domains, measurement properties, and aspects of measurement properties**

Term			Definition
Domain	Measurement property	Aspect of a measurement property	
<b>Reliability</b>			The degree to which the measurement is free from measurement error
	<b>Internal consistency</b>		The degree of the interrelatedness among the items
	<b>Reliability</b>		The proportion of the total variance in the measurements which is due to true differences between patients
	<b>Measurement error</b>		The systematic and random error of a patient's score that is not attributed to true changes in the construct to be measured
<b>Validity</b>			The degree to which a PROM measures the construct(s) it is intended to measure
	<b>Content validity</b>		The degree to which the content of a PROM is an adequate reflection of the construct to be measured
		<b>Face validity</b>	The degree to which (the items of) a PROM really looks as though they are an adequate reflection of the construct to be measured
	<b>Construct validity</b>		The degree to which the scores of a PROM are consistent with hypotheses based on the assumptions that the PROM validly measures the constructs to be measured
		<b>Structural validity</b>	The degree to which the scores of a PROM are an adequate reflection of the dimensionality of the construct to be measured
		<b>Hypotheses testing</b>	Same definition as construct validity
		<b>Cross-cultural validity</b>	The degree to which the performance of the items on a translated or culturally adapted PROM are an adequate reflection of the performance of the items of the original version of the PROM
	<b>Criterion validity</b>		The degree to which the scores of a PROM are an adequate reflection of a "gold standard"
<b>Responsiveness</b>			The ability of a PROM to detect change over time in the construct to be measured
	<b>Responsiveness</b>		Same definition as responsiveness
<b>Interpretability*</b>			The degree to which one can assign clinical or commonly understood meaning to a PROM's quantitative scores or change in scores

PROM, patient-reported outcome measure. \*Interpretability is not considered a measurement property, but an important characteristic of a PROM. Adapted from Mokkink et al 2010.

### *Cross-cultural validity*

Cross-cultural validity is an aspect of validity, which includes the process of translation and re-evaluation of the measurement properties of a PROM in another language or cultural setting (92). The recommended method to linguistically and conceptually validate a PROM in a new language and culture consists of six steps (137, 138). These steps include a 3-stage translation, a review of an expert committee and a pre-testing of



the new version of the PROM (137). Lastly, the measurement properties of the PROM should be evaluated in an adequate sample ( $n \geq 50$ ) of the target population (138).

### *Responsiveness*

The definition of responsiveness is the ability of a PROM to detect change over time in the construct to be measured (92). In the evaluation of treatment outcome after an injury or disease, PROMs are often used to assess outcome over time. In that aspect, responsiveness is an important measurement property. According to the COSMIN guidelines, responsiveness should be assessed by testing hypotheses regarding the strength of correlations between change scores in a PROM and change scores in other PROMs that measure related constructs (139). Another approach for responsiveness assessment is the calculation of effect sizes. Cohen's effect size and the Standardized Response Mean (SRM) have been suggested to be appropriate measures to assess responsiveness (140). In addition, it has been suggested that a standardized effect size known as Cliff's delta should be calculated when data deviates from the normal distribution (141). These two approaches, hypotheses testing and different calculations of effect sizes, are suggested to evaluate the validity of change (longitudinal validity) and the magnitude of change, respectively (142).

The responsiveness of a PROM can vary depending on the specific populations, treatments and follow-up periods that are used (143). Hence, it is important to test and assess the responsiveness in the context the specific PROM is to be used. Furthermore, relevant PROMs should be assessed and compared alongside within the same study to facilitate the selection of appropriate PROMs in the evaluation of change in treatment outcome.

## Rationale of the thesis

Knee injuries are severe injuries that are common in the young and physically active population. At present, there are numerous patient-reported outcome measures available to assess outcome after knee injury treatment. Highly physically active individuals, that have high demands on their knee function, need to be evaluated accordingly during and after knee injury treatment. The ARS, which assesses the frequency of knee-specific activity participation, may be an appropriate outcome measure for this purpose. Until now, a Swedish version of the ARS has not been validated.

It is recommended to establish the responsiveness of a PROM in the target population and in the relevant setting (92). The responsiveness of PROMs commonly used in the evaluation of knee injury treatment, including the KOOS, the TAS, the ARS, the K-SES and the SF-36, have previously, yet, separately been investigated in populations

with knee injury (85, 86, 144-147). The responsiveness, in terms of both magnitude and validity of change, of these knee-specific and generic PROMs has not yet been assessed and compared head-to-head within the same knee injury cohort. Increased knowledge about the responsiveness of these PROMs may facilitate the selection and the use of appropriate PROMs to evaluate change in outcome after knee injury.

The associations between physical performance and knee-specific PROMs in individuals with ACL injury have been investigated to a certain extent. Yet, the evidence is limited and there are differences in the methods used in previous studies, in terms of post-injury and post-surgical time intervals, the physical performance tests and the PROMs that are assessed (124, 125, 128, 129, 148, 149). Furthermore, the associations between physical performance after ACL injury/ACLR and future knee-related self-efficacy have not been investigated before. Understanding which components of physical performance are associated with improved patient-reported outcomes after ACL injury or ACLR may contribute to optimization of exercise therapy programs, improve adherence to rehabilitation and assist patients and clinicians in the decision and advisement of different treatment strategies.

High self-efficacy can facilitate one's initiative for action, level of effort and resilience to setbacks (150). After ACL injury, knee-related self-efficacy may be low but has been shown to improve during the course of rehabilitation (146). However, the levels of future knee-related self-efficacy in patients treated with exercise therapy alone or in combination with either early or the option of delayed ACLR have not previously been reported. Therefore, the impact of surgical or non-surgical treatment strategies on knee-related self-efficacy is largely unknown.

Consequently, the studies in this thesis aim to investigate and present the measurement properties, specifically the responsiveness, of several knee-specific and generic PROMs, in individuals undergoing knee injury rehabilitation. In addition, the included studies are intended to complement and increase the knowledge about which physical performance factors and treatment strategies may be associated with improved PROMs after ACL injury or ACLR.



# Aims of the thesis

## **Overall aims**

The overall aims of this thesis were to 1) assess the measurement properties, in particular the responsiveness, of knee-specific and generic PROMs and to 2) investigate the association between lower extremity physical performance and knee-specific PROs in individuals with knee injury.

## **Specific aims**

Study I: To 1) translate and cross-culturally adapt the ARS into Swedish and 2) assess measurement properties of the Swedish version of the ARS.

Study II: To evaluate and compare the responsiveness, in terms of magnitude and validity of change, of commonly used knee-specific and generic PROMs in patients undergoing rehabilitation for a knee injury.

Study III: To investigate the cross-sectional and longitudinal associations between lower extremity physical performance at 3 years and knee-specific PRO scores at 5 years after ACL injury/ACLR.

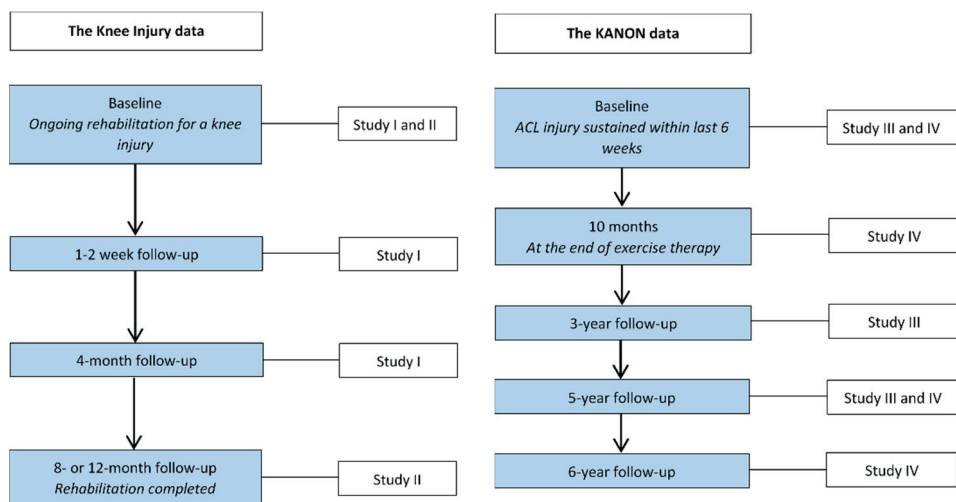
Study IV: To 1) report knee-related self-efficacy 6 years after acute ACL injury in patients treated with exercise therapy alone or in combination with either early or the option of delayed ACLR, and to 2) investigate associations between objectively measured single-leg physical performance at various time points after ACL injury/ACLR and self-reported knee self-efficacy at 6 years after injury.



# Methods

## Study designs and cohorts

The research for this thesis was performed using data from two separate study cohorts, the Knee Injury cohort and the Knee Anterior Cruciate Ligament, Nonsurgical versus Surgical Treatment (KANON) cohort (Figure 2). The Knee Injury data, including individuals in rehabilitation for a knee injury, was specifically collected for studies I and II in this thesis. The KANON data originates from the KANON study (40), a randomized controlled trial, which included 121 individuals with acute ACL injury. The measures used in the studies include quantitative variables from patient-reported questionnaires and physical performance tests.



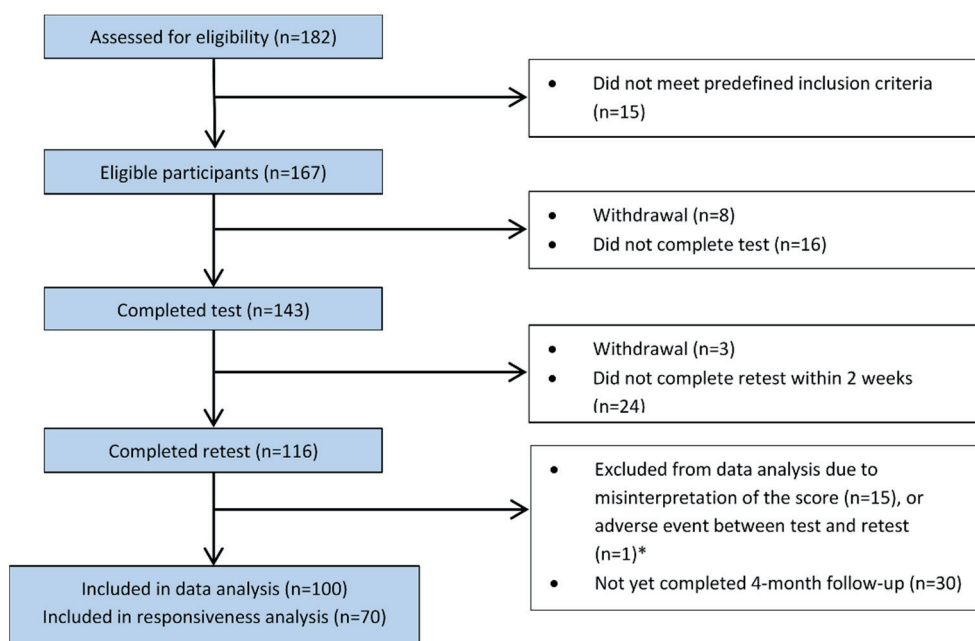
**Figure 2.**  
Settings and follow-ups in study I-IV

## The Knee Injury data

### Study I

The data for study I was collected between December 2014 and May 2016. The participants were recruited at seven physical therapy clinics in southern Sweden. The inclusion criteria for the participants were: ongoing rehabilitation for a knee injury (ligament, meniscus or cartilage) or post-injury knee osteoarthritis, surgically or non-surgically treated, and age 15-49 years. Participants were excluded if they had completed their knee injury rehabilitation between recruitment and baseline, were not limited in their activities due to their knee injury, had other disease or disorders overriding their knee injury, if they had an overuse knee injury (i.e. jumper's or runner's knee), or if they were physically inactive (Tegner Activity Scale score < 3). In May 2016, 182 individuals had completed the baseline assessment (Figure 3).

In study I, the measurement properties of the Swedish version of the ARS were assessed according to the COSMIN guidelines (138). Participants (n=100) that had completed the test-retest assessment were included in the reliability and the validity analyses. Participants (n=70) that had completed the assessment of the patient-reported questionnaires at the 4-month follow-up were included in the responsiveness analysis.

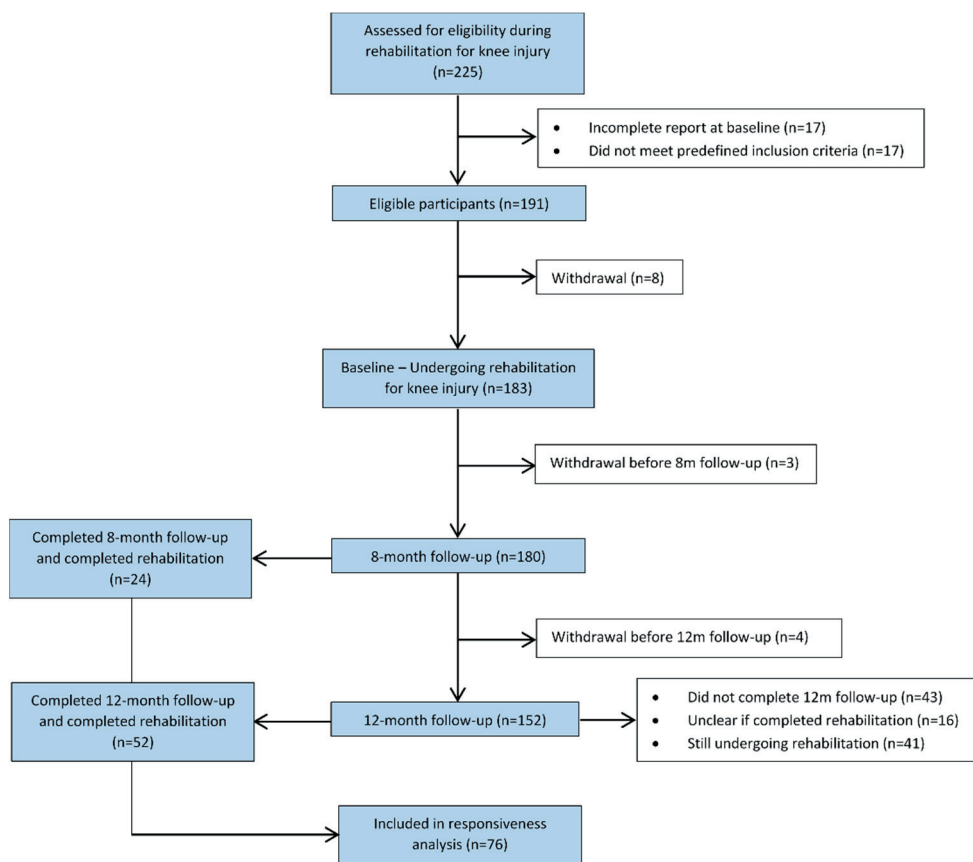


**Figure 3.**  
Flow diagram study I. Recruitment and eligibility assessment performed until May 2016.

## Study II

The data collection for study II continued through June 2017, using the same inclusion and exclusion criteria as were used in study I. At the end of the data collection, 225 individuals had completed the baseline assessment (Figure 4).

In study II, the responsiveness of the KOOS, the ARS, the TAS and the SF-36 was assessed according to the COSMIN guidelines (138). Participants (n=76) that had completed the patient-reported questionnaires at follow-up (8- or 12-months) and at that time reported that they had completed their knee injury rehabilitation were included in the responsiveness analysis.



**Figure 4.** Flow diagram study II. Recruitment and eligibility assessment performed until July 2017.

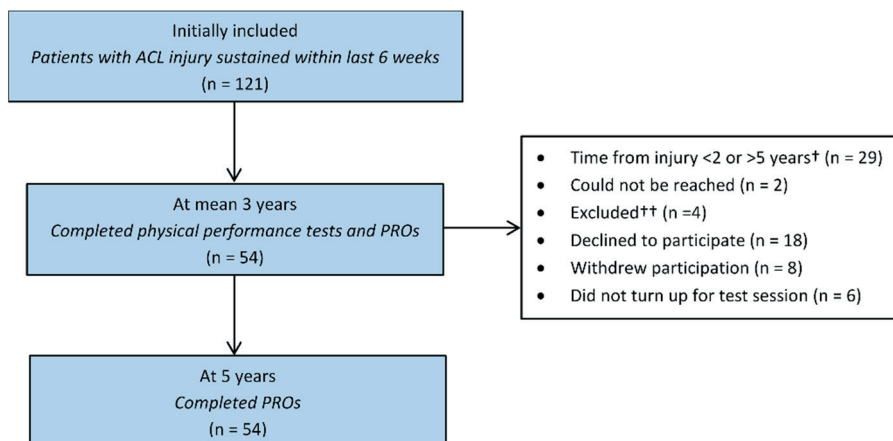


## The KANON data

### Study III

In study III, we used data from the original KANON (40) study, a treatment RCT, and data from an ancillary study of the RCT by Ageberg et al. (69). The inclusion criteria for the KANON study were: an acute ACL injury sustained within the last 4 weeks, a moderate to high physical activity level (Tegner Activity Scale score 5-9), and age 18-35 years. The main exclusion criteria were: professional athlete (TAS score 10), less than moderate physical activity level (TAS score < 5), a complete collateral ligament rupture, or full thickness cartilage lesion. All participants underwent a structured exercise therapy program, supervised by a physical therapist, for at least 4 months. The participants were randomized to a treatment consisting of exercise therapy only, or exercise therapy in addition to an early or an optional delayed ACL reconstruction. Inclusion criteria for the ancillary study (69) were: 2-5 years since injury.

In study III, the associations between physical performance and knee-specific PROMs scores were investigated. Participants (n=54) that had completed an extensive physical performance testing at mean 3 years after injury were included in the analyses (Figure 5). These participants also completed knee-specific PROMs, including the KOOS, the TAS and the ARS, at mean 3 and 5 years after ACL injury or ACLR.



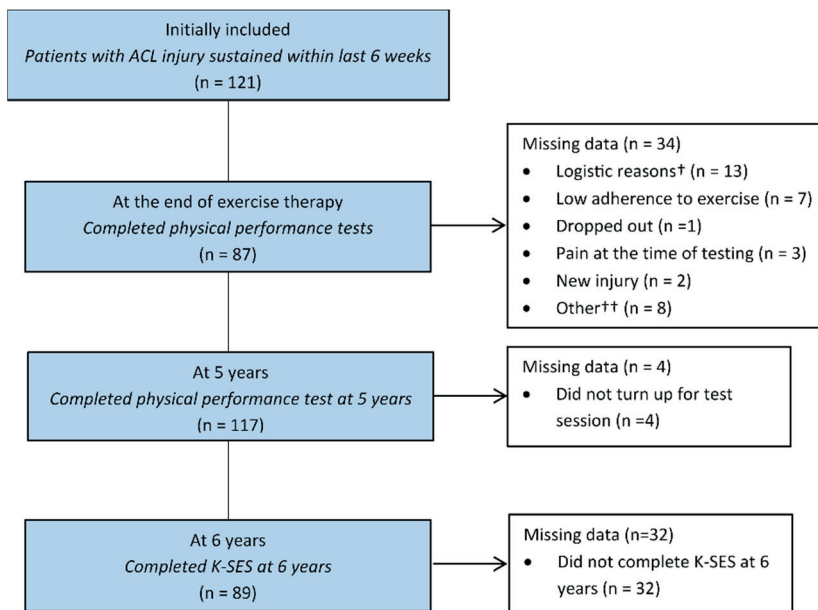
**Figure 5.**

Flow diagram study III. † Inclusion criterion for physical performance tests, †† Pregnancy (n=1), still using crutches (n=3).

### Study IV

In study IV, we used data from the original KANON study (40) and data from an ancillary study of the KANON study by Ericsson et al. (70). In the ancillary study (70), 87 participants, of the original 121, underwent physical performance testing at the end of the exercise therapy (at mean 10 months).

In study IV, the K-SES scores for the groups-as-treated at 6 years were reported, and the associations between physical performance and K-SES scores were investigated. Participants (n=89) that had completed the physical performance tests at the end of the exercise therapy and at 5 years, and, in addition to having completed K-SES at 6 years were included in the analyses (Figure 6).



**Figure 6.**

Flow diagram study IV. †Long-distance relocation or transferal to a physical therapist (PT) not involved in the study. ††Pregnancy (n=1), disc herniation (n=1), advised against performing test by PT (n=3), missing test protocols (n=3).

## Participants in studies I-IV

**Table 2. Settings and baseline characteristics of the participants included in studies I-IV**

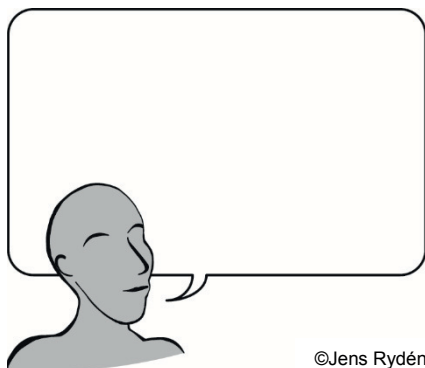
	Study I	Study II	Study III	Study IV
<b>Data origin</b>	Knee injury cohort	Knee injury cohort	KANON-trial	KANON-trial
<b>Setting</b>	Ongoing rehabilitation for a knee injury	Completed rehabilitation for a knee injury	Exercise therapy only or in addition to early or option of delayed ACLR after ACL injury	Exercise therapy only or in addition to early or option of delayed ACLR after ACL injury
<b>Number of participants</b>	100	76	54	89
<b>Age, mean <math>\pm</math> SD, y</b>	27.0 $\pm$ 10.5	28.3 $\pm$ 8.8	29.7 $\pm$ 5.3	26.2 $\pm$ 5.1
<b>Female, n (%)</b>	55 (55)	40 (53)	15 (28)	25 (28)
<b>BMI, mean <math>\pm</math> SD, kg/m<sup>2</sup></b>	24.7 $\pm$ 3.8	24.3 $\pm$ 3.3	24.6 $\pm$ 3.0	23.8 $\pm$ 2.8*
<b>Type of knee injury, n (%)</b>				
<b>ACL</b>	74 (74)	54 (71)	54 (100)	89 (100)
<b>Meniscal</b>	12 (12)	11 (14)	NA	NA
<b>Cartilage</b>	4 (4)	2 (3)	NA	NA
<b>MCL or LCL</b>	4 (4)	5 (7)	NA	NA
<b>Patellar dislocation</b>	5 (5)	3 (4)	NA	NA
<b>PCL</b>	1 (1)	1 (1)	NA	NA
<b>Surgical treatment, n (%)</b>	58 (58)	48 (63)	36 (67)	69 (78)

\*n=87. NA, not applicable in these studies

# Outcome measures

## Patient-reported outcome measures, PROMs (I-IV)

The patient-reported outcome measures that are assessed in the studies in this thesis include four knee-specific and one generic PROMs. Four additional PROMs were exclusively used for comparative purposes in the validity assessment in studies I and II.



## Knee-specific PROMs (I-IV)

In study I, the Swedish version of the Activity Rating Scale (ARS) for disorders of the knee was cross-culturally adapted and validated. In study II, the ARS, the Tegner Activity Scale (TAS), the Knee Self-Efficacy Scale (K-SES), and the Knee injury and Osteoarthritis Outcome Scores (KOOS) were assessed for responsiveness. In studies III and IV, the knee-specific PROMs were used to investigate cross-sectional and longitudinal associations with physical performance in individuals after ACL injury/ACLR.

### *Activity Rating Scale for disorders of the knee, ARS*

The ARS (151) is a scale used to assess the frequency of participation in four separate activities with high demands on knee function; running, cutting, decelerating and pivoting. The frequency of activity participation is scored on a five-level scale from 0 (no participation) to 4 (participation four or more times a week), resulting in a total score between 0 and 16. The ARS has demonstrated good face, content and construct validity, and good test-retest reliability for the evaluation of physical activity participation in individuals with knee injury (151).

### *Tegner Activity Scale, TAS*

The TAS (152) is a 11-level scale used to assess physical activity level based on recreational/sporting or occupational activities. The TAS ranges from 0 (sick leave or disability due to knee problems) to 10 (participation in competitive sports at national or international level). The TAS has demonstrated good construct validity and adequate test-retest reliability for evaluation of activity level in groups with knee injury (ACL and meniscal injury, patellar dislocation and knee OA) (144, 152, 153). Moderate to large effect sizes have been reported for the TAS at 9, 12 and 24 months after ACLR (153) and at 2 years after meniscal surgery (154).

### *Knee Self-Efficacy Scale, K-SES*

The K-SES (145) holds four sections; A) daily activities, B) sports and leisure activities, C) knee function tasks, and D) future knee function. The certainty about the capability of performing an activity is rated on an 11-point Likert scale, with a range from 0 (not at all certain) to 10 (very certain). The full K-SES includes 22 items, which are summarized and divided by the number of items, producing a total K-SES score (A-D) ranging from 0 to 10. In sections A through C, the perception about one's present capability of performing knee-related tasks is reported, resulting in the subscore K-SES Present. In section D, the perception about one's future knee function capability is reported, i.e. perception about return to preinjury level sport and fear of reinjury (and future knee function if undergoing ACLR), resulting in the subscore K-SES Future. The subscores are calculated separately, with a range of 0 to 10. The K-SES has shown good internal consistency, test-retest reliability, face validity, content validity and construct validity in individuals after ACL injury or ACLR (145, 146).

### *Knee injury and Osteoarthritis Outcome Score, KOOS*

The KOOS (155) is a 42-item score that includes five subscales with separate normalized subscale score with a range from 0 (worst) to 100 (best). The KOOS subscales cover knee-related pain, symptoms, activities of daily living (ADL), function in sports and recreational activities (Sport/Rec), and quality of life (QOL). In the subscale QOL, item 3 (Q3) covers perceived knee confidence. The KOOS has demonstrated good face validity, content validity, construct validity and good internal consistency and test-retest reliability in individuals undergoing surgery due to knee injury (ACL injury, meniscus or chondral injury) (144). Large effect sizes have been reported for the KOOS in individuals at 6 months after ACL (155) and moderate to large effect sizes have been reported at 3 months after meniscectomy (156, 157).

## Generic PROM (II)

In study II, the magnitude of change was assessed for the SF-36 and compared with the magnitude of change for the knee-specific PROMs. The SF-36 was also used as a comparative instrument in the hypotheses testing for the responsiveness assessment of the knee-specific PROMs.

### *The Medical Outcomes Study 36-Item Short-Form Health Survey, SF-36*

The SF-36 (158) holds 36 items scored within eight components of generic health: Physical Functioning (PF), Role Limitations due to Physical Health (Role-Physical, RP), Bodily Pain (BP), General Health Perceptions (GH), Vitality (VT), Social Functioning (SF), Role Limitations due to Emotional Problems (Role-Emotional, RE), and General Mental Health (MH). The score of the physical components (PF, RP, BP, GH) is summarized in the Physical Component Summary (PCS) and the mental components (VT, SF, RE, MH) are summarized in the Mental Component Summary (MCS). The eight components and the two component summaries each produce separate scores between 0 (worst health) and 100 (best health). The SF-36 has shown good criterion and construct validity and good internal consistency in a normative population (159, 160).

## Comparative PROMs (I and II)

We used the following PROMs as comparative instruments in the hypotheses testing for the construct validity assessment of the Swedish version of the ARS and for the responsiveness assessment of the ARS, the KOOS, the TAS and the K-SES.

### *Modernized Saltin-Grimby Physical Activity Level Scale, SGPALS*

The SGPALS (161) is a 4-level scale used to evaluate the level of general physical activity with a score ranging from 1 (physical inactivity) to 4 (regular, hard training for competitive sports). The SGPALS has demonstrated good construct validity and reliability in a general population (162, 163).

### *Visual Analogue Scale for Pain, VAS Pain*

The VAS Pain (164) is an analogue scale used to assess pain intensity. In our study (II), the scale was marked on a horizontal line, generating a score from 0 (no pain) to 100 (worst imaginable pain). We asked the participants to grade their pain based on the question “How much knee pain did you experience during the past week?”. The VAS Pain has demonstrated good construct validity and good test-retest reliability to be used in individuals with acute and chronic joint pain (165).

### *Pain manikin for measurement of musculoskeletal pain, Pain manikin*

The Pain manikin (166) is a manikin displaying 44 body parts, 21 anterior and 23 posterior parts. The participants marked painful sites on the manikin to indicate whether they had pain from any muscles, joints or bones for at least one week during the last month. The pain should not be related to menstruation or influenza. In our study (II), the prevalence of pain was calculated for the number of marked sites. Pain assessed with the Pain manikin has demonstrated high agreement with pain assessed using written questions (166). Pain manikins have demonstrated good test-retest reliability in individuals with low back pain (167).

### *Global Rating of Change, GRC*

We used GRC scales to assess the perceived change in the specific constructs of the PROMs (ARS, TAS, K-SES and KOOS) being evaluated in studies I and II. At follow up, the participants answered the eight following questions based on a 7-point Likert scale. 1) GRC reflecting changes in the ARS: "How often do you perform knee-demanding activities (running, cutting, decelerating to a quick stop, twisting/pivoting with your foot planted while playing sports) now compared to 8/12 months ago?" The response options: much more often, more often, somewhat more often, about the same, somewhat less often, less often or much less often. 2) GRC reflecting changes in the TAS: "How is your current activity level compared with 8/12 months ago?" The response options: much higher, higher, slightly higher, about the same, slightly lower, lower or much lower. 3) GRC reflecting changes in the K-SES: "How certain are you that you can perform physical activities, such as running after a bus, go on bike trip, jump on one leg or make quick turns, compared to 8/12 months ago?" The response options: much more certain, more certain, slightly more certain, about the same, slightly less certain, uncertain or very uncertain. GRC scales reflecting changes in the KOOS subscales Pain, Symptoms, ADL, Sport/rec, and QOL, respectively: 4) "How is your knee pain now compared to 8/12 months ago?" 5) "How are the other symptoms in your knee (swelling, stiffness, decreased range of motion) now compared to 8/12 months ago?" 6) "How is your ability to perform daily activities (sitting, standing, walking, stairs, dressing and household work) now compared to 8/12 months ago?" 7) "How is your ability to perform sport and recreational activities (running, jumping, squatting, kneeling, twisting on loaded knee) now compared to 8/12 months ago?" 8) "How is your quality of life that relates to your knee (trust in knee, life style, how often you think of your knee, etc.) now compared to 8/12 months ago?" The response options for questions 4-8 were: better, somewhat better, very small change (but not enough to be an important improvement), about the same, very small change (but not enough to be an important worsening), worse, or much worse.

## Performance-based outcome measures (III and IV)

The Limb Symmetry Index (LSI) was calculated as the performance of the injured leg divided by that of the uninjured leg and multiplied by 100. For the analyses in study III, we used both absolute values (W, cm) and the LSI. In study IV, the LSI was used for all analyses of physical performance.

### *Muscle power tests*

In study III, the muscle power tests were performed in weight training machines intended for knee extension, knee flexion and leg press, respectively, where the average power output (W) was measured using an electronic system (Muscle Laboratory; Ergotest Technology) (69). The knee extension power was recorded from 110° knee flexion to full extension, the knee flexion power was recorded from full knee extension to 110° knee flexion, and the leg press test was used to assess lower extremity power from 90° knee and hip flexion to fully extended knee and 30° hip flexion.

In study IV, the muscle power tests for hamstring and quadriceps strength were performed in an isokinetic device (BIODEX(168)) or in weight training machines intended for knee extension and knee flexion, respectively, using the principle of one maximal repetition (1 RM) (169).

### *Hop performance tests*

In all of the four hop performance tests, both legs were assessed separately.

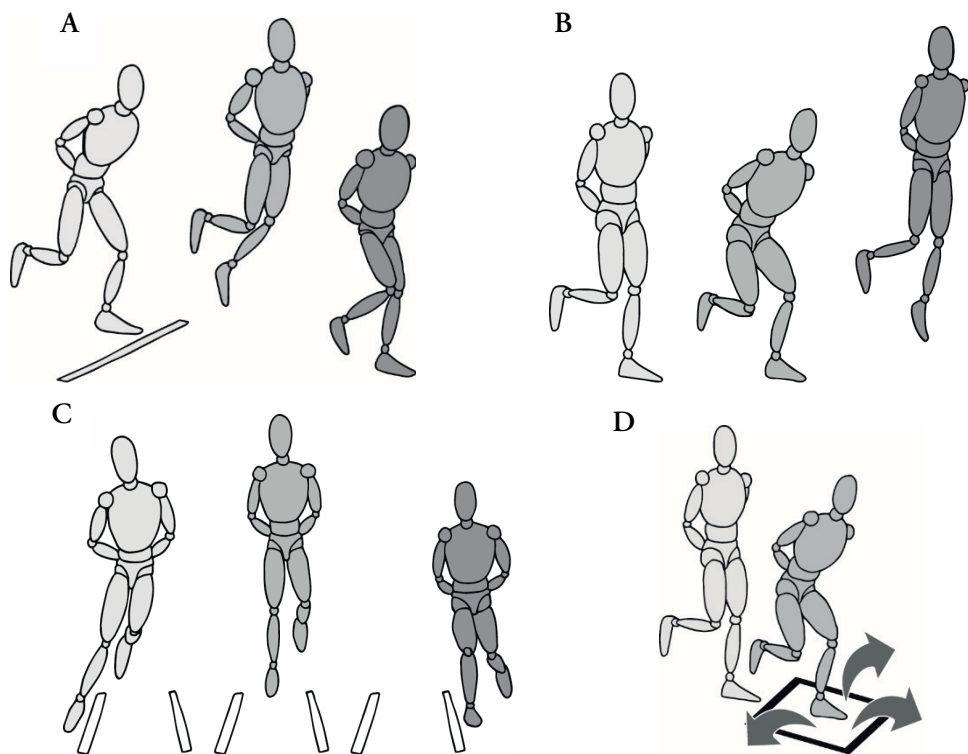
The single-leg hop for distance test (116) was performed from a standing starting position on one leg, with both hands placed on the lower back. From this position, the participants were instructed to jump as far as possible and land on the same foot (Figure 7). For a qualified jump, balance had to be remained at landing for 2-3 seconds and hands had to remain on the back during jump and landing. The distance (cm) was measured from the toes at the starting position to the heel at the landing position.

The vertical hop test (116) included an upright starting position on one leg and instructions to jump as high as possible (Figure 7). The participants were allowed to bend their knee as much as desired to initiate the jump. In study III both arms were held behind the back during the jump, whereas, in study IV the arms were free to help during the jump.



The side hop test (116) was performed standing on the test leg with both hands placed on the back. The participants jumped on one leg from side to side between two parallel lines on the floor, 40 cm apart (Figure 7). The instructions were to jump as many times as possible during 30 seconds, without touching the lines. Only the number of successful jumps was counted.

The square hop test (170) started with the participants standing outside a square (35×35 cm) marked with tape on the floor. The instructions were to jump in and out of the square in a clockwise rotation, as many times as possible, during 30 seconds. The number of landings inside the square, without touching the taped frame of the square, was recorded.



**Figure 7. Hop performance tests in studies III and IV**

A: Single-leg hop test for distance, B: Vertical hop test, C: Side hop, D: Square hop. ©Jens Rydén

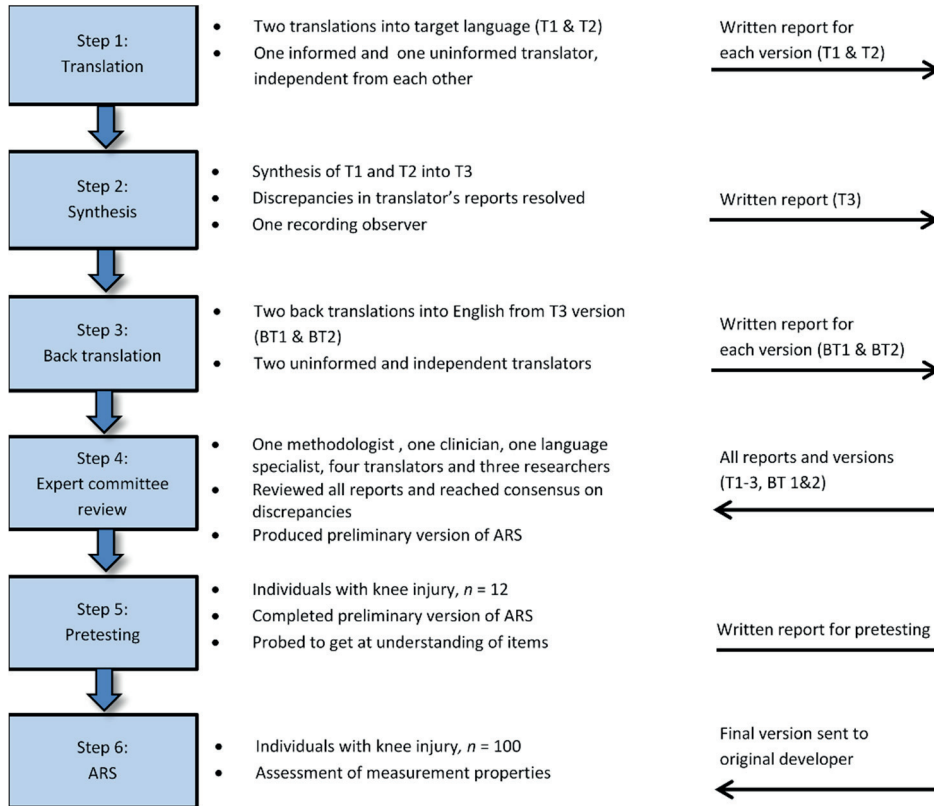
### *Additional physical performance tests*

In study III, the Test for Substitution Patterns (TSP) was used to visually assess postural orientation during the performance of five lower extremity functional tasks: 'Body weight-altering', 'Tip-toe standing knee flexion', 'Knee flexion-extension standing on one leg', 'Forward lunge from stairs' and 'Mini-squat' (120). The TSP contains a total score for all five tasks based on the orientation of several body segments. The total TSP scores has a range of 0 to 54 points where lower scores indicate better outcomes. The absolute values for the injured leg (TSP total score) and the difference between the absolute values of the injured and the uninjured leg (TSP diff) were used in the analyses of postural orientation.

In study IV, the single-leg rise and the single-leg balance test were used to assess hip-knee extensor strength and single-leg balance (70). In the single-leg rise test (170), the participants were asked to rise from a sitting to a standing position using the test leg with the other leg and both arms lifted in front of the body. The sitting height was adjustable and was lowered for each successful standing. The participants got three trials on each new height. The test continued until a failure to stand or until a height of 0 cm was recorded. The lowest height for a successful standing was recorded in centimeters. In the single-leg balance test (70) the participants were asked to stand as long as possible on the test leg, inside a marked square (35 x 35 cm), with the other leg fixed in maximal hip and knee flexion by both hands. Time (in seconds) was recorded from the closing of eyes until failure to stand on one leg (touching of the borders of the square with the test leg, touching the floor with the other leg or opening eyes).

## Translation and cross-cultural adaptation of the ARS

In study I, the ARS was translated and cross-culturally adapted to Swedish in five steps according to recommended guidelines (Figure 8) (137, 138). This process included initial translation, synthesis of the translations and back translation by four translators, an extensive review by an expert committee and a pre-testing (n=12) of the preliminary Swedish version of the ARS. In the sixth and final step, the measurement properties of the Swedish version of the ARS were assessed in terms of reliability, validity and responsiveness.



**Figure 8.**  
The process of translation and cross-cultural adaptation of the Activity Rating Scale in study I.

## Data analyses

Statistical analyses were performed using IBM SPSS for Windows, V.22.0 (I and III) and V.23.0 (II and IV) (IBM Corp., Armonk, New York, USA). Descriptive statistical methods were used to describe baseline characteristics. The data in all studies was tested for normality by visual interpretation of histograms, Q-Q plots and the Kolmogorov-Smirnov test. The assumptions for normal distribution were not met for any of the PROMs, and therefore, non-parametric tests were used in the analyses. Depending on data type, the Chi-square test (categorical) or the Mann-Whitney  $U$  test (continuous), were used for between group comparisons. The Wilcoxon signed-rank test (continuous and ordinal) was used for within-group comparison. The one-way ANOVA test (categorical) and the Kruskal-Wallis test (continuous and ordinal) were used for comparisons between three groups. In all correlation analyses, correlation coefficients

thresholds suggested by Cohen (1971) were used as follows;  $\geq 0.10$  to  $0.29$  denote low association,  $\geq 0.30$  to  $0.49$  moderate association and coefficients  $\geq 0.50$  large association.  $P$  values  $\leq 0.05$  were considered statistically significant. Further analyses were performed as follows.

## Studies I and II

### *Floor and ceiling effects (I and II)*

Floor and ceiling effects were considered present if more than 15% of the participants achieved the lowest or the highest score (143) in the ARS (I) or in any of the PROMs included in the analyses of longitudinal validity (II).

### *Face validity (I)*

The face validity of the ARS was assessed by the expert committee during the cross-cultural adaptation process and through qualitative analysis of the pretest interviews.

### *Reliability (I)*

Cronbach alpha was used to measure the scale and item internal consistency, where a Cronbach alpha of  $0.70$  to  $0.95$  was considered as good internal consistency (172). In the assessment of test-retest reliability; to prevent recall bias and a change in activity level among the participants, the questionnaires were completed on two different occasions 1-2 weeks apart (median, 7 days; interquartile range 7-9 days). The intraclass correlation coefficient (ICC), derived from a 2-way random –effects model (absolute agreement definition), was used to evaluate relative test-retest reliability. An ICC of  $\geq 0.70$  was regarded as the minimum standard for reliability testing (143). Bland Altman plots with 95% limits of agreement (LOA), i.e. the mean difference  $\pm 1.96 * SD_{diff}$  (173), were used to determine the absolute reliability. The standard error of measurement ( $SEM = SD_1 \times \sqrt{1 - r}$ ), with  $SD_1$  representing the standard deviation at baseline and  $r$  representing the ICC, was calculated including systematic differences to investigate to what extent the scores were the same for the repeated measurements. (92) The smallest detectable change (SDC) was determined both at an individual level ( $SDC_{Ind} = 1.96 \times \sqrt{2} \times SEM$ ) and at a group level ( $SDC_{Group} = SDC_{Ind}/\sqrt{n}$ ) (172).

### *Construct validity (I)*

Construct validity was assessed by comparing the scores of the ARS with other knee-specific PROM scores by testing predefined hypotheses (Appendix B). Spearman's rank-order correlation analyses were used to test the associations between the scores. For the ARS to be accepted as a measure of good construct validity at least 75% of the predefined hypotheses had to be confirmed (172).

### *Responsiveness – Longitudinal validity (I and II)*

The responsiveness of the ARS, the TAS, the KOOS, and the K-SES was assessed by comparing the change scores in these PROMs to the change scores in other construct-related PROMs and Global Rating of Change, by testing predefined hypotheses (Appendices B and C). To test the associations between the change scores Spearman's rank-order correlation analyses were used. To be accepted as a measure of good responsiveness at least 75% of the hypotheses had to be confirmed (172).

### *Responsiveness - Magnitude of change (II)*

To evaluate the magnitude of change, the effect sizes (ESs) were calculated using Cohen's *d*, standardized response mean (SRM), and Cliff's *d*. Cohen's *d* (171) was calculated as the difference between the baseline mean scores and the post-rehabilitation mean scores divided by the SD at baseline. The SRM was defined as the mean change scores, divided by the SD of the change scores (140). Cliff's *d* (141) was used to compare all post-rehabilitation scores (A) to all baseline scores (B). When an A score was higher than a B score a value of +1 was noted, and when reversed, a value of -1 was noted. A tie yielded a value of zero. The sum of all scores was divided through the total number of counts ( $n_A n_B$ ) resulting in Cliff's *d* (141). Cliff's *d* was classified as small ( $\geq 0.11$ ), medium ( $\geq 0.28$ ), and large ( $\geq 0.43$ ) (174).

## **Study III**

Spearman's rank-order correlation analysis was used to test the associations between the physical performance tests, where correlation coefficients above 0.8 between two physical performance tests resulted in the exclusion of one of the tests. The knee flexion (W), the leg press (W) and the one leg hop tests were excluded based on prior findings showing higher sensitivity for the knee extension and the side hop tests (69). The correlation coefficient between TSP difference and TSP total exceeded 0.90, thus, only the TSP total for the injured leg was included in further analyses. Spearman's and partial Spearman's rank-order correlation analyses were used to assess cross-sectional (3-year) and longitudinal (5-year) associations between physical performance and PROs, controlling for gender and treatment (surgical/non-surgical). Based on the exploratory character of the study, no adjustments were made for multiple comparisons.

## **Study IV**

The data in this study were analyzed on a post-hoc as treated basis. Spearman's, and partial Spearman's, rank-order correlation analyses were used to assess associations between physical performance and K-SES, controlling for age, gender and treatment (exercise therapy only or with the addition of early or optional delayed ACLR).

# Ethics

## *Studies I and II*

The Research Ethics Committee at Lund University, Sweden, approved the studies (Dnr. 2014/672). The participants received information (verbal and written) about the data collection, its purpose, and its use. Since the data collection included sensitive personal data regarding health, we thoroughly explained that all data would be de-identified, i.e. the results could not be individually distinguished. Furthermore, all personal data was handled according to the Data Protection Act (personuppgiftslagen, PuL). All participants gave their written consent before entering the study. Data was collected through RedCap, a web based application for electronic data collection. The data was stored in RedCap, via the Medical Faculty of Lund University, according to current regulations. The ethical principles for medical research proposed in the Declaration of Helsinki were followed.

## *Studies III and IV*

All participants received information about their participation and gave their written consent. The Research Ethics Committee at Lund University, Sweden, approved the studies (LU 535-01). The ethical principles for medical research proposed in the Declaration of Helsinki were followed.



# Results

The general results of the studies are presented in this part of the thesis. The full details are available in the separate studies (I-IV).

## Study I

### **Translation, cross-cultural adaptation and validation of the ARS**

The translation and the cross-cultural adaptation of the ARS into Swedish included minor modifications of the original English version. We found the measurement properties of the Swedish version of the ARS (appendix A) to be adequate.

#### *Steps 1-4: Translation and Cross-Cultural Adaptation*

The English version of the ARS was translated into Swedish with minor adaptations. The expert committee questioned and discussed the wording of the second item and the recited sports in the fourth items. The word “cutting” was changed to “fast change of direction” in the Swedish version. In the cultural adaptation, three changes were made to the fourth item: “pivoting”, where the wording “kicking, throwing, hitting a ball” was changed to “ball sports/games” and the sample sports were changed to “soccer, team handball, floorball, basketball, and racquet sports” were added. In addition, the a flexible recall period, i.e., 1 month or 1 week, was proposed as an option to 1 year in the English version to facilitate treatment follow-up. The review by the expert committee resulted in a preliminary Swedish version of the ARS.

#### *Steps 5: Face Validity and Pretesting*

The Swedish version of the ARS was considered a comprehensive and an appropriate outcome measure for knee-specific activity levels by the expert committee and the pretesting participants. No modifications of the Swedish version of the ARS were made after the pretesting.



## Step 6: Assessment of Measurement Properties

### Floor and Ceiling Effects

More than half of the participants (56%) reported the lowest score (0) in ARS<sub>Month</sub> at baseline. We observed a floor effect of 22% and a ceiling effect of 20% for ARS<sub>Year</sub>. Participants who had sustained their injury during sports activity reported significantly higher ARS<sub>Year</sub> scores (mean,  $8.6 \pm 5.7$ ), than those who had sustained an injury during other activity (mean,  $2.8 \pm 3.9$ ) ( $P < .001$ ). When we analyzed these groups separately, we observed no floor effect for ARS<sub>Year</sub> (14.5%) in the group of participants with an injury sustained during sports activity, whereas, the floor effect (59%) remained for the group of participants with an injury sustained during other activity.

### Reliability

The results from the assessment of test-retest reliability, internal consistency, SEM and SDC of the ARS are presented in table 5.

**Table 5**

Mean ARS scores at first and second assessment, test-retest reliability, internal constincency, SEM, and SDC of the ARS (n = 100)

	ARS Month	ARS Year
<b>Mean score (SD) 1<sup>st</sup> assessment</b>	3.6 (5.3)	7.6 (5.9)
<b>Mean score (SD) 2<sup>nd</sup> assessment</b>	3.6 (5.2)	8.1 (5.7)
<b>Mean diff (95% CI)</b>	-0.06 (0.65 to 0.53)	-0.42 (-1.08 to 0.24)
<b>ICC (95% CI)</b>	0.91 (0.87 to 0.94)	0.91 (0.87 to 0.94)
<b>95% LOA</b>	-5.86 to 5.74	-6.97 to 6.13
<b>Cronbach's alpha</b>	0.957	0.958
<b>SEM</b>	1.55	1.78
<b>SDC ind</b>	4.29	4.93
<b>SDC group</b>	0.43	0.49

Range of ARS scores = 0 (no participation) to 16 (very frequent participation). ARS, Activity Rating Scale; ICC, intraclass correlation coefficient; LOA, limits of agreement; SDCGroup, smallest detectable change at group level; SDCInd, smallest detectable change at individual level; SEM, standard error of measurement.

### Construct Validity

Seven out of the eight (88%) predefined hypotheses were confirmed. The only rejection was the hypothesis regarding the correlation between higher ARS<sub>Month</sub> scores and longer time since injury ( $r_s = 0.134$ ). The correlations observed between ARS scores and TAS, SGPALS, and single KOOS item scores were at least moderate ( $r_s \geq 0.310$ ). Higher ARS scores correlated with longer time since surgery and injury sustained during sports activity ( $r_s \geq 0.342$ ).

## Studies I and II

### Responsiveness of knee-specific and generic PROMs

#### *Longitudinal validity of the ARS in young adults undergoing knee injury rehabilitation (I)*

The ARS reached the criterion of 75% with six out of the seven (86%) predefined hypotheses being confirmed.

The single hypothesis that was rejected was the one regarding changes in ARS<sub>Month</sub> scores and KOOS item P2 scores ( $r_s = -0.027$ ). As hypothesized, the change in the ARS scores correlated higher with a change in the TAS scores ( $r_s = 0.229$ ) than with the SGPALS scores ( $r_s = 0.197$ ). The correlations between the change in the ARS scores and the change in single-item subscores of the KOOS Sport/Rec subscale and the perceived change in the ability to perform sports and recreational activities were  $r_s \geq -0.270$ . There was a low correlation between the change in the ARS scores and the change in the KOOS ADL subscores and the perceived change in function in ADL, respectively ( $r_s \geq 0.011$ ).

#### *Longitudinal validity of knee-specific PROMs in young adults after completed knee injury rehabilitation (II)*

The ARS, the K-SES Present and all the subscales of the KOOS achieved the criterion of confirming at least 75% of the predefined hypotheses. For the TAS and the K-SES Future only one out of the seven (14%) predefined hypotheses could be confirmed, respectively.

The correlations between the specific GRCs and change scores in the ARS, K-SES Present and Future were at least moderate ( $r_s \geq 0.332$ ). As hypothesized, the change scores in the KOOS Sport/Rec and QOL, and in the SF-36 Physical functioning and Role physical correlated at least moderately with the changes in ARS and K-SES Present scores ( $r_s \geq 0.341$ ), respectively. The change scores in the ARS, the K-SES Present and the KOOS subscales correlated higher ( $r_s \geq 0.173$ ), with the change scores in the SF-36 Physical component summary than with the change scores in the SF-36 Mental component summary. Change scores in TAS and the K-SES Present correlated higher with change scores in knee-specific activity than in generic activity, respectively ( $r_s \geq 0.180$ ). The change scores in all the subscales of the KOOS correlated at least moderately with the specific GRC ( $r_s \geq 0.321$ ), except the change scores in the KOOS QOL ( $r_s = 0.263$ ). As we hypothesized, the change scores in the VAS knee pain, the Pain manikin and the SF-36 subscores Bodily pain, Physical functioning and Role physical correlated at least moderately with the change scores of each of the KOOS subscales ( $r_s \geq 0.315$ ). Only the change scores in the KOOS Sport/Rec and QOL correlated as hypothesized with the change in ARS scores ( $r_s = 0.357$ ).

### *Magnitude of change in knee-specific and generic PROMs in young adults after completed knee injury rehabilitation (II)*

The Cohen's *d* for the KOOS Sport/Rec, QOL, K-SES, K-SES Present, SF-36 Physical component summary and SF-36 Physical functioning, Role Physical and Bodily Pain ranged between 0.81 and 1.36, and were considered large. The Cohen's *d* for the ARS, KOOS Symptoms, Pain, ADL, SF-36 Mental component summary and SF-36 Vitality ranged from 0.50 to 0.79, and were considered moderate. The Cohen's *d* for the TAS and K-SES Future was 0.26 and 0.05, respectively, and were considered small.

The majority of the effect sizes calculated using the SRM and the Cliff's *d* were classified at levels corresponding to the classification levels when using Cohen's *d*. The SRM for the SF-36 Physical functioning and Role physical were 0.78 and 0.73, respectively, and were considered moderate. The SRM for the ARS was 0.43 and was considered small. For three of the PROMs, the classification increased one level when using Cliff's *d* compared to Cohen's *d*. For the KOOS Pain and ADL the Cliff's *d* were 0.49 and 0.48, respectively, and were considered large. The Cliff's *d* for the SF-36 Social Functioning was 0.31 and was considered moderate.

## Studies III and IV

### **Knee-specific PROs**

#### *Changes in KOOS, TAS and ARS scores between 3 and 5 years (III)*

We observed no statistically significant changes in the KOOS scores between 3 and 5 years (KOOS Pain -1 (95% CI -3 to 2), KOOS Sport/rec 2 (95% CI -3 to 7) and KOOS QoL -6 (95% CI -6 to 3)). Out of 54 participants, ten (19%) reported worse scores in the KOOS Q3, 15 (28%) in the TAS and 22 (41%) in the ARS at 5 years in comparison to 3 years.

#### *K-SES scores at 6 years (IV)*

At 6 years after injury, the median K-SES scores for all participants (n=89) were K-SES 7.8 (IQR 5.9-9.0), K-SES present 8.7 (IQR 6.8-9.6) and K-SES future 4.8 (IQR 2.5-7.5). We observed no differences between the three treatment groups in K-SES scores 6 years after ( $p \geq 0.501$ ).

## Associations between physical performance and knee-specific PROs

We found several associations between physical performance and PROs above 0.1 but we observed no correlation coefficients equal to or above 0.5. The correlation coefficients were quite similar when using Spearman's ( $r_s$ ) and partial Spearman's rank-order correlation ( $r_{sp}$ ) analyses. Therefore, only the results from the partial correlation analyses are presented.

### *Associations at 3 years (III)*

At 3 years, worse performance in the vertical hop (cm, LSI) and the TSP total score were associated with worse scores on the KOOS Pain ( $r_{sp} \geq 0.302$ ,  $p \leq 0.031$ ). Worse performance in the vertical hop (cm), the side hop (n, LSI) and the TSP total score, at 3 years, were associated with worse scores on KOOS Sport/rec ( $r_{sp} \geq 0.320$ ,  $p \leq 0.021$ ). Worse knee extension power (LSI), worse performance in the vertical hop (cm, LSI), the side hop (LSI) and the TSP total score were associated with worse KOOS QoL ( $r_{sp} \geq 0.314$ ,  $p \leq 0.023$ ), at 3 years.

Worse knee extension power (W), worse performance in the vertical hop (cm), the side hop (n, LSI) and the TSP total score were associated with lower TAS score ( $r_{sp} \geq 0.330$ ,  $p \leq 0.017$ ) at 3 years. Worse performance in the vertical hop (cm, LSI) and the TSP total score were associated with lower ARS score ( $r_{sp} \geq 0.302$ ,  $p = 0.031$ ) at 3 years.

The correlations observed between the remaining physical performance tests and the PROs at 3 years ranged from  $r_{sp} = 0.003$  ( $p = 0.984$ ) to  $r_{sp} = 0.272$  ( $p = 0.051$ ).

### *Associations over time (III and IV)*

Worse performance in the vertical hop (cm), at 3 years, was associated with worse scores on KOOS Pain ( $r_{sp} = 0.308$ ,  $p = 0.026$ ), at 5 years. Worse performance in the side hop (LSI), at 3 years, was associated with worse KOOS Sport/rec ( $r_{sp} = 0.280$ ,  $p = 0.045$ ) at 5 years. Worse performance in the vertical hop (LSI, cm), at 3 years, was associated with worse KOOS QoL ( $r_{sp} = 0.281$ ,  $p = 0.044$  and  $r_{sp} = 0.284$ ,  $p = 0.041$ , respectively), at 5 years. Worse TSP total score, at 3 years, was associated with worse KOOS QoL ( $r_{sp} = 0.334$ ,  $p = 0.017$ ), at 5 years. Worse performance in the vertical hop (LSI) and worse TSP total score, at 3 years, were associated with worse KOOS Q3 scores ( $r_{sp} = -0.324$ ,  $p = 0.019$  and  $r_{sp} = 0.372$ ,  $p = 0.007$ , respectively) at 5 years. Worse knee extension strength (W) at 3 years was associated with lower ARS score ( $r_{sp} = 0.281$ ,  $p = 0.044$ ) at 5 years. The correlations observed between the remaining physical performance tests at 3 years and the PROs at 5 years ranged between  $r_{sp} = 0.008$  ( $p = 0.955$ ) and  $r_{sp} = 0.274$  ( $p = 0.052$ ).

Worse knee flexion power LSI ( $r_{sp} = 0.341$ ,  $p = 0.042$ ) at the end of the exercise therapy, as well as worse single-leg hop LSI at 5 years ( $r_{sp} = 0.310$ ,  $p = 0.005$ ), correlated with worse scores on K-SES at 6 years after injury (Table 3). The associations observed

between the remaining physical performance tests at the end of the exercise therapy and the scores on the K-SES, ranged from  $r_{sp} = 0.148$  ( $p = 0.264$ ) for the single-leg hop LSI to  $r_{sp} = 0.265$  ( $p = 0.045$ ) for the square hop LSI.

# Discussion

The first aim of this thesis was to assess the measurement properties, in particular the responsiveness, of knee-specific and generic PROMs, in young adults undergoing rehabilitation for a knee injury. For that reason, we conducted two methodological studies in accordance with the COSMIN guidelines. Our results showed that the Swedish version of the ARS has good reliability and validity in the settings of and after knee injury rehabilitation. Furthermore, based on the results we can recommend the use of the ARS, the K-SES, the KOOS, and the SF-36 Physical Component Summary to evaluate changes in activity participation, knee-related self-efficacy, knee-related pain, symptoms, function in daily living, function in sports and recreation and knee-related quality of life, and general physical health, respectively, in young adults undergoing rehabilitation for a knee injury.

The second aim of this thesis was to investigate the association between lower extremity physical performance and self-reported activity participation, knee function and knee self-efficacy in individuals after ACL injury/ACLR. The results demonstrated that worse single-leg physical performance correlated moderately with lower future self-reported activity participation, worse future knee function and lower future knee self-efficacy after ACL injury/ACLR. In addition, treatment strategy, in terms of exercise therapy only, or in combination with early or delayed ACLR, after ACL injury did not have an impact on future knee self-efficacy.

## Evaluation of measurement properties

### **Cross-cultural adaptation and validation of the Activity Rating Scale for disorders of the knee (ARS)**

The ARS was successfully translated and cross-culturally adapted into Swedish. Our results show that the Swedish version of the ARS demonstrates good reliability and validity to evaluate the frequency of knee-demanding activities during the past year, or the past month, in young to middle-aged adults with knee injury.

The floor and the ceiling effects that we observed supported that the ARS<sub>Month</sub> may be better suited for use later in the treatment phase, i.e. when knee-demanding exercises have been introduced, and that the ARS<sub>Year</sub> is appropriate for use in individuals that are physically active in sports.

The reliability of the Swedish version was considered good based on the high internal consistency and high test-retest reliability (172). Our results are in line with previous studies assessing the measurement properties of the original (151) and the Persian version (175) of the ARS. As many knee-specific PROMs (176-178), the ARS appears to be useful for group comparisons, supported by the low SDC<sub>group</sub> values. In contrast, the high values observed for the SDC<sub>ind</sub>, SEM, and LOA, indicate a need for quite a large change in ARS scores (> 6 points) to detect a real difference for an individual.

We concluded the construct validity of the Swedish version of the ARS to be good since 88% of the hypotheses were confirmed (172). As we hypothesized, frequent participation in knee-demanding activities correlated with higher physical activity level, less trouble during running and pivoting activities, longer time since surgery and injury sustained during sports activity. However, longer time since injury did not correlate with a more frequent participation in knee-demanding activities. A possible explanation for this may be activity modifications among the participants resulting in reduced participation in knee-demanding (i.e. pivoting) activities based on clinical advice or personal reasons (96, 179).

The ARS was originally developed as a baseline measure of activity participation (151). However, our results show that when using a recall period of one month, instead of one year, the ARS can be used to evaluate change in activity participation in young adults in rehabilitation for a knee injury. This may facilitate treatment follow-up of activity participation in individuals that are active in pivoting and cutting sports. Further assessment of the responsiveness of the ARS is discussed in the following section of this thesis.

## **Responsiveness of knee-specific and generic PROMs**

In the assessment of the magnitude and validity of change, several instruments and subscales stood out. For the knee-specific PROMs, we observed large effect sizes for the KOOS subscales Sport/Rec, and QOL, the K-SES, K-SES subscore Present. As for the generic PROM, the SF-36 Physical Component Summary, and SF-36 subscales Physical Functioning, Role Physical and Bodily Pain demonstrated large effect sizes. Our results also demonstrated good longitudinal validity for the ARS, the K-SES subscore Present and all the subscales of the KOOS, with more than 75% confirmation of the predefined hypotheses (172). We observed small effect sizes for the TAS and the K-SES Future, and, in addition, only 14% of the predefined hypotheses could be confirmed for these instruments. Taken together, our results of the evaluation of

responsiveness of commonly used knee-specific PROMs indicate that the ARS, the K-SES and the KOOS are valid instruments to assess change in activity participation, knee self-efficacy and knee-related pain, symptoms, function in daily living, function in sports and recreation and knee-related quality of life, respectively, in individuals undergoing rehabilitation for a knee injury.

#### *TAS and ARS – Change in knee-specific activity participation*

In a recent systematic review (180), it was concluded that among the four most common activity scales (including the ARS) used for knee-specific activity participation, the TAS was the only scale showing adequate reliability, validity and responsiveness in an ACL injured population. However, the authors (180) called for a comparative analysis of the measurement properties of these four scales. In this thesis, we compared two of these activity scales. In our cohort, we observed low magnitude and validity of change for the TAS, and, therefore, we did not consider it responsive to rehabilitation after knee injury, surgically or non-surgically treated. However, in previous studies, effect sizes between 0.6-1.1 have been reported after ACLR (153) and meniscus surgery (154). The low effect sizes we observed for the TAS may be explained by the difference in starting points between the studies. Our cohort reported TAS scores when they were in rehabilitation for a knee injury, whereas in previous studies (153, 154) the TAS scores were reported before the participants received any intervention. It is possible that our participants reported higher TAS scores at the starting point, in comparison to previous studies (153, 154), which consequently may have resulted in lower change scores, and, thereby, lower effect sizes. Another potential explanation is that changes in the intensity of activity participation may have occurred within each activity level of the TAS, and simply were not detected. This may be supported by the moderate magnitude and good longitudinal validity that we noted for the ARS. The TAS is based on the intensity and type of activity participation, whereas the ARS is based on the frequency of participation. Our results suggest that the construct measured by the ARS better reflected the changes in activity participation than the TAS. In addition, our results indicate that the ARS is a responsive measure of changes in knee-specific activity participation in young adults during and after completed rehabilitation for a knee injury.

#### *K-SES – Change in knee-related self-efficacy*

There was a marked difference between the responsiveness demonstrated by the K-SES Present and the K-SES Future. These subscores measure separate constructs, the perception of present functional knee capability (K-SES Present) versus the fear of reinjury and uncertainty of future knee function (K-SES Future). The large effect sizes we noted are in line with previous findings that have shown significant changes in K-SES Present scores, and no changes in K-SES scores, during rehabilitation at 4-, 6-, and 12-month follow-up after ACL injury (106). The confirmation of all the seven



predefined hypotheses, where associations between change scores in K-SES Present showed high correlations with changes in perceived knee-related quality of life, knee-specific and generic physical function, support the good longitudinal validity of K-SES Present. However, for the K-SES Future the observed effect sizes were close to none, and with only one out of the seven predefined hypotheses being confirmed, the standards for longitudinal validity were not fulfilled. Based on our results, in addition to previous results (106), this may suggest that the perception of present functional knee capability is more modifiable than the perception of one's ability to return to sport and future knee function as well as fear of reinjury. On the other hand, this may indicate that rehabilitation after knee injury require additional interventions aimed at reducing fear of reinjury and increasing the certainty of future knee function. We found the K-SES subscore Present may be used to evaluate change in knee-related self-efficacy in individuals undergoing rehabilitation for a knee injury.

*KOOS – Change in knee-related pain, symptoms, function in daily living, function in sports and recreation and knee-related quality of life*

All the KOOS subscales met the requirements for good longitudinal validity, through change scores that correlated as hypothesized at a moderate to large level with changes in related PROs, in terms of pain, knee-specific activity participation, and specifically with general physical functioning. We noted the highest effect sizes for the KOOS subscales Sport/Rec and QOL, which is in line with results presented in a recent systematic review and a meta-analysis evaluating the measurement properties of the KOOS (176). Our results, based on individuals with a range of acute knee injuries (ligament, meniscal and cartilage injuries), surgically or non-surgically treated, add to these previous results (176), primarily based on individuals undergoing ACLR. The KOOS subscale ADL was the only subscale that demonstrated ceiling effects at baseline (in rehabilitation), which increased even more after completed rehabilitation. Despite this, we observed moderate to large effect sizes and a significant change in scores for the KOOS ADL, as for the KOOS Pain and Symptoms. This indicates that all the KOOS subscales, yet, specifically the KOOS subscales Sport/Rec and QOL, can be used to evaluate change in self-reported knee-related pain, symptoms, function in daily living, function in sports and recreation and knee-related quality of life, respectively, after rehabilitation for a knee injury.

*SF-36 – Change in general physical and mental health*

Our results showing higher effect sizes for the SF-36 physical components compared to mental components are consistent with previous findings (86) in individuals undergoing meniscectomy or ACLR. Since the goals of knee injury rehabilitation and treatment include improved knee function and reduced knee symptoms it is reasonable that the treatment effect is higher for components that measure physical health in comparison to mental health.

In the evaluation of outcome after treatment, it is recommended to use at least one generic health-related PROM, in addition to disease-specific PROMs (181). The SF-36 is the most widely used health-related PROM (158, 182). On the basis of our results, we can endorse the use of the SF-36, in particular the SF-36 Physical Component Summary, as a generic PROM to complement the knee-specific PROMs in the assessment of change in general physical health after knee injury rehabilitation.

## Associations between physical performance and knee-specific PROs

We observed several moderate correlations ( $r_{sp} \approx 0.3$  to  $0.5$ ) in the cross-sectional and the longitudinal analyses between physical performance and knee-specific PROs. In the longitudinal analyses, worse single-leg hop performance was associated with worse future knee-related function and self-efficacy, worse postural orientation was associated with worse future knee-related function, worse knee extension muscle power was associated with lower future knee-specific activity participation, and worse knee flexion muscle power was associated with worse future knee self-efficacy.

### Associations at 3 years after ACL injury

In the cross-sectional analyses at 3 years after ACL injury/ACLR, four of the physical performance tests showed moderate associations with knee-related pain, symptoms, quality of life, knee confidence and activity participation (study III). These levels of correlations are in line with previous results (129, 183), demonstrating at most moderate correlations between physical performance and patient-reported measures at 2-3 years after ACLR. Among the performance tests included in our analyses (study III), we found that absolute performance in the vertical hop test and postural orientation showed the strongest correlation with KOOS Pain, Sport/Rec, QOL, TAS and ARS scores at 3 years. Our results support previous findings showing that measures that evaluate performance versus perception, indeed measure similar, yet, different constructs, and therefore, complement one another as outcome measures after ACL injury/ACLR (82, 183, 184).

### Associations over time

In studies III and IV, we observed that physical performance assessed at the end of rehabilitation period, at 3 years (time point of optimal muscle function) and at 5 years

correlated moderately with future knee-related pain and quality of life, knee-related activity participation and self-efficacy. In particular, we found that performance in the vertical hop and the single-leg hop tests was associated with future knee-related pain, knee confidence and knee self-efficacy. Furthermore, knee extension and flexion strength demonstrated moderate correlations with future knee-related activity participation and self-efficacy, respectively. Finally, postural orientation was moderately associated with future knee-related function in sports and recreational activities, quality of life and knee confidence.

To our knowledge, this is the first prospective study to investigate the associations between physical performance and the ARS in individuals with ACL injury. In a previous study (148), where the TAS was used as a measure of activity participation, physical performance (knee flexion and extension strength and hop performance) at 6 months after ACLR was shown to correlate with the TAS at 4 years. We observed only one significant association in our analyses (study III) between worse knee extension muscle strength at 3 years and lower future knee-related activity participation, measured with the ARS, at 5 years. Furthermore, no physical performance tests correlated with future physical activity level measured with the TAS. The main difference between our study and the study by Sousa et al (148) was the time point for the assessment of physical performance and the difference in sample sizes, 54 versus 223 participants (148), which may explain the difference in results. Yet, we expected physical performance to be more associated with future activity participation since the ability to generate high forces during high movement velocities is considered an important factor in physical and athletic performance (185). Furthermore, recent results have shown that worse hop performance, at 1 year after ACLR, was associated with lower rates of return to pre-injury sport level at 2 years (103). We noticed a large difference in the numbers of associations in the cross-sectional (at 3 yrs) compared to the longitudinal analyses (from 3 to 5 yrs). In our cohort, near half of the participants modified their activity participation from 3 to 5 years. It is possible that the participants had a change of perspectives due to adaptation or acceptance (186) or that contextual factors, such as social or life-style changes may have led to activity modifications (88, 102, 187). Yet, our results showing that physical performance was more associated with the frequency of activity participation (ARS) than with the level of activity participation suggest that individuals that are active in knee-demanding activities (cutting and pivoting sports) could benefit from optimized physical performance for present and future frequency of activity participation.

We observed that worse vertical hop performance (cm, LSI) and worse postural orientation (TSP total score) at 3 years was associated with worse scores on the subscales KOOS subscales Sport/rec, QOL and item Q3 at 5 years after ACL injury or ACLR (study III). In line with our findings, longitudinal associations have previously been reported (124, 125) between single-leg hop performance (single-leg, triple and cross-over hop), tested within 6 months after ACL injury or ACLR, and worse future knee

function (International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form) at 1 year. In addition, at 10 months after ACL injury or ACLR, performance in the single-leg rise has been shown to correlate with self-reported knee function (KOOS<sub>4</sub>) at 2 to 5 years (70). However, in one study (188), with a considerably longer follow-up, no associations were reported between performance in single-leg hop or muscle strength tests at 2 years and KOOS scores at 9.5 years after ACLR. It is reasonable that other factors may have affected the results (188), given the long time between assessment of physical performance and PROs.

Several previous studies have focused on the influence of psychological responses on physical function and performance (121). To our knowledge, in study IV, we are the first to investigate the impact of physical performance on knee-related self-efficacy after ACL injury or ACLR. Thomee et al (105) showed that higher knee-related self-efficacy, measured with K-SES prior to ACLR, was associated with higher (better) LSI for single-leg hop performance (single-leg hop, side hop, counter movement jump) at 1-year follow up after ACLR. Our results demonstrated that higher LSI for knee flexion strength at the end of exercise therapy, and higher LSI in single-leg hop performance at 5 years, correlated moderately with knee-related self-efficacy at 6 years after ACL injury or ACLR. This suggests that symmetry between legs in single-leg physical performance is one factor that contributes to good future knee-related self-efficacy.

Although the associations between physical performance and knee-specific PROs, presented in this thesis, are only moderate, our results are supported by findings from previous longitudinal studies (70, 103, 124, 125). Altogether, despite differences in physical performance tests, PROMs and time points for baseline and follow-up assessments, the results indicate that single-leg physical performance after exercise therapy and up to 3 years after ACL injury or ACLR, is one factor that contributes to good future self-reported outcomes, in terms of physical activity participation, self-reported knee function and knee-related self-efficacy (103, 124, 125). This stresses the possibility that targeted training to optimize physical performance after ACL injury or ACLR may improve future self-reported outcomes. Still, further studies are required to investigate the relative contribution of single-leg physical performance, in addition to other factors, which may have an impact on self-reported outcomes after ACL injury or ACLR.

## Associations between treatment strategy and knee-related self-efficacy after ACL injury

We found that knee-related self-efficacy at 6 years after ACL injury was not associated with treatment strategy (ACL-D, ACL-R and ACL-X), in terms of exercise therapy alone or in combination with early or optional delayed ACLR. These findings are in line with previous observations in the KANON-trial, where there was no difference across treatment groups in various outcomes, i.e. self-reported outcomes (40) and osteoarthritis (40, 41) at 2 and 5 years, and muscle function (69) assessed at 3 years after ACL injury. One possible explanation for our findings of similar K-SES scores for the as treated groups could be the extensive exercise therapy program that all participants followed regardless of treatment strategy. The progression of the exercise program was based on the achievement of different goals for muscle function, range of motion and functional performance, in contrast to a pre-set number of exercise sessions (40). Participants that received exercise therapy only progressed faster and required fewer exercise sessions than the participants who had early or delayed ACLR in addition to exercise therapy. This approach, of extensive exercise therapy, was chosen to make sure that all participants, regardless of treatment strategy, would achieve a similar and good level of physical function (40). As we presented in study IV, there were no differences in physical performance between the as treated groups. Consequently, the exercise program may be the common factor explaining the similarity in K-SES scores across all treatment groups, rather than the early or the optional delayed reconstruction.

In our cohort (study IV), at 6 years after ACL injury or ACLR, the K-SES scores (median 7.4-8.2) were similar or better than K-SES previously observed in other Swedish cohorts (145, 146, 189). Thomee et al. reported K-SES scores of mean 6.8 and 7.6 at 12 months after ACL injury and ACLR, respectively (146), mean 7.3 at 12 months after ACL injury or ACLR (189), and median 6.7 at 1-12 months after ACL injury and 3-12 months after ACLR (145). There are no normative or cut-off values available to grade the K-SES scores as high or low. Yet, previously, similar levels of K-SES scores (mean 6.9-8.3) have been shown to correlate with greater likelihood of satisfaction with outcome, in terms of self-reported knee function, at 3 years after ACLR (97). Furthermore, considering the subscores in our cohort, the K-SES Present scores (perception about one's present capability of performing knee-related tasks) can be regarded high in comparison to the K-SES Future scores (perception about one's return to preinjury level sports and fear of reinjury plus decreasing knee function if undergoing ACLR), for all three treatment groups. In previous studies (106, 145, 146, 189), the subscore K-SES Future has been reported to be comparable or higher than the K-SES Present scores. The main difference between our study (IV) and the previous studies (106, 145, 146, 189) is the time point for the assessment of knee-related self-efficacy. Our participants reported K-SES at 6 years after ACL injury or ACLR,

whereas, in previous studies K-SES scores were reported within one month after ACL injury or prior to ACLR and only up to 1 year after injury or ACLR (106, 145, 146, 189). Consequently, time as a factor may be the explanation for the difference in K-SES Present and Future scores in our cohort. As previously reported in the KANON-trial (41) at 5 years after ACL injury or ACLR, only about 20% of the participants were active at their preinjury activity level or higher. This suggests similar levels of return to preinjury activity levels for our participants (approx. 20 %) at 6 years. This is in line with previous reports showing that at 2-7 years after ACLR, no more than 50% return to sports, at preinjury or competitive level (94). The K-SES Future scores are based on the perception about return to preinjury level sports, fear of reinjury and decreasing knee function. It is reasonable to assume that over time the expectations and motivation for return to preinjury level sports and the perception of acceptable knee function may change. Also, results from previous studies have shown that individuals report high, and possibly overoptimistic, expectations before ACLR or meniscus surgery (65, 98, 190). As for our participants, lower, and perhaps more realistic, expectations may be reported some years later. Therefore, the low K-SES scores among our participants may be a reflection of natural changes that occur over time, such as increasing age or changes in social commitments. An additional explanation for the discrepancy between the K-SES Present (perception of good knee function capability) and the K-SES Future (uncertainty about return to preinjury level sports) scores may be that despite perceptions of good knee function return to sports is hindered due to fear of reinjury (191, 192). Furthermore, in spite of athletes returning to their pre-injury level of sports after ACLR, there are indications that these individuals end their sports participation earlier compared to individuals without ACL injury (4, 193). More longitudinal research is needed to further investigate these potential explanations for change in future knee self-efficacy in individuals after ACL injury.

## Methodological considerations and limitations

There are some limitations to this thesis. The heterogeneity of the cohort in study I and II, in terms of age, gender and time spent in rehabilitation, may constitute a limitation. This may have influenced the results of the assessment of the measurement properties of the ARS. The floor effects that we observed may have been present due to participants that had spent a shorter time in rehabilitation, those at an early rehabilitation phase without engagement in knee-demanding activities. Measurement error and SDC are dependent on the standard deviation at baseline, where a higher standard deviation results in a higher SEM and an increased SDC. Therefore, a more homogenous sample could have resulted in lower SEM and SDC for the ARS. The majority of the participants (74% and 71%) in the studies had ACL injury. Based on this, it may be argued that we should have only included participants with ACL injury

in the analyses, since there may be differences associated with the various injuries that may have influenced the results. However, we performed subgroup analyses, where we only included ACL injured participants, which showed similar results for the main analyses in studies I and II. Still, we considered the knee injury rehabilitation to be the main treatment factor that would influence change in PROs when rehabilitation was completed. Therefore, the heterogeneity among the participant, including the variety of surgically and non-surgically treated knee injuries, may make the results of these studies more generalizable.

In the assessment of responsiveness in studies I and II, we chose to use both the traditional method by calculating effect sizes and standardized response mean, in addition to using the hypotheses testing according to the COSMIN guidelines. In line with the COSMIN guidelines, we consider effect sizes a measure of the magnitude of change and the hypotheses testing a measure of validity of change. It may be argued that the use of effect sizes facilitates cumulative research, as effects can be examined across studies. In additions, effect sizes can be used to calculate sample size for longitudinal studies. The COSMIN approach may be considered a qualitative approach in comparison to the quantitative calculations of ESs and SRM. It may be speculated that the COSMIN approach leaves more room for interpretation, and that it is dependent on the comparative PROMs that are chosen as external criterions. In addition, the content and the number of predefined hypotheses may be considered arbitrary, which may influence the results. However, in study II, we chose to combine these two methods of responsiveness assessment aiming for more complete analyses and valid results. Furthermore, the sample sizes were good (172), the response rates ( $\geq 64\%$ ) were higher than the minimum recommended (194) and the results can be generalized at least to patients with ACL injury.

The comparative PROMs that were used as external criterions in the hypotheses testing had not all been validated according to the COSMIN principles, which may question their use as comparative PROMs. Our results may have been different if we would have used other PROMs for comparison in the hypotheses testing. However, the majority of the PROMs that are included in our studies have been validated using other methods and are widely used for evaluation of treatment after knee injuries (85).

It may be considered a limitation that we did not calculate the minimal important change (MIC) for the PROMs included in study II. Recently, it has been suggested that no single value of MIC can be assigned to a PROM across different settings (195, 196). MIC is commonly used in RCTs to assess clinically relevant differences between groups; yet, the MIC for a PROM can vary greatly depending on the definitions and the methods that are used. Therefore, despite the great importance of clinical relevance, it may not be established through MIC.

A limitation to studies III and IV is the limited and conflicting evidence of the measurement properties of physical performance tests, despite their frequent use (197).

In addition, the naming of the tests and the methods used to conduct the tests differ across studies (198). Nonetheless, many physical performance tests are easy to conduct, require no equipment and are based on functional movements. In addition, physical performance tests often provide instant feedback and can be used to increase motivation and compliance during exercise therapy. The single-leg hop test has shown moderate responsiveness and can be used to assess progress during knee injury rehabilitation (198). This performance test has demonstrated moderate responsiveness and can be used to assess progress during knee injury rehabilitation (198). The single-leg hop test appears to be able to differentiate between injured and non-injured leg in individuals with ACL injury, in addition to be able to detect differences in the ACL-injured knee and the non-injured knee in age-matched controls (198).

The use of correlation analyses in study III and IV did not allow us to determine causality between physical performance and patient-reported outcomes. Also, since K-SES scores were only reported at 6 years after injury, we could not adjust for baseline scores or analyze change in K-SES scores. Although it may be simplest to speculate that improved physical performance causes better PROs, it is possible that individuals reporting better PROs engage in activities that in turn improve physical performance. Therefore, future prospective studies are required to fully understand the association between physical performance and PROs after ACL injury.

In study IV, we chose only to use the LSI to represent the values of the physical performance tests. However, studies have shown that bilateral deficits are present after ACL injury (111, 199, 200), which may result in misleading LSI values. Furthermore, results from previous studies have shown that the use of LSI may overestimate physical performance in comparison to the use of absolute values (201) or the use of LSI adjusted for BMI (202). However, the use of LSI is common in clinical studies and is included in the criteria for successful outcome (84) and return to sports (115) after ALC injury and ACLR.





# Clinical implications

The ARS can be used to assess the frequency of activity participation in individuals that are physically active in cutting and pivoting sports. When the frequency of activity participation before and after a knee injury is compared, a recall period of one year can be used. During and after knee injury treatment, a recall period of one month or a week can be used when knee-demanding exercises or activities have been introduced to the exercise program. As many PROMs, the ARS is appropriate for comparisons on a group level. However, on an individual level, the change in ARS score must be relatively high ( $> 5$  points, on the 0-16 point scale), to exclude measurement error.

Individuals that are highly physically active and participate in high-demand sports and activities need to be assessed accordingly in their physical activity participation. In clinical practice and in research of knee injuries, it is useful and relevant to evaluate the frequency of activity participation in activities that are challenging for the knee, in addition to the level or type of activity participation. However, the frequency and the level or type of activity do not necessarily converge. Individuals can be frequently physically active and place high demands on their knees, despite being physically active at a low recreational or competitive level. For that reason, the ARS can be used adjacent with self-reported measures of knee-specific activity level and knee function, e.g. the TAS and the KOOS, to assess treatment outcome after knee injury.

In the evaluation of outcome after treatment, it is important to recognize the responsiveness of the PROMS that are used to enable a valid evaluation. In this thesis, when comparing several knee-specific and generic PROMs, we found that the KOOS subscales Sport/Rec and QOL, the K-SES Present and the SF-36 Physical Component Summary appear to have the highest ability to detect change in outcomes that are relevant to individuals after completing rehabilitation for a knee injury. Furthermore, the ARS appears to be more appropriate than the TAS for evaluation of change in knee-specific activity participation in individuals after undergoing rehabilitation for a knee injury.

The results of this thesis support previous findings suggesting that rehabilitation of an ACL injury should include exercises aimed at optimizing and maintaining good single-leg physical performance and symmetry between legs in hop and strength performance. In particular, single-leg hop performance, knee flexion and extension strength in addition to postural orientation appear to be important factors for future self-reported

knee-related function, knee-specific activity participation and knee-related self-efficacy. In contrast, ACL treatment strategy, in terms of exercise therapy only, or exercise therapy in addition to an early or an optional delayed ACL reconstruction, does not appear to have an impact on knee-related self-efficacy at 6 years after ACL injury or ACLR.

# Conclusions

- The Swedish version of the ARS is a valid, reliable and responsive instrument to evaluate activity participation in terms of frequency of participation in knee-demanding sporting activities in young adults with a knee injury.
- The KOOS subscales Sport/Rec and QOL, the K-SES Present and the SF-36 Physical Component Summary showed the greatest potential for detecting change in outcomes relevant to patients after completing knee injury rehabilitation. The ARS may be preferred over TAS to optimize the evaluation of change in knee-specific activity participation following knee injury rehabilitation.
- The performance in the vertical hop and the side hop tests and postural orientation at 3 years were moderately associated with self-reported knee function and knee-specific activity participation, at 3 and 5 years after ACL injury/ACLR. Knee extension strength at 3 years was more associated with self-reported frequency rather than type and intensity of knee-specific activity participation at 5 years after ACL injury/ACLR.
- Knee-related self-efficacy at 6 years after an acute ACL injury/ACLR did not differ between patients treated with ACL reconstruction, performed early or as a delayed procedure, or those treated with exercise therapy alone. The self-efficacy for present knee function capability was higher than the self-efficacy for return to preinjury level sport and not being reinjured. Worse knee flexion strength LSI at the end of the exercise therapy, and worse LSI for the single-leg hop test at 5 years, correlated moderately with worse knee-related self-efficacy at 6 years. Targeted training to improve the symmetry between legs in knee flexion muscle strength and in the single-leg hop for distance may have a positive, yet small, impact on knee-related self-efficacy after ACL injury/ACLR.



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