Linköping University Medical Dissertations No. 1525

One Anterior Cruciate Ligament injury is enough!

Focus on female football players

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Linköping 2016

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Henny Yngve, injured her ACL in the left knee when playing football. She returned to football and re-ruptured the ACL graft. Today, she plays the guitar and works as a physiotherapist among other things for the female football team she once played for.

Evelina Kimmehed, goalkeeper with an ACL reconstructed (right) knee.

Ellen Bertilsson, first injured her left ACL, then, after returning to football, injured the ACL in her right knee. Today, she is interested in music and theatre – but she is not playing football anymore.

Mikael Eriksson, former elite football player with bilateral ACL injuries sustained when playing football. Today, he is an assistant coach for a football team.

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Printed in Sweden by LiU-Tryck, Linköping, Sweden, 2016

ISBN 978-91-7685-736-6

ISSN 0345-0082

All my love to my family!

Be happy for this moment. This moment is your life!

- Omar Khayyam

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ABSTRACT

Background: Anterior cruciate ligament (ACL) injury is a severe and common injury, and females have 2-4 times higher injury risk compared to men. Return to sport (RTS) is a common goal after an ACL reconstruction (ACLR), but only about two thirds of patients RTS. Young patients who RTS may have a 30-40 times increased risk of sustaining an additional ACL injury to the ipsi- or contralateral knee compared with an uninjured person.

Aims: The overall aim of this thesis was to increase the knowledge about female football players with ACLR, and patients with bilateral ACL injuries, and to identify predictors for additional ipsi- and/or contralateral ACLR.

Methods: This thesis comprises four studies. Study I and II were cross-sectional, including females who sustained a primary ACL rupture while playing football and underwent ACLR 6–36 months prior to study inclusion. In study I, 182 females were included at a median of 18 months (IQR 13) after ACLR. All players completed a battery of questionnaires. Ninety-four players (52%) returned to football and were playing at the time of completing the questionnaires, and 88 (48%) had not returned. In study II, 77 of the 94 active female football players (from study I) with an ACLR and 77 knee-healthy female football players were included. A battery of tests was used to assess postural control (the Star excursion balance test) and hop performance (the one-leg hop for distance, the five jump test and the side hop). Movement asymmetries in the lower limbs and trunk were assessed with the drop vertical jump and the tuck jump using two-dimensional analyses. Study III, was a cohort study including all patients with a primary ACLR (n=22,429) registered in the Swedish national ACL register between January 2005 and February 2013. Data extracted from the register to identify predictors for additional ACLR were: patient age at primary ACLR, sex, activity performed at the time of ACL injury, primary injury to the right- or left knee, time between injury and primary ACLR, presence of any concomitant injuries, graft type, Knee injury and Osteoarthritis Outcome Score and Euroqol Index Five Dimensions measured pre-operatively. Study IV was cross-sectional. In this study, patient-reported knee function, quality of life and activity level in 66 patients with bilateral ACL injuries was investigated and outcomes were compared with 182 patients with unilateral ACLR.

Results: Factors associated with returning to football in females were; short time between injury and ACLR (0–3 months, OR 5.6; 3–12 months OR 4.7 vs. reference group >12 months) and high motivation (study I). In all functional tests, the reconstructed and uninvolved limbs did not differ, and players with ACLR and controls differed only minimally. Nine to 49% of the players with ACLR and controls had side-to-side differences and movement asymmetries and only one

fifth had results that met the recommended guidelines for successful outcome on all the different tests (study II). Main predictors for revision and contralateral ACLR were younger age (fourfold increased rate for <16 vs. >35-year-old patients), having ACLR early after the primary injury (two to threefold increased rate for ACLR within 3 months vs. >12 months) and incurring the primary injury while playing football (study III). Patients with bilateral ACL injuries reported poorer knee function and quality of life compared to those who had undergone unilateral ACLR. They had a high activity level before their first and second ACL injuries but an impaired activity level at follow-up after their second injury (study IV).

Conclusions: Female football players who returned to football after an ACLR had high motivation and had undergone ACLR within one year after injury. Players with ACLR had similar functional performance to healthy controls. Movement asymmetries, which in previous studies have been associated with increased risk for primary and secondary ACL injury, occurred to a high degree in both groups. The rate of additional ACLR seemed to be increased in a selected group of young patients who desire to return to strenuous sports like football quickly after primary ACLR. Sustaining a contralateral ACL injury led to impaired knee function and activity level.

Keywords: ACL, ACL reconstruction, contralateral, football, functional performance, knee, patient-reported outcome measures, return to sport, return to play, revision, soccer, subsequent injury

ISBN: 978-91-7685-736-6

LIST OF PAPERS

- I. **Anne Fältström**, Martin Hägglund, Joanna Kvist. Factors associated with playing football after anterior cruciate ligament reconstruction in female football players. *Scand J Med Sci Sports*. 2015 Nov 21. doi: 10.1111/sms.12588. [Epub ahead of print]
- II. **Anne Fältström**, Martin Hägglund, Joanna Kvist. Functional performance among active female soccer players after primary unilateral anterior cruciate ligament reconstruction compared with knee-healthy controls. Accepted. *Am J Sports Med*. 2016.
- III. **Anne Fältström**, Martin Hägglund, Henrik Magnusson, Magnus Forssblad, Joanna Kvist. Predictors for additional anterior cruciate ligament reconstruction: data from the Swedish national ACL register. *Knee Surg Sports Traumatol Arthrosc*. 2016 Mar;24(3):885-94.
- IV. **Anne Fältström**, Martin Hägglund, Joanna Kvist. Patient-reported knee function, quality of life, and activity level after bilateral anterior cruciate ligament injuries. *Am J Sports Med*. 2013 Dec;41(12):2805-13.

DESCRIPTION OF CONTRIBUTION

Study I and II

Study Design	Anne Fältström, Martin Hägglund, Joanna Kvist
Data Collection	Anne Fältström
Data Analysis	Anne Fältström
Manuscript Writing	Anne Fältström
Manuscript Revision	Anne Fältström, Martin Hägglund, Joanna Kvist

Study III

Study Design	Anne Fältström, Martin Hägglund, Henrik Magnusson, Magnus Forssblad, Joanna Kvist
Data Analysis	Anne Fältström, Henrik Magnusson
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Study IV

Study Design	Anne Fältström, Joanna Kvist
Data Collection	Anne Fältström
Data Analysis	Anne Fältström
Manuscript Writing	Anne Fältström
Manuscript Revision	Anne Fältström, Martin Hägglund, Joanna Kvist

ABBREVIATIONS

ACL	Anterior Cruciate Ligament
ACLR	Anterior Cruciate Ligament Reconstruction
ACL-RSI	Anterior Cruciate Ligament- Return to Sport after Injury
ACL-QoL	Anterior Cruciate Ligament- Quality of Life
BPTB	Bone-Patellar-Tendon-Bone autograft
DVJ	Drop Vertical Jump
EQ-5D	Euroqol Index Five Dimensions
EQ VAS	Euroqol Visual Analogue Scale
5JT	Five Jump Test
HR	Hazard Ratio
HT	Hamstrings autograft
IKDC	International Knee Documentation Committee
IQR	Interquartile Range
KAM	Knee Abduction Moment
KOOS	Knee injury and Osteoarthritis Outcome Score
KT-1000	Knee arthrometer
LSI	Limb Symmetry Index
M	Mean
MCID	Minimal clinically important difference
MDC	Minimal Detectable Change
OA	Osteoarthritis
pKAM	Probability of high Knee Abduction Moment
PROM	Patient-Reported Outcome Measures
ROM	Range of Motion
RTS	Return to Sport
SD	Standard Deviation
SEBT	Star Excursion Balance Test
SMPS	Sport Multidimensional Perfectionism Scale
SSP	Swedish universities Scales of Personality
2D	Two Dimensional
3D	Three Dimensional

DEFINITIONS

ACL graft	The substitute used for replacement of a ruptured anterior cruciate ligament in a reconstruction procedure
Contralateral ACL	The ACL in the opposite knee compared with the ACL injured knee
Football	Association football, soccer
Functional performance	Describes the way the body works in activities performed in daily life
Motivation	Consist of two parts; intrinsic, which refers to doing an activity for the satisfaction of the activity itself and extrinsic, which refers to doing an activity in order to attain some separable outcome [187]
Neuromuscular control	A complex interaction between the nervous system and the musculoskeletal system leading to the ability to produce controlled movement through coordinated muscle activity [234]
Postural control	The act of maintaining, achieving or restoring a state of balance during any posture or activity [173]
Perfectionism	A personality disposition characterized by excessively high standards for performance [79]
Predictor	An independent variable associated with the occurrence of an outcome
Re-rupture	Rupture of the ACL graft
Revision ACLR	Replacement of a previous ruptured ACL graft
Valgus collapse	A combination of hip internal rotation, knee valgus, and tibial internal or external rotation [176]

INTRODUCTION

Working as a physiotherapist focusing on patients with anterior cruciate ligament (ACL) injuries, a number of questions were raised. Approximately 20 years ago, when a physiotherapist was unable to rehabilitate the patient back to sport within 6 months after an ACL reconstruction (ACLR), it was considered as a failure. Historically, clearance to return to sport (RTS) was based mainly on time. Today, the function of the trunk and lower extremities are more in focus, but time after ACLR is still important regarding the graft healing and cartilage in the knee. Clinicians agree that it takes around 9-12 months to RTS (especially pivoting sports) after ACLR, even if media still always talk about 6 months. Many young patients are eager to return to their pre-injury level of sport after an ACL injury and want an ACLR performed as soon as possible. However, rehabilitation after an ACL injury is tough and many can lose sight of their RTS goal. Living a healthy and active life is very important; however, participating in a contact sport such as football, is maybe not the best activity after an ACL injury or an ACLR knee. Professor Eric Lindgren stated in the 1960's that "Football is not a sport, it is a knee disease". Many hours on the football field and 20 years as a physiotherapist have led me understand the truth to this quote.

A dilemma as a physiotherapist is to know when it is safe for a patient to RTS. What tests should be done and how do I know if the results are good enough for safe RTS? It definitely feels like a great failure if the patient RTS and injures his/her knee again or injures the ACL in the opposite knee. The physiotherapist might wonder "What have I missed in rehabilitation?" or "Were the RTS criteria not strict enough to identify patients at high risk of injury?"

The four studies included in this thesis will be briefly described; factors that differ between females with ACLR who return to football or not, functional performance between females who returned to football after ACLR and knee-healthy football players, predictors for additional ACLR and patient-reported knee function, quality of life and activity level in patients with bilateral ACL injuries.

Enjoy reading!

BACKGROUND

Anatomy and biomechanics of the ACL

The ACL is situated in the centre of the knee. The ligament averages 31 mm in length and 10 mm in width [157], and is an intraarticular structure with limited ability to heal [8]. The ACL is the main stabilizer in the knee preventing anteroposterior displacement of the tibia relative to the femur, but also assists with restraining tibial internal rotation [35]. The ACL consists of two major fibre bundles: the anteromedial (AM) and posterolateral (PL) bundle. The AM bundle tightens during flexion and is the primary restraint against anterior tibial translation. The PL bundle is tight when the knee is extended and stabilizes the knee near full extension, particularly against rotatory loads. The ligament appears to turn itself in a lateral spiral when knee is flexed [169].

Epidemiology and aetiology of a primary ACL injury

In the general Swedish population aged 10-64 years, ACL injury occurs with an incidence of approximately 81/100 000 people/year [65]. The incidence increases several-fold in sports, and is as high as 500-8500/100 000 participants/year in football [221], the main sport in Sweden. The most common sport for both females and males performed at ACL injury and who later undergo ACLR in Sweden is football (36% vs. 49%), and after that alpine skiing (18% vs. 10%), handball (9% vs. 3%) and floorball (8% vs. 10%) [114]. The female-to-male ACL injury rate is different depending on sport. For females, wrestling and handball has approximately 4 times higher risk, basketball and football have a 3 times higher risk, and rugby 2 times higher risk compared to males. In lacrosse and alpine skiing the risk ratio female-to-male are equal [175]. Females tend to sustain their ACL injury at a younger age compared to males [221].

In contact sports, ACL injury typically occurs in a noncontact situation [5,24], when an individual is trying to decelerate the body from a jump or running prior to a change of direction, and the knee is in near full extension with combined rotation in the knee. Contact ACL injuries are frequently associated with a powerful valgus stress and concomitant injury to the medial collateral ligament (MCL) and medial meniscus [24]. Females may injure the ACL through different mechanisms to males [24,91]. Valgus collapse, a combination of knee valgus, tibial rotation and hip internal rotation, is more common in females while males are believed to have a more sagittal plane loading, which means that the knee joint is more flexed and the hip and ankle are in a more neutral position [24,176]. However, Waldén et al [222] speculate if valgus collapse is a

sex-specific consequence after the injury due to factors such as lower limb muscle strength and higher joint laxity, rather than an injury mechanism. A further proposed ACL injury mechanism in females, associated with valgus collapse, is poor trunk control [89].

Multiple risk factors have been associated with ACL injury, meaning that the risk factor profile for ACL injury is very complex [1,5,167,196,197]. Risk factors can be classified as intrinsic or extrinsic, and can be modifiable or non-modifiable. Despite the multifactorial nature of ACL injury, most studies have examined isolated risk factors [179,195]. Many articles of proposed risk factors for ACL are narrative reviews [1,88,89,203], systematic reviews [5,19,92,196,197,221] or current concepts statement [180,195] that include case-control studies [38,82,91,110,123,139,144,174,204] in addition to prospectively designed studies [90,95,117,149,159,160,164,165,199,216,218,219,241,242] (Table 1). To definitively establish risk factors for ACL injury, high quality prospective studies are needed.

Table 1. Proposed risk factors for sustaining a primary ACL injury

Intrinsic	Extrinsic
<i>Non-modifiable</i>	<i>Non-modifiable</i>
<ul style="list-style-type: none"> • Female sex [221] • High ligamentous laxity (generalized and specific) [110,144,216] • Small femoral notch size [199,216] • Small ACL volume [38] • Increased posterior tibial slope [82] • Genu recurvatum [110,123] • Increased subtalar pronation [123] • Previous ACL injury [165,218] • Previous ankle injury [110] • Heredity for ACL [95,174] • Preovulatory menstrual status [92] 	<ul style="list-style-type: none"> • Weather condition (hot, dry) [160-162]
<i>Modifiable</i>	<i>Modifiable</i>
<ul style="list-style-type: none"> • High BMI [216] • Neuromuscular control deficits [90,91,241,242] • Biomechanical deficits [90] • Muscle fatigue [5,27] • Neurocognitive function deficits [204] 	<ul style="list-style-type: none"> • High shoe surface friction [117] • Artificial playing surface [19,159,164] • Contact sport [64] • Cutting and pivoting sports [64] • High level of competition [149,219]

Intrinsic factors

Neuromuscular and biomechanical factors include differences in landing and pivoting biomechanics between injured and non-injured patients [1]. ACL-injured females have decreased isokinetic hamstring strength and recruitment (relative to quadriceps) [139], increased lateral trunk displacement, knee abduction and intersegmental abduction moment, and greater ground reaction force during a drop vertical jump (DVJ) compared to uninjured females [90]. Deficits in neuromuscular control of the trunk are associated with ACL injuries in female athletes [90,91,241,242]. Muscle fatigue alters neuromuscular control and may increase the risk of injury [5,27]. Neurocognitive function like slower reaction time, slower processing speed and lower visual and verbal memory scores are associated with noncontact ACL injuries in intercollegiate athletes [204].

There is less evidence regarding the role of personality or psychological factors as risk factors for incurring an ACL injury. However, Ivarsson et al [99] studied Swedish male and female elite football players and found that traits of anxiety, negative life stress and "daily hassles" were significant predictors for sustaining an injury among professional football players. Swedish universities Scales of Personality (SSP) [78] has also been used in the football context and higher scores in somatic trait anxiety [98,99,101], mistrust [101], psychic trait anxiety, stress susceptibility, and trait irritability [98] were associated with the occurrence of sport injuries in general among junior [101], senior [98] and elite football players [99].

Factors related to the increased risk for ACL injury in females are general joint laxity [144], increased quadriceps angle, increased posterior tibial slope, decreased femoral notch width, smaller ACL cross-sectional area, hormonal factors, and biomechanical factors [203]. Hewett et al [88] described four neuromuscular imbalances most seen in females, which may be associated with sustaining an ACL injury;

- Ligament dominance (knee collapses into a valgus position). The muscles do not absorb the ground reaction forces during activities so the anatomic and static stabilizers (ligaments) must absorb high amount of force.
- Quadriceps dominance (land with less knee flexion angles) refers to the tendency to stabilize the knee by primarily using quadriceps instead of hamstrings, which leads to more stress on the ACL.
- Leg dominance. The tendency is to be one-leg dominant in tasks leading to side-to-side asymmetry.
- Trunk dominance (core dysfunction). Athletes do not adequately sense the trunk position in 3D space and have excess side-to-side movement of the trunk.

There is no clear answer regarding the role of hormonal status in ACL injury [1,196], but female athletes may have an increased risk for ACL injuries during the preovulatory phase of the menstrual cycle [92].

Extrinsic factors

Extrinsic non-modifiable and modifiable risk factors are presented in Table 1.

A potential non-modifiable extrinsic non-contact ACL injury risk factor is weather condition. ACL injuries were more likely to incur in teams playing in warmer climate zones in football, probably due to surface factors [162]. Hot weather [161] and periods of low rainfall [160] were associated with an increased risk for ACL injuries in Australian and American football, and one proposed mechanism is higher shoe-surface traction.

Modifiable risk factors for ACL injury include: footwear, playing environment, equipment, level of competition, and type of sport [1,5]. The type of playing surface also appears to have a role in injury risk, especially surfaces with higher shoe-surface friction. In female team handball, play on synthetic floors is associated with higher risk for ACL injuries compared with wooden floors [159]. A similar result was found in female floorball [164]. Playing on artificial turf compared with natural grass has been debated as a risk factor for ACL injury. Studies support an increased rate of ACL injury on artificial turf in American football, but there is no apparent increased risk in football (soccer) [19,95]. There is a lack of randomized controlled studies regarding footwear, but one study regarding football cleat designs found a higher number and longer cleats were associated with a higher risk of sustaining an ACL injury [117]. Very little is known about the influence of referees, the coach's leading style, and rules on the risk of sustaining ACL injuries [179].

Diagnosis and symptoms of ACL injury

The three most commonly used tests to diagnose an ACL injury are the Lachman test, anterior drawer test and pivot shift. Assessing the injured knee using a battery of assessments, as opposed to isolated tests is recommended, and is highly predictive for an ACL injury if performed by orthopaedic physicians [198]. Magnetic resonance imaging (MRI) is an added diagnostic tool used and could also identify concomitant injuries [65]. It is very common (85%) that associated injuries to the articular surface, meniscus, or MCL occur with an ACL injury [109]. Patients who sustain an ACL injury often describe a giving way feeling at the time of injury, feeling or hearing a popping sound, followed by pain, swelling and a feeling of instability leading to inability to continue the activity [156].

Consequences of ACL injury

The main acute problem after an ACL injury is typically instability and "giving way" episodes that cause difficulties for participation in knee-demanding activities. Other common symptoms and problems are decreased strength in hip muscles and hamstrings, altered movement pattern, impaired postural control and functional performance [30,40,48,145,201]. There may also be long-term consequences of ACL injury. Radiographic osteoarthritis (OA) may affect up to 71% of patients 10-15 years after their ACLR [158], and the prevalence of OA is similar, irrespective of whether patients have ACLR or not [81].

Treatment of ACL injury

The treatment after an ACL injury may be surgical (ACLR combined with rehabilitation) or non-surgical (rehabilitation only). In both cases, the goal of treatment is to reach the best functional level without increasing the risk of subsequent injuries or degenerative changes in the knee above the level of risk experienced by an uninjured person [112]. The best treatment for ACL injury is still fiercely debated, and there is lack of knowledge about the long-term consequences of surgical and non-surgical treatment for the knee. In a Cochrane review examining reconstructive versus non-reconstructive treatment only two, poor qualitative randomised studies from nearly 30 years ago, met the inclusion criteria and further studies are needed [122]. In a more recent randomized controlled trial comparing structured rehabilitation and early ACLR (within 10 weeks after injury) with structured rehabilitation and optional delayed ACLR if needed, there was no difference in patient-reported knee function and radiographic outcomes at 5 years between people who had ACLR and those who had non-surgical treatment [66].

Rehabilitation

Rehabilitation is an important part of the treatment after an ACL injury. Supervised rehabilitation is usually completed for up to 4 months after ACL injury [75], or until knee function does not continue to improve with rehabilitation. The majority of patients with ACL injury treated non-surgically can achieve good knee muscle strength, functional performance and subjective knee function, knee related quality of life and activity level [3,137]. Rehabilitation, whether part of a surgical or non-surgical treatment approach, should be individually tailored to each patient [75,230]. For example, the presence of concomitant injury and intervention might necessitate modification to the rehabilitation program [2]. Rehabilitation programs account for healing processes and biomechanics in the knee joint after injury and ACLR, together with physiological aspects [112]. Rehabilitation is mentally and emotionally demanding, and time consuming [84]. Motivation for rehabilitation might be enhanced through patient educa-

tion regarding why strength and neuromuscular function are important, and the importance of goal-setting and repeated functional testing as feedback [76].

Rehabilitation after surgical is in many ways similar to rehabilitation initiated as part of a non-surgical treatment approach, although after surgery it is necessary to protect the healing graft. Animal studies indicate that a bone-patellar-tendon-bone (BPTB) graft may be weakest at 6-8 weeks after ACLR [34] and that it can take up to 12 weeks for incorporation of a hamstring tendon autograft (HT) graft into the osseous tunnel [182]. The principles of early weight bearing, use of both non-weight-bearing and weight-bearing exercises, and the use of objective measures for determining progression and RTS are guidelines in the rehabilitation programs [2]. Running and sport-specific exercises are allowed from approximately 3-4 months after ACL injury and 4-6 months after ACLR, respectively [133]. RTS is often allowed after 6-12 months [134], but the decision for RTS should be based on fulfillment of specific criteria and a patient-tailored process [56]. Time frames are approximate for the average patient [238].

Reconstruction

In Sweden, approximately half of patients with an ACL injury choose to have ACLR [64] and more than 90% of all ACLRs performed in Sweden are included in the Swedish national ACL register [114]. In the United States (US) orthopaedic surgeons have a strong preference for ACLR – approximately 90-95% of patients with an ACL injury undergo ACLR [126]. The incidence of ACLR in US increased between 1994 and 2006, particularly in those younger than 20 and those older than 40 years of age [128]. The number of ACLR performed in females increased from 32% to 42% of the total number of ACLR in US between 1994 and 2006, with a near doubling (74%) of incidence in females, but increased only 12% in men [128]. In Sweden, there was no change in the proportion of males (58%) and females (42%) undergoing ACLR between the years 2005 and 2014 [64].

Surgical treatment may be considered if the patient, during or after rehabilitation, has continued knee symptoms, functional instability and an unacceptably low level of activity and quality of life. The indication for ACLR depends on the individual's symptoms. Generally, the indication for ACLR increases with more knee-demanding activity level, willingness to follow the rehabilitation regime, and if there are associated injuries (e.g. combined ligament injuries, meniscal injury suitable for repair) [25]. The suggestion is that ACLR should not be performed before quadriceps strength in the involved leg is at least 80% of the non-involved leg, otherwise there are consequences for the long-term outcome (lower quadriceps strength and patient-reported knee-function) after the ACLR [53].

Surgical treatment is often recommended for young, active patients with high demands on their knees [122,180]. The timing of ACLR is debated and many experienced surgeons believe that the optimal time for surgery is when the knee has normal range of motion and no effusion [180]. Patients who had ACLR within 3 months after injury had similar functional-, clinical- and patient-reported (knee function) outcomes, but higher activity levels compared with patients who had ACLR >3 months after ACL injury at follow-up 2-5.5 years after ACLR [104]. With delayed ACLR, a significant increase in the number of meniscus and cartilages injuries is observed [61,104]. In Scandinavia, the median time from injury-to-surgery ranged from 7-10 months [72] (median 8 months in Sweden [114]). In the US, the median time was 2.4 months [126].

Graft used in ACLR

Contemporary surgical technique includes so-called anatomic reconstruction, individualised to the patient's conditions and the surgeon's experience, using a single- or double-bundle technique [106]. Internationally, the most commonly used grafts for ACLR are HT (semitendinosus or semitendinosus and gracilis) or the middle part of the patellar tendon (BPTB autograft) [190]. In Scandinavia the most common graft is HT (61-86%) [72], as in Sweden (approximately 92% in 2014) [64], while in the US, the HT and BPTB graft are equally used. In the US allograft is also more compared to in Scandinavia [126].

Graft choice for ACLR continues to be debated. In a meta-analysis including 22 studies rated as relatively high quality studies, HT and BPTB graft were equivalent options for ACLR regarding instrumented laxity measurements and Lachman test, patient-reported outcome of knee function, graft failure and knee joint range of motion (ROM). However, patients who received BPTB grafts reported a higher prevalence of postoperative kneeling discomfort and more anterior knee pain, but less positive pivot shift and a higher return to preinjury activity level [240]. Receiving a HT graft may favour returning to competitive level sport [10].

Epidemiology and aetiology of an additional ACL injury

Young patients with ACLR, who return to sport (RTS) may have 30-40 times greater risk of sustaining an additional ACL injury (to either knee) compared to a young person who has never had an ACL injury [231]. However, it is unclear why the risk is so high [201]. ACL graft re-rupture rates range from 1.8% to 25% and the rate of contralateral ACL injury ranges from 3% to 26% [94,119,166,167,171,189,229,236,239] depending on follow-up time (2-15 years), age and activity level in the population. Several of the studies reported a higher incidence for contralateral ACL injuries than sustaining an ACL graft rupture [94,119,166,167,171,229,239]. Most new ACL inju-

ries occurred in the first 2-3 years after ACLR, and the ACL graft ruptures typically occurred earlier than contralateral ACL injuries [189,194]. The exact rate of re-injury to the ACL graft and the contralateral ACL is difficult to determine, because some patients may not contact a healthcare practitioner, therefore, the injury remains undiagnosed.

Female – male ratio in a second ACL injury

There are conflicting results regarding whether there is an increased risk for an additional ACL injury in females compared with males. After ACLR, males tend to sustain more ACL graft ruptures [28,94,119,127] and females tend to sustain more contralateral ACL injuries [127,165,166,194]. In a systematic review and meta-analysis of the importance of patient sex in the outcome of ACLR, females had a higher revision rate (relative risk, 1.15; 95% CI, 1.02-1.28), but graft rupture (33 studies included) or failure (18 studies included) did not differ compared with males. Regarding revision rate, 23 of the 26 including studies did not report any significant sex difference [208].

Risk factors for sustaining an additional ACL injury

Non-modifiable and modifiable risk factors for sustaining an additional ACL injury are presented in Table 2. Some of the studies of proposed risk factors for sustaining an additional ACL injury are prospective [102,119,165-167,171,193,194,226], but several are follow-up case-control studies [26,28,94,116,189,229] and systematic reviews [206,231]. Similar to the risk factors for primary ACL injury, many of the suggested risk factors for additional ACL injury have a low level of evidence.

Table 2. Proposed risk factors for sustaining an additional ACL injury

Re-rupture	Contralateral
<i>Non-modifiable</i>	<i>Non-modifiable</i>
<ul style="list-style-type: none"> Young age at first injury [26,64,102,226,229,231] 	<ul style="list-style-type: none"> Young age at first injury [26,64,102,226,229,231]
<i>Modifiable</i>	<i>Modifiable</i>
<ul style="list-style-type: none"> Return to cutting and pivoting sports [26,229,231] Neuromuscular control deficits [167] Biomechanical deficits [167] Movement asymmetries [167] Allograft [26,102,226] Surgical complications [103,215] 	<ul style="list-style-type: none"> Return to cutting and pivoting sports [26,229,231] Neuromuscular control deficits [167] Biomechanical deficits [167] Movement asymmetries [167]

No exact definition of failure after ACLR exists, but three main categories can be distinguished: patient dissatisfaction with recurrent instability, different postoperative complications (infection, motion loss, arthritis), and other comorbidities (meniscus, chondral defects, quadriceps inhibition, donor site pain) [103]. Causes for recurrent instability (i.e. graft failure of a primary ACLR) are: technical problems (tunnel placement or fixation problems) in half of the cases, new trauma in one third of the cases, and unknown reasons in 15% [215]. Recurrent instability can occur early (< 6 months) or late (> 6 months) after ACLR. Early instability is often due to surgical problems where the most common technical error is likely incorrect tunnel position. Poor graft quality or inadequate graft tensioning may also cause problems [103].

Returning to cutting and pivoting sports increased the odds of ACL graft rupture by a factor of 3.9 and a contralateral ACL injury by a factor of between 5 [229] and 10 [189]. At the time of RTS [40,145] and up to 7 years after ACLR [201], side-to-side differences in postural control [40], differences in muscle activation patterns of the hamstrings [30], altered movement patterns in the knee and hip, and deficits in force development in the vertical jump [48,145,201] persist in ACLR athletes compared with uninjured controls. These may be factors that could contribute to increasing the risk for new ACL injury.

There is inconsistent evidence for other proposed risk factors, including sex [28,119,194], family history of ACL injury [28,189,229], femoral notch width [193], graft type [28,119], and early return to full activity (within 6-7 months after ACLR) [116,194]. Patients with BPTB graft sustain more contralateral ACL injuries or undergo more contralateral ACLR than after HT [119,127,171].

Predictors for undergoing an additional ACLR

Many patients who suffer an additional ACL injury also undergo an additional ACLR. ACL registers show a revision rate of 3.3–7.7% for the primary ACLR after 5–6 years of follow-up [4,86,114,120,127,200], and a rate of 3.8–6.5% for ACLR in the contralateral knee [4,86,114,127,200]. Ahldén et al [4] reported that the total additional ACLR rate during a 5-years period for female football players aged 15-18 years were 22% compared with 9.8% for males in the same age group.

Predictors for additional ACLR (revision and contralateral) include:

- Primary ACLR at an younger age [124,127,168,226]
- BMI <25 [127]
- ACLR performed by lower-volume surgeons or at lower-volume hospitals [124].

HT autograft [127,168], allograft [102,127] and ACLR at an academic hospital were predictors for revision ACLR [226]. Using metal interference, screw fixation of semitendinosus tendon autograft on the tibia at the primary ACLR was associated with a lower rate of revision ACLR [6].

The influences of other potential predictors for additional ACLR (such as activity at the time of primary injury, time between injury and primary ACLR, presence of concomitant injuries, and injury side) have not been well studied in large cohorts with multivariable analyses.

Outcome measures of ACL injury treatment

Clinical and functional tests, and patient-reported outcomes of knee function and quality of life provide different yet complementary information regarding the patient's functional ability. Combinations of these assessments are proposed to be used in the evaluation of "successful outcome" after ACL injury and ACLR [125]. Clinical tests and patient-reported outcomes do not always correlate [150], and in recent years, assessments have focused on the ACL injured patient's self-reported knee function and quality of life using various questionnaires [109,150,158,205,235].

Patient-reported outcome measures

Patient-reported outcome measures (PROMs) can be either generic or disease-specific [235], and should reflect the most important concerns of the patient [80]. The advantage of general health PROM is that impacts of treatment can be compared despite various diseases and conditions [235]. PROMs need to measure patient-relevant issues, be user-friendly, and have good reliability, validity and responsiveness to clinical changes [185]. The Medical Outcomes Study 36-Item Short Form (SF-36) [225] is the most popular general health PROM in orthopaedics [235]. The SF-36 is responsive to changes with surgical and non-surgical treatment over time [192]. Another commonly used generic health measure is Euroqol Index Five Dimensions (EQ-5D) and Euroqol Visual Analogue Scale (EQ VAS) [177].

There are several ACL- and knee-specific PROMs that evaluate knee function, knee-related pain, symptoms and quality of life (e.g. Lysholm knee score [210], Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [22], Knee injury and Osteoarthritis Outcome Score (KOOS) [185], International Knee Documentation Committee (IKDC) Subjective Knee Form [96,97], Cincinnati Knee Rating Scale [155] and ACL-Quality of Life questionnaire (ACL-QoL) [135]).

To measure activity level after ACL injury, the Tegner activity scale [210] and Marx activity scale [131] are commonly used in conjunction with other PROMs – forming a global assessment.

A range of different questionnaires have been used to assess psychological and personality factors including:

- Knee self-efficacy scale (K-SES) [211] (evaluates participants' perceived self-efficacy of current and future knee function)
- Emotional Responses of Athletes to Injury Questionnaire (ERAIQ) [136] (evaluates athletes' emotions after injury)
- Multidimensional Health Locus of Control scale (HLOC) [223] (evaluates participants' beliefs in what determines what affects their health, own actions or external events)
- ACL-Return to Sport after Injury scale (ACL-RSI) [115,228] (evaluates psychological readiness to return to sport after ACL injury)
- Tampa Scale of Kinesiophobia (TSK) [108,113] (evaluates fear of re-injury due to movement and physical activity)
- Swedish universities Scales of Personality (SSP) [78] (evaluates 13 personality traits)
- Sport Multidimensional Perfectionism Scale (SMPS) [71] (evaluates perfectionism in sports (considered an enduring personality trait)).

There is no gold standard PROM for patients after ACL injury. Therefore, one challenge is to choose which PROM is best to use in clinical practice and in research. It is generally recommended to use a general health scale, a disease-specific scale and an activity scale [235].

Clinical assessment

There are several common clinical tests used to assess impairments after ACL injury. The manual Lachman test and anterior drawer test [198], and the instrumented KT-1000 knee arthrometer [18] are often used to measure anterior translation of the tibia relative to the femur. A general knee joint examination is often performed [198]. However, measures of passive anterior translation of the tibia relative to femur is not considered by expert clinicians to be an important factor contributing “successful outcome” after ACL injury or ACLR [125]. Rotational stability is often measured with the pivot shift test. Patients with rotational instability (positive pivot shift) reported lower satisfaction with knee function and had more activity limitations [107].

Functional performance tests

Strength, proprioception and neuromuscular control are important for dynamic stability and restoration of full function [233] after ACLR. Many single tests and test batteries have been developed to evaluate the function of the lower extremity after ACL injury and ACLR. These tests evaluate different demands (e.g. strength, postural control, and hopping ability). Most recommended test batteries evaluate strength and hop performance (quantitative) [151], but not postural control and movement asymmetries, such as foot, knee, hip, and trunk movement (qualitative), because these assessments often require sophisticated equipment and are time consuming.

Many single tests and tests batteries are developed to screen for ACL injury risk. However, the most frequently used tests lack validity to predict ACL injuries or re-injuries [83]. Single tests are also unlikely to accurately predict injuries given how complex injury risk is. High knee abduction moment (KAM) in a DVJ measured with more advanced equipment like 3-dimensional (3D) motion analysis could be associated with the risk of sustaining an ACL injury in healthy athletes (football, basketball, and volleyball) [90] and in ACLR patients [167].

Outcome after primary ACLR

The outcome of the ACLR is influenced by a range of factors including surgical factors (e.g. graft selection, tunnel placement, graft tension, graft fixation and graft tunnel healing pathology [129,231]), education, smoking habits, concomitant injuries, age, BMI and follow-up time [52]. Rehabilitation is also an important factor for outcome of ACLR.

Generally, patient expectations of ACLR are high, especially among younger patients, highly active patients, and patients without a history of knee surgery. They expect to return to pre-injury level of sport, RTS within one year after ACLR, to have normal or nearly normal knee function, and no increased risk of OA [60]. However, having surgical treatment does not automatically lead to satisfactory outcomes, and this may be related to expectations about RTS, knee stability, and ability to recover [213]. In the short term after ACLR, approximately 90% of patients achieved normal or nearly normal knee function regarding strength and stability [13], but in long-term studies a high incidence of OA has been reported [81,158].

Outcomes after an ACLR are, at best, similar, and at worst, inferior, for females compared with males. Females had inferior outcomes in instrumented laxity, Lysholm knee score and Tegner activity scale. Outcomes were similar regarding manually knee stability testing, hop tests, quadriceps and hamstrings strength, knee joint ROM loss, KOOS, IKDC score and OA development [208].

Outcome after secondary ACL injury

Approximately 6–10% of ACLRs result in graft failure and recurrent instability 5 years after primary ACLR [189,239]. Further advances in ACLR technique should continue, in order to develop a surgical procedure that is more close to the natural ACL anatomy and prevent future knee pathology [106,129]. There is also room for improvement in post-operative rehabilitation. All predisposing factors that may lead to an additional injury should be identified and addressed during rehabilitation [232].

Patient-reported knee function and quality of life after a revision ACLR is worse compared with primary surgery [114]. The failure rate, defined as repeat revision or a side-to-side difference of > 5 mm measured with KT-1000, after revision ACLR was 3–4 times greater than after primary ACLR. The rate of return to previous activity level was 54% [237], compared with 65% after primary ACLR [10]. At revision surgery, higher rates of concomitant injuries (meniscus and chondral lesions) should be expected. Setting up realistic expectations regarding outcomes is vital – patients should be informed and asked about expectation and outcome after revision. Excellent knee stability can be achieved, but other concomitant injuries to the knee may cause persistent pain [103].

Patients undergoing revision ACLR have lower expectations than after a primary ACLR, although expectations are still high [60]. Patient-reported outcomes regarding knee function, activity level and quality of life in patients who have sustained a contralateral ACL injury and undergone bilateral ACLR have been published recently and after implementation of study IV [114,181]. A study from the Swedish national ACL register reported similar patient-reported knee function and quality of life for patient undergoing bilateral ACLR compared with unilateral ACLR up to 5 year after primary ACLR [114]. The study by Ristic et al [181] has low quality with few participants and no control group. Therefore, it is unclear whether sustaining contralateral ACL injuries or undergoing bilateral ACLR leads to inferior outcome compared with a primary ACL injury or ACLR.

ACL injury prevention

A multifactorial approach to addressing all factors implicated in ACL injury risk, and the injury mechanism should be considered when trying to prevent ACL injuries. Reduction of noncontact ACL injury is the primary aim of most prevention programs, and the main focus of these programs has been female football [5,68,105,217] and handball players [148].

Primary ACL injury prevention

Most injury prevention programs are multimodal and focus on modification of intrinsic risk factors. These factors are typically neuromuscular and biomechanical factors such as landing technique, knee control (i.e. avoiding knee valgus motion), postural control, strengthening, core stability and technique training. These programs have shown positive results [5,68,105,148,217]. A meta-analysis including 8 prospective controlled studies with overall average quality, indicated strong evidence for the effect of ACL injury preventing programs for reducing ACL injuries [188]. However, compliance is a key factor for the success of ACL injury prevention programs [202].

Secondary ACL injury prevention

Preventive programs for reduction of additional ACL injuries after an ACLR are lacking. However, Gilchrist et al [68] showed that preventive training used for uninjured female football players also could prevent additional ACL injuries for players with a previously reconstructed ACL. Movement asymmetries and biomechanical abnormalities can persist in athletes after ACLR despite good functional performance and are likely a residual from, and exacerbated by, the initial injury [87]. Elite female football players, who are at risk for sustaining ACL injuries, may have a profile of risk factors that includes aggressive playing style, anatomical and neuromuscular characteristics [59]. Rehabilitation after ACLR should aim to minimize limb asymmetries to prevent additional ACL injury [70]. The preinjury level of function, that often is unknown, and the uninjured limb used in comparison after ACLR are probably not enough as RTS criteria and the goal should be to reach a higher level of function to minimize the risk of re-injury [232]. Activity modification, neuromuscular training, improved rehabilitation and RTS guidelines may reduce additional injury in the at-risk population, but there are no data regarding these interventions.

Return to sport after ACL injury and ACLR

The goal of many patients with an ACL injury or ACLR is to resume their activities and RTS as soon as possible [20]. A satisfactory activity level without ACLR could be achieved, despite impairments and decreased activity level. The activity level is affected by the time since injury, and physical and psychological factors [243]. The rate of return to pre-injury activity level is similar with or without surgical treatment [66]. Even return to elite professional football is possible, although uncommon, after an ACL injury treated non-surgically [230].

RTS is an important clinical outcome after ACLR [10]. In a meta-analysis, 81% returned to some kind of sport, 65% of patients returned to their preinjury level after a mean follow-up of 40 months after unilateral ACLR, but only 55% returned to competitive sports, despite having good physical function [10]. The long term sport partic-

ipation after an ACLR is not known, but after 5 years, one out of five was still active regardless of treatment (ACLR or not) [67]. Roos et al [186] reported that 30% of ACL-injured football players were active in football three years after injury compared with 80% in an un-injured control population. A recent study by Waldén et al [220], reported that 86% of elite male football players 3 years after an ACLR still played football, 65% at the same level as before ACL injury.

Young athletes (<25 years) are 1.5 times more likely, and elite athletes are >2 times more likely to RTS after ACLR [10]. Fewer females RTS than males [208] – males are approximately 50% more likely to return to their previous level of sport or to competitive sport [10]. Females also RTS later than males after ACLR [14]. When RTS, females had more concern than males about the environmental conditions and the risk of re-injury 2-7 years after ACLR [9]. In two cohorts with female and male elite ACLR football players, 86% vs. 100% had returned to football training within 12 months [219]. In two football player cohorts of different ages and level of play, the return rate was only 46-67% for females compared to 60-76% for males [33,191]. Male sex [33,191] and younger age [33] are factors associated with a return to football after ACLR, while activity-related knee pain and cartilage injury [191] are factors associated with not returning to football. Higher quadriceps strength, less pain and less effusion are factors associating with RTS, although the evidence supporting these factors is weak [45].

General recommendations are that strength and ROM should be near pre-injury level or equal to the uninjured side, and that there should be no instability, tenderness, inflammation or effusion at the time of RTS [44]. A gradual progression through sport specific training is important and movement quality is as important as quantitative performance before RTS [146]. Functional performance tests and evaluation of PROMs are often used to identify patients who are ready to RTS. Suggested RTS criteria incorporate evaluation of functional performance including muscle strength (power and endurance), knee stability, bilateral limb symmetry, postural control, agility, technique with sport-specific tasks, and PROMs [56,147]. Functional performance tests are important pieces of the RTS puzzle, but should not be used independently – a test battery is likely more appropriate [212]. The RTS decision should be taken collaboratively between the coach, the physiotherapist, the surgeon and the patient.

Previous research has tended to focus on functional performance tests in the evaluation of a patient with an ACLR and RTS. However, more recently, there has been increased attention on psychological factors including psychological readiness to RTS, low fear of sustaining a new injury, and trust in the knee [118,214]. Evaluating an athlete's psychological profile has proven useful in identifying those with a high chance of returning to preinjury activity levels [69]. Psychological factors likely have a strong influence on RTS. Low fear of re-injury, self-motivation, confidence, psychological

readiness to RTS, positive mood and emotions facilitate RTS [9,11,45]. Fear of re-injury has been identified as the most important reason for not returning to pre-injury sport [9,113,214]. Patients who had undergone ACLR within 3 months after injury had a lower fear of re-injury than those who had waited longer. Those who had RTS to their pre-injury level participated in sport with low fear of re-injury [9].

Motivation to RTS is also an important factor [214]. Those with high motivation to RTS preoperatively [69] and 1 year after ACLR [12] were also more likely to RTS. At an average of 35 months after ACLR, psychological readiness to RTS was the factor most strongly associated with returning to the preinjury activity [16].

Personality factors may also influence RTS after ACLR, although these factors are not so well studied. Factors like being cautious, pessimistic, lack of self-confidence and self-motivation are associated with not returning to sport [58,214].

Rationale of the thesis

ACL injury is a severe and common injury in football players, and females have 2-4 times higher ACL injury risk compared to males [175,221]. RTS is a common goal after an ACLR [125], but females RTS [10,208] and to football specifically [33,191] to a lower degree than do males. There is lack of knowledge about factors associated with return to football in females after ACLR. Understanding the associations between demographic, personality and psychological factors, and returning to football might help improve the rehabilitation approach and increase the possibility of returning to football (if that is the player's preference). A key dilemma is the high re-injury risk after ACLR in female football players [33,165]. The goal is to safely re-integrate those who wish to return to playing football back to sport. It has been suggested that changes in the biomechanics of the knee during sports activities [201] or movement asymmetries [90,167] may be contributing factors to an increased risk for new ACL injury [201]. However, several of the functional tests used in previous studies have been done in a laboratory setting, and may have limited clinical utility.

Understanding predictors for additional ACL injury and ACLR is important inform efforts to prevent such recurrences. An ACL injury is a major trauma to young and active patient. Subsequent additional trauma to the ACL injured knee has been associated with poor patient-reported outcome [205]. Patients undergoing revision ACLR also reported poorer knee function and quality of life compared with patients undergoing primary ACLR [237]. Knowledge about patient-reported outcomes regarding knee function, quality of life and activity level in people with bilateral ACL injuries and bilateral ACLR is poor. This knowledge can be used to guide patients with bilateral ACL injuries to have realistic expectations about knee function and activity level and help clinicians to adapt treatment and rehabilitation.

Consequently, the studies included in the thesis aim to complement the knowledge about different physical and psychological factors that influence whether females with an ACLR knee return to football or not, and if there are any differences in functional performance, using a battery of tests commonly used in clinical practice, between females who return to football after ACLR and knee-healthy football players. The studies also broaden the knowledge of factors associated with undergoing an additional ACLR and the understanding of the patient with bilateral ACL injuries.

AIMS OF THE THESIS

Overall aim

The overall aim of this thesis was to increase knowledge about female football players with ACLR and patients with bilateral ACL injuries, and to identify predictors for additional ipsi- and/or contralateral ACLR.

Specific aims

The specific aims were:

- To investigate factors that influence whether females with a primary ACLR return to football or not. In addition, the aim was to compare current knee function, quality of life and readiness to RTS between those who returned to football and were currently playing and those who had not returned (study I).
- To investigate possible side-to-side differences in functional performance and movement asymmetries in female football players with a primary unilateral ACLR knee, and to compare with knee-healthy controls (study II).
- To identify predictors for additional ACLR after a primary ACLR in a large cohort (study III).
- To investigate patient-reported knee function, quality of life, and activity level in patients with bilateral ACL injuries and to compare them with patients who had undergone unilateral ACLR (study IV).

MATERIAL AND METHODS

Overview of the studies

This thesis is based on four separate studies: three cross sectional studies (study I, II and IV) and one cohort study (study III). An overview of the studies is presented in Table 3.

Table 3. Overview of the studies in the thesis

	Study I	Study II	Study III	Study IV
Design	Cross-sectional	Cross-sectional	Cohort	Cross-sectional
Aim	To investigate factors that influence whether females with a primary ACLR return to football or not. In addition, the aim was to compare current knee function, quality of life and readiness to RTS between those who returned to football or not	To investigate possible side-to-side differences in functional performance and movement asymmetries in female football players with a primary unilateral ACLR, and to compare to healthy controls	To identify predictors for additional ACLR after a primary ACLR in a large cohort	To investigate patient - reported knee function, quality of life, and activity level in patients with bilateral ACL injuries and to compare to patients who had unilateral ACLR
Participants	1. 94 current football players with ACLR 2. 88 players that had not returned to football after ACLR	1. 77 current football players with ACLR 2. 77 knee-healthy controls recruited from the same football team	20 824 patients with ACLR; 1. 19531 no new ACLR 2. 702 revision ACLR 3. 591 contralateral ACLR	1. 66 patients with bilateral ACL injuries 2. 182 patients with unilateral ACLR
Sex	Females	Females	Females (46%) and males	Females (bilateral 47%, unilateral 42%) and males
Age, years Mean $\pm$ SD	1. 20.1 $\pm$ 2.3 2. 20.8 $\pm$ 3.0	1. 20.1 $\pm$ 2.3 2. 19.5 $\pm$ 2.2	1. 27.0 $\pm$ 9.9 2. 21.9 $\pm$ 7.3 3. 22.3 $\pm$ 8.4	1. 29.1 $\pm$ 7.2 2. 28.5 $\pm$ 8.2
Data collection	Questionnaires – Patient-reported outcomes	Clinical assessment and functional performance tests	From the Swedish national ACL register. Outcome variables included additional revision or contralateral ACLR	Questionnaires – Patient-reported outcomes
Analysis	Parametric and non-parametric statistics (between-group comparisons). Logistic regression	Parametric and non-parametric statistics (within- and between-group comparisons)	Cox regression	Parametric and non-parametric statistics (between-group comparisons)

Participants

Study I

Inclusion criteria were: female football players identified through the Swedish national ACL register or football clubs; age 16–25 years; primary ACL injury incurred in football play and having undergone ACLR between 6–36 months ago at any clinic in three adjacent counties of Sweden. Exclusion criteria were: never being an active football player; intending to return to football but lacking clearance from the responsible physiotherapist (self-reported); having an associated posterior cruciate ligament (PCL) injury and/or surgically treated injuries to either the MCL or lateral collateral ligament (LCL). Ninety-four females who were currently playing football and 88 former football players (had not returned to football) were included (Figure 1). “Return to football” was defined as resuming playing football (training with the team) after ACLR and currently playing at any level at the time of follow-up (current players). Those who stated that they had returned to football at some point after their ACLR, but who were not currently playing ($n = 36$), were not included in study I. However, some of the results of these former players will be presented elsewhere in this thesis.

Study II

The population was the same as in study I, but only the players who were currently playing football and were available for the functional performance tests ($n=77$) were included (Figure 1). These football players were matched with knee-healthy players (without ACL injury or ACLR) recruited from the same team as players with ACLR with similar football exposure, age and playing position ($n=77$).

Figure 1. Study flowchart of study I and II.

Study III

All patients (males and females) with a primary ACLR registered in the Swedish national ACL register between the January 1, 2005 and February 27, 2013 were included. This resulted in a total of 22,429 patients among whom 20,824 (93%) had surgery with HT autograft, 1,429 (6%) with BPTB graft, and 174 (1%) with other grafts (including 37 allografts). Patient outcomes were followed to August 27, 2013, for a minimum of six months follow-up (range, 6-104 months) (Table 4). To ensure a homogeneous cohort, subsequent analyses only included patients with primary HT autograft ($n = 20,824$), of whom 702 had revision ACLR and 591 had contralateral ACLR during the follow-up period.

Table 4. Inclusion and exclusion criteria for study III

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> • Primary ACLR between January 1, 2005 and February 27, 2013 • Registered in the Swedish national ACL register 	<ul style="list-style-type: none"> • Previous ACLR to the ipsi- or contralateral knee • Missing information about graft type • Associated posterior cruciate ligament or postero-lateral corner injury • Any fractures, nerve injuries, osteotomies, or surgically treated injury to either the medial or lateral collateral ligament

Study IV

Patients with bilateral ACL injuries in study IV, were identified from one of five orthopaedic units. Medical records were reviewed for the diagnostic code representing an ACL injury, distortion of the knee, or knee instability, according to the diagnosis system of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). Participants were included if they had bilateral ACL injuries, were aged 18-45 years at the time of medical record review, and had a maximum time from the first ACL injury of 12 years (Table 5). Finally, 83 met the inclusion criteria and 66 of the 83 patients with bilateral ACL injuries (47% female; mean age, 29.1 ± 7.2 years) answered the questionnaires (80% response rate). Forty-three (65%) had ACLR in both knees, 18 (27%) in one knee, and 5 (8%) were treated non-surgically in both knees. A cohort of 182 patients with unilateral ACLR, identified at 4 of the 5 orthopaedic units, was used for comparison. The mean age was 28.5 ± 8.2 years (42% female) and ACLR was performed 2 to 5 years before completing the questionnaires.

Table 5. Inclusion and exclusion criteria for patients with bilateral ACL injuries in study IV

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> • Age 18-45 years • Able to read and understand Swedish language • Bilateral ACL injury with 12 years as a maximum time from the first injury 	<ul style="list-style-type: none"> • Major activity-limiting disorders/injury • Combined intracondylar fracture • Total rupture of the medial or lateral collateral ligament • Posterior cruciate ligament injury

Data collection

Study I

In *study I*, patient-reported outcomes were collected via several questionnaires:

- A study-specific questionnaire
- Knee injury and Osteoarthritis Outcome Score (KOOS) [185]
- International Knee Documentation Committee (IKDC) Subjective Knee Form [96,97]
- Anterior Cruciate Ligament-Quality of Life scale (ACL-QoL) [135]
- Anterior Cruciate Ligament-Return to Sport after Injury scale (ACL-RSI) [115,228]
- Swedish universities Scales of Personality (SSP) [78]
- Sport Multidimensional Perfectionism Scale (SMPS) [51]
- Tegner activity scale [210].

The study-specific questionnaire included information about:

- Demographic data
- Injury related information
- Duration of supervised rehabilitation before and after ACLR, whether contact with the physiotherapist was finished and an appraisal of the importance of the physiotherapist for current knee function, with responses on a 5-response scale ranging from “necessary for my current knee function” to “not necessary at all”
- Satisfaction with current knee function (seven-point scale [39]) and activity level (a scale ranging from 1 (not satisfied at all) to 10 (very satisfied) [16])
- Motivation to return to the previous activity level, and to RTS was assessed using three questions that were graded using a scale ranging from 1 (low motivation) to 10 (high motivation) [12,69]
- Football-related factors included playing position, preferred kicking leg and level of football play before ACL injury
- Reasons for playing football before ACL injury (by importance) [54]
- Risk behaviour during football before ACL injury; responses on a 4-response scale [54,115]
- Any reason for not returning to football.

Study II

The female football players were given a questionnaire about demographic and football-related factors to fill out at home before the testing session. Players with ACLR also filled out the IKDC Subjective Knee Form [96,97]. Data collection (Figure 2) occurred at a single testing session and measuring;

- Players' height and weight
- General joint laxity assessment using the Beighton method [21]
- General clinical knee examination
- Knee joint ROM
- Knee stability- manually with the Lachman and pivot shift tests and instrumented with KT-1000 arthrometer (MEDmetric, Corp., San Diego, CA) [18,46].

The players performed a postural control test and a battery of 5 hop tests as measures of functional performance;

- Star excursion balance test (SEBT) [172]
- One-leg hop test for distance [77]
- Five jump test (5JT) [36]
- DVJ [141-143]
- Tuck jump [140]
- Side hop [77].

Figure 2. Eleven cities (Umeå, Vansbro, Stockholm, Norrköping, Linköping, Jönköping, Hultsfred, Västervik, Halmstad, Växjö and Kalmar) in Sweden where the testing of female football players were performed in study II.

All measurements and tests of the players were performed and supervised by the same experienced test leader (AF). The hop tests were selected to reflect various qualities (movement asymmetries, maximum and endurance hop performance) with different demands, and due to their measurement properties and feasibility for use in a clinical setting.

Study III

Data extracted from the Swedish national ACL register were;

- Age at primary ACLR (divided into <16, 16–25, 26–35, or >35 years)
- Sex
- Primary injury to the right or left knee
- Activity at the time of primary injury (“football”, “other contact ball sports”, “other sports/recreation”, and “other causes”)
- Pre-operative KOOS and EQ-5D scores
- Time between injury and primary ACLR (divided into 0–90 days, 91–365 days, or >365 days) [104]
- Presence of any concomitant injuries (lesion of the medial or lateral meniscus or cartilage as registered at the primary ACLR)
- Graft type (BPTB autograft, HT autograft, or other grafts).

Outcome variables included additional revision or contralateral ACLR. Patients were followed up to the first additional revision ACLR or contralateral ACLR, or up to the end of the follow-up period.

Study IV

Four questionnaires were sent to patients with bilateral ACL injuries:

- Study-specific questionnaire
- KOOS [185]
- ACL-QoL [135]
- EQ-5D [177].

Two further questionnaires were filled in via a telephone interview:

- Lysholm knee score [210]
- Tegner activity scale [210].

In the telephone interview, patients graded both the first and second injured knee, and scores were noted for each knee. For the analysis of the Lysholm knee score, the lower score for either knee was used for each question. Patients reported the kind of physical activity they participated in before the first injury, before the second injury, and currently. The researcher noted the appropriate grading on the scale. Questions about the activities performed when patients sustained their first and second ACL injuries were asked.

The study-specific questionnaire included information about:

- BMI
- Occupation
- Change of profession or study plans because of his/her knee/knees
- Any other injuries that affected activity level
- Family history of ACL injury (i.e. ACL injury in a first relative)
- Any reason for not RTS
- Estimation of their current global knee function in the first and second injured knees (scales ranging from 1 [very bad] to 10 [normal, as before the injury])
- Satisfaction with current knee function (seven-point scale [39]), knee function in the first and second injured knees and activity level (scales ranging from 1 [not satisfied at all] to 10 [very satisfied] [16]).

For patients with unilateral ACLR, the KOOS, ACL-QoL, Tegner activity scale, questions about the type of activity and activity level before ACL injury and currently, satisfaction with their knee function and activity level were used for comparison to patients with bilateral ACL injuries.

Outcome measures

An overview of the outcome measures used in the studies I-IV is presented in Table 6.

Table 6. Overview of the outcome measures in studies I-IV

Outcome measures	Study			
	I	II	III	IV
Patient-reported				
Study-specific questions	X	X		X
KOOS	X		X	X
ACL-QoL	X			X
EQ-5D			X	X
Lysholm knee score				X
Tegner activity scale	X			X
Satisfaction with knee function	X			X
IKDC Subjective Knee Form	X	X		
ACL-RSI	X			
SSP	X			
SMPS	X			
Clinical assessment				
Beighton score		X		
Knee joint range of motion (extension-flexion)		X		
Knee joint examination		X		
Leg length		X		
KT-1000		X		
Functional performance tests				
Star excursion balance test		X		
One-leg hop for distance		X		
Five jump		X		
Side hop		X		
Drop vertical jump		X		
Tuck jump		X		

KOOS; Knee injury and Osteoarthritis Outcome Score, ACL-QoL; Anterior Cruciate Ligament-Quality of Life, EQ-5D; Euroqol Index Five Dimensions, IKDC; International Knee Documentation Committee, ACL-RSI; Anterior Cruciate Ligament-Return to Sport after Injury scale, SSP; Swedish universities Scales of Personality, SMPS; Sport Multidimensional Perfectionism Scale

Patient-reported outcome measures

Knee function and knee-related quality of life

- Knee injury and Osteoarthritis Outcome Score (KOOS)

The KOOS [185] evaluates knee-related problems in five subscales: pain, symptoms, activities of daily living (ADL), function in sports and recreation (Sport/Rec), and knee-related quality of life (QoL). A subscale is scored, ranging from 0 (worst) to 100 (best) [184,185]. The subscales Sport/Rec and QoL are the most responsive for patients after ACLR [80]. The KOOS has adequate internal

consistency (Cronbach's α coefficients for the five subscales: Pain: 0.84–0.91, Symptoms: 0.25–0.75, ADL: 0.94–0.96, Sport/Rec: 0.85–0.89 and QoL: 0.64–0.9), moderate to high test-retest reliability (Intraclass correlation coefficient [ICC] 0.61–0.95) and convergent and divergent construct validity [43]. The suggested minimal clinically important difference (MCID) is 8–10 points on an individual subscale [184]. The KOOS is useful for evaluating the short- and long-term consequences (i.e. OA) of an ACL injury [224]. Low self-reported knee function (< 80) in the subscales ADL, Sport/Rec and QoL in adolescent female football is associated with an increased risk of sustaining a future knee injury [42].

- Anterior Cruciate Ligament-Quality of Life scale (ACL-QoL)

The ACL-QoL [135] is an injury-specific questionnaire that evaluates health-related quality of life. It consists of 31 items (32 items in the Swedish version), divided into five different subscales: symptoms, physical complaints, work-related concerns, physical activity and sport participation, and life-style and social concerns [135]. It has been shown to be reliable, valid and responsive to clinical change [100]. In the Swedish version of the scale, scores range from 1 (worse) to 10 (best), and this version has good to high test-retest reliability (ICC 0.71–0.93) and high internal consistency (Cronbach's α 0.97) (Kvist, unpublished data, 2006). The ACL-QoL has excellent reliability with an average error in test-retest reliability of 6%, is responsive to clinical change, and a valid construct of quality of life with a range of scores from 8 to 99 [135]. The suggested MCID is 15 points (0–100 scale) [73].

- Lysholm knee score

The Lysholm knee score consists of eight questions that evaluate subjective perception of pain and instability. The score ranges from 0 (worst) to 100 (best), and a score ≥ 95 indicates no knee problem (excellent), 84–94 indicates problems during sports (good), 83–65 indicates knee problems in sports and sometimes in daily life (fair), and < 65 indicates problems in daily life (poor) [109,210]. The Lysholm knee score has good reliability (ICC 0.95), validity and responsiveness to clinical change [130]. The Lysholm knee score has acceptable psychometric parameters (test-retest reliability, internal consistency, floor and ceiling effects, criterion validity, construct validity, and responsiveness). The minimal detectable change (MDC) is 8.9 [31]. The Lysholm knee score does not measure functioning in ADL, sports, and recreational activities [224], but is easy to use and has been used with ACL populations for 30 years, in combination with the Tegner activity scale [31].

- International Knee Documentation Committee (IKDC) Subjective Knee Form [96,97]

IKDC Subjective Knee Form contains 10 items (18 questions) that evaluate knee symptoms, function, and activity limitations, in daily living and sports. The IKDC Subjective Knee Form scores range from 0 (worst) to 100 (best) and it is valid, responsive for change and test-retest reliable [74,96,97]. The MDC is 8.8-20.5 points [43]. The IKDC Subjective Knee Form assesses any condition involving the knee, and can be used to compare between groups with different knee diagnoses. The IKDC Subjective Knee Form is considered more useful than the KOOS to evaluate patients with recent ACL injury, and those in the first year after ACLR [224].

- Satisfaction with knee function

Satisfaction with knee function was measured with the question: “If you had to live with your current knee function for the rest of your life just the way it has been in the last week, would you feel?”. The response options ranged from 1 to 7: delighted (1), pleased, mostly satisfied, mixed, mostly dissatisfied, unhappy, and terrible (7) [39]. Cherkin et al [39] found the scale to be valid and reliable in patients with low back pain. There is also known-groups validity for this question in ACLR population [15].

Health-related quality of life

- Euroqol Index Five Dimensions (EQ-5D) and Euroqol Visual Analogue Scale (EQ VAS)

The EQ-5D assesses health-related quality of life [177]. It consists of two parts: the EQ-5D descriptive system and the EQ VAS. The EQ-5D descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has a three-point scale: no problems, some problems, and extreme problems. The scores are presented as different index values ranging from <0 (worst) to 1 (best) elicited from a general population. In this thesis, the UK EQ-5D index was used, which is the original for estimating EQ-5D index scores [49]. The second part, the EQ VAS, records self-rated health on a vertical VAS (0-100) where the endpoints are “Worst imaginable health state” (0) and “Best imaginable health state” (100). The EQ-5D is reliable and valid [32]. MCID have been suggested: UK EQ-5D index 0.08 and EQ-5D VAS 8-12 [170].

Activity level

- Tegner activity scale

The Tegner activity scale assesses activity level and grades activity with regard to knee function on a scale from 0 to 10, where 0 corresponds to the least strenuous activity for the knee and 10 is equal to participation in football on a national level [210]. The Tegner activity scale score has acceptable psychometric parameters (test-retest reliability, internal consistency, floor and ceiling effects, criterion validity, construct validity, and responsiveness). The MDC is 1 point [31]. Sports not included in the original Tegner activity scale were graded for these studies based on the consensus of an expert group of orthopaedic surgeons, physical therapists, and researchers (Figure 3). The Tegner activity scale has been criticized because it relates activity to sports, and not to the function required. Despite this, the Tegner activity scale is commonly used [235].

10. Competitive sports:	Football– national or international level, <i>Acrobatics, American football, Figure-skating, Rugby</i>
9. Competitive sports:	Football– lower divisions, Ice hockey, Wrestling, Gymnastics, <i>Mogul skiing</i>
Recreational sports:	<i>Acrobatics, American football. Figure-skating, Rugby</i>
8. Competitive sports:	Bandy, Squash, Badminton, Athletics (jumpings, etc), Downhill skiing, <i>Ski jumping, Javelin, Floorball, Taekwondo, Budo sports</i>
Recreational sports:	<i>Mogul skiing, Wrestling</i>
7. Competitive sports:	Tennis, Athletics (running), Motocross, Speedway, Handball, Basketball, <i>Volleyball</i>
Recreational sports:	Football, Bandy, Ice hockey, Squash, Athletics (jumping), Cross-country track findings, <i>Ski jumping, Javelin, Floorball, Budo sports</i>
6. Competitive sports:	<i>Snowboard, Telemark skiing</i>
Recreational sports:	Tennis, Badminton, Handball, Basketball, <i>Volleyball</i> , Downhill skiing, Jogging at least 5 times/week
5. Competitive sports:	Cycling, Cross-country skiing, <i>Fencing, Aerobics</i>
Recreational sports:	Jogging on uneven ground at least twice a week, <i>Snowboard, Telemark skiing</i>
Work:	Heavy labor (e.g. fireman)
4. Recreational sports:	Cycling, Cross-country skiing, Jogging on even ground at least twice a week, <i>Boxing, Aerobics, Weight lifting, Discus throwing</i>
Work:	Moderately heavy labor (e.g. truck driving)
3. Competitive/recreational sports:	Swimming, Walking in forest possible, <i>Dancing, Table tennis, Water polo, Windsurfing</i>
Work:	Light labor (e.g. nursing)
2. Recreational sports:	Walking on uneven ground, <i>Strength training, Bowling, Curling, Golf, Sailing, Horse riding</i>
Work:	Light labor (e.g. shop assistant, Preschool teacher)
1. Recreational sports:	Walking on even ground, <i>Bridge, Archery, Canoeing, Shooting</i>
Work:	Sedentary work (e.g. barber, office work)
0.	Sick leave or disability pension because of knee problems

Figure 3. Tegner activity scale with some sports added (italics) based on the consensus of an expert group to use for study I and IV.

Personality and psychological components

- Anterior Cruciate Ligament-Return to Sport after Injury scale (ACL-RSI)

The ACL-RSI [115,228] is a questionnaire that measures psychological components in relation to RTS. The scale evaluates emotions (five items), risk appraisal (two items) and confidence in knee function and performance (five items). Each item is assessed using a 10-point numeric scale (VAS in the original ACL-RSI). Answers are summed and averaged to index a total score ranging from 1 (worse)-10 (best) in the Swedish version. A higher score indicates more positive psychological readiness to RTS. The ACL-RSI has high internal consistency (Cronbach's α 0.95), high reproducibility (ICC 0.89), and moderately strong correlation with other impairment-specific questionnaires, demonstrating evidence of construct validity [115]. The MDC is 1.9 points (individually) and 0.3 points (comparing groups) (1-10 scale) [115]. A score of ≥ 56 points (0-100 scale) on ACL-RSI pre-ACLR and after 4 months post-ACLR predicted return to the pre-injury level of sport [11].

- Swedish universities Scales of Personality (SSP)

The SSP [78] is a questionnaire comprising 91 questions. It highlights 13 personality traits (7 questions in each area): somatic anxiety, psychic anxiety, stress susceptibility, lack of assertiveness, impulsiveness, adventure seeking, detachment, social desirability, embitterment, trait irritability, mistrust, verbal trait aggression, and physical trait aggression. Each question is scored on a 4-point Likert scale, with possible responses ranging from 1 (does not apply at all) to 4 (applies completely). The score is summarized in each personality trait and computed into a normative standard T-score. The T-score is constructed to have a mean of 50 and a standard deviation of 10. The Cronbach's alpha coefficients ranged from 0.59 to 0.84. The mean inter-item correlations (MIIC) range from 0.17 to 0.43 and the median inter-correlation is low (0.25) [78].

The SSP has been used in evaluation of ACL outcome where low ratings on trait embitterment were correlated to a superior KOOS score at 5.6 years after ACL injury [205]. The SSP has also been used in the football context and higher scores in somatic trait anxiety [98,99,101], mistrust [101], psychic trait anxiety, stress susceptibility, and trait irritability [98] were predictors of occurrence of sport injuries among junior [101], senior [98] and elite football players [99].

- Sport Multidimensional Perfectionism Scale (SMPS)

The SMPS [71] evaluates perfectionism in sports (considered an enduring personality trait) [93]. It consists of 30 statements, divided into four dimensions of "perfectionism" in sport. These dimensions relate to personal standards (7 statements, e.g. "I have extremely high goals for myself in my sport"), concern over mistakes (8 statements, e.g. "Even if I fail slightly in competition, for me, it is as

bad as being a complete failure”) and perceived pressure from parents (9 statements e.g. “My parents set very high standards for me in my sport”) or the coach (6 statements e.g. “I feel like my coach criticises me for doing things less than perfectly in competition”). Each statement has five possible answers from 1 = strongly disagree to 5 = absolutely agree. Sub-statements give an average value (1-5) with higher scores indicating a high degree of perfectionism. The SMPS has good internal consistency (Cronbach’s α 0.76–0.89) [51] and convergent and divergent construct validity [50]. The Swedish version of SMPS has not been tested for reliability and validity. Clinically relevant differences are unclear.

- **Motivation**

Motivation to return to the previous activity level was assessed using three questions, modified from Gobbi et al [69] and previously used by Arden et al [12], that are rated on a 10-point scale. Higher scores indicate higher motivation. There is some evidence of known-groups validity in ACLR population regarding the three motivation questions [12]:

1. How important is it for you to return to your previous activity level?
2. Did you think it is possible for you to return to your previous activity level?
3. How much are you willing to invest to return to your previous activity level?

Clinical assessment

Clinical assessments were used in study II.

- **Beighton’s score**

General joint laxity assessment was performed using the Beighton method [21]. This test is based on the existence of laxity in the following joints: passive dorsiflexion over 90° of the fifth metacarpophalangeal joints, passive apposition of the thumbs to the flexor aspects of the forearms, hyperextension of the elbows and knees beyond 10° and the ability to flex the trunk with knee extended and touch the floor with the palms of the hands rested easily on the floor (Figure 4) [21]. The score for this test range from 0–9, with >4 indicating generalized joint laxity. The intra- and inter-tester reliability of the 0–9 scale and category scores are good to very good (Spearman ρ = 0.81–0.86 and 0.75–0.87, respectively) [29].

Figure 4. The Beighton’s score positions. Reprinted with permission from AXELINA. Copyright AXELINA.

- Knee joint range of motion (ROM)

Knee joint ROM, extension and flexion, was measured in supine position using a goniometer. The intra-tester reliability of knee joint ROM measurements obtained with a goniometer is high (ICC 0.98-0.99) [227].

- Leg length

Leg length (from the anterior superior iliac spine to the center of the medial malleolus) and tibia length (lateral knee joint line to the center of the lateral malleolus) were measured with a measuring tape in supine position to adjust some of the test scores. Clinician-measured tibia length was highly correlated with the static laboratory-based motion analysis ($r=0.98$) [143].

- Knee joint stability

Knee joint stability was evaluated manually with the Lachman and pivot shift tests. The instrumented knee joint stability test was performed using a KT-1000 arthrometer (MEDmetric, Corp., San Diego, CA) to assess the amount of anterior translation of the tibia relative to the femur. The manual maximum test, where one hand pulls the tibia forward, was used. A side-to-side difference of ≥ 3 mm was defined as abnormal [18,46]. The inter-rater reliability of KT-1000 is good (ICC, 0.79) with experienced raters [23]. Side-to-side difference of < 3 mm on instrumented testing is considered a criterion for successful outcome up to 2 years after ACLR [125].

Functional performance tests

Functional performance tests were used in study II. The limb symmetry index (LSI) was calculated as “ACLR limb/uninvolved limb $\times 100$ ” or “non-dominant limb/dominant limb $\times 100$ ” for the controls and used as one variable for the Star excursion balance test, one-leg hop for distance, and side hop.

- Star Excursion Balance Test (SEBT) for evaluating postural control [172] (Figure 5).

Players stood on one leg (the measured leg) in the middle of a star with the standing foot on a standardized position (great toe at 10 cm in the anteriorly projected line). The star was drawn on a plastic mat so the surface was standardised. The aim was to reach with the free limb as far as possible, maintaining balance, in the (i) anterior, (ii) posteromedial and (iii) posterolateral directions. Players had three practice trials and then performed three attempts in each direction. The hands were placed behind the back. The best result (m) of the three attempts was normalised to leg length (test value/leg length $\times 100$). A composite score was calculated for each limb as the average of the three normalised measurements in the different directions [121]. The SEBT has high test re-test and inter-rater reliability (ICC, 0.82–0.98) [41,172]. A difference between limbs in SEBT in the anterior

or reach distance ≥ 0.04 m and composite score reach distance $\leq 94\%$ of limb length predicted lower extremity injuries in high school basketball players [172].

Figure 5. Star excursion balance test.

- One-leg hop for distance measures maximum single hop performance [77] (Figure 6).

Players hopped as far as possible, taking off and landing on the same foot, with a controlled, balanced landing. The hands were placed behind the back. Each player performed two practice trials on each leg, followed by three maximum trials. If a player increased her hop lengths in all three hops, additional hops were performed until no increase was measured. The one-leg hop for distance has excellent test re-test reliability (ICC, 0.88–0.98) [77,178]. The LSI can vary $\pm 5.7\%$ due to measurement error, and the MDC is 8.1% [178]

- Five jump test (5JT) estimates lower limb explosive power [36] (Figure 6).

Players started the 5JT standing on both feet, then performed a series of five jumps with alternating left and right foot contacts, finally landing on both feet to conclude the test. Players were instructed to jump as far as possible with a controlled, balanced landing. They performed two practice trials, followed by three accepted maximum trials. The 5JT has high test re-test reliability (ICC, 0.91) [37].

- Side hop measures performance while developing fatigue [77] (Figure 6).

Players stood on the test leg and jumped from side to side outside two parallel strips of tape (40 cm apart). The hands were placed behind the back. Players were instructed to perform as many hops as possible for 30 seconds. If the foot touched the strips of tape, the hop was not counted. All trials were recorded to enable analysis of successful jumps. Players were permitted to practice the side hop task on each leg until they felt comfortable before the test trial. Players had

to rest for at least 1 minute before testing the opposite leg. The side hop has high test re-test reliability (ICC, 0.87–0.95) [77].

Figure 6. One-leg hop for distance, five jump test and side hop.

- Drop vertical jump (DVJ) measures knee motion in the frontal plane [143] (Figure 7).

Players stood on a 31 cm high box with their feet on marks that were 35 cm apart. The instruction was to drop down and immediately jump as high as possible, while trying to reach, with both arms, a suspended ball that was placed at a height of 260 cm. Data were captured with two video cameras (Panasonic HC-V500M), 70 cm high. One camera was placed 3.5 m from the player in the frontal plane. The second camera was placed 2.5 m from the expected landing position, in the sagittal plane. Video was recorded at 50Hz with AVCHD Full HD at 1080/50p. To ensure that the cameras were aligned with the target motion plane, pre-set templates were used, where angles were checked and marked. The three jumps were assessed from the films.

The assessment was based on the quality of the performed jump in the frontal plane including symmetry in the take-off and landing from the box, knee motion, feet position at landing, and weight displacement. The worst assessed jump of the three trials, based on all criteria, was used in the analysis. Knee motion (medial/valgus or lateral/varus knee displacement) was calculated in metres as the frontal plane displacement of the knee from initial contact to the end of the deceleration phase of the DVJ. The knee flexion ROM (degrees) was also measured from initial contact to the end of the deceleration phase of the DVJ. To simplify the measurement, the greater trochanter, the lateral knee joint line, the head of the fibula, lateral malleolus, patella tendon, and center of the patella were marked with a marker pen. Knee motion and flexion angle, measured with motion analysis software Dartfish ProSuite (Dartfish Ltd, Fribourg, Switzerland), were used to calculate KAM according to a nomogram, to predict the probability of high knee

abduction moment (pKAM) [141]. These calculations were assessed from the films by the same person (IM), who was blinded to group belonging. The range of pKAM is 0–1, which is comparable to 0 (lowest)–100% (highest). The nomogram is based on the player's weight, tibia length, knee motion in the frontal plane, and knee flexion ROM, and a surrogate value for hamstring–quadriceps ratio (multiplying the player's mass by 0.01 and adding the resultant value to 1.10) [141–143].

This clinic-based assessment technique has strong correlation with simultaneous laboratory-based measurements [141,143], with most variables having good to excellent reliability (ICC, 0.75–0.99) [63]. Biomechanical laboratory measurements predict pKAM landing mechanics with high sensitivity (85%) and specificity (93%) [141]. Clinical correlates to laboratory-based measures and pKAM is predicted with high sensitivity (73–84%) and specificity (67–71%) [141–143].

- Tuck jump identifies movement asymmetries in a plyometric activity [140] (Figure 7).

Players performed repeated tuck jumps for 10 seconds. The instructions were to lift the knees to hip height and attempt to land in the same place as the player took off from. Players performed one or two practice tuck jumps before the measured trial. Two standard video cameras, one in the frontal and one in the sagittal plane, 5 m and 3.5 m respectively from the player, were used. The tuck jump was analyzed from the films according to a clinician-friendly screening tool [85], by the same blinded assessor (IM). The screening tool consists of 10 criteria grouped into 3 areas: knee and thigh motion, foot position during landing, and plyometric technique. Six or more flawed techniques are considered as abnormal. Flawed techniques may include: thighs not equal side-to-side, lower extremity valgus at landing, foot placement not parallel, pause between jumps, techniques declining during the 10 seconds. Inter- ($k = 0.88$) and intra-tester reliability ($k = 0.86$ – 1.0) are very good to excellent when the test is analysed from video [85]. Further research is needed to determine the validity of the screening tool [140].

Figure 7. The drop vertical jump and tuck jump.

Recommended guidelines for successful outcome

In study II, values indicating scores outside recommended guidelines were as follows:

- For the SEBT, a difference between limbs in the anterior reach distance ≥ 0.04 m and composite score reach distance $\leq 94\%$ of limb length [172]
- For the hop tests, an LSI of $<90\%$ and $>110\%$ [77]
- For the tuck jump, six or more flawed techniques [140].

No recommended guidelines regarding cut-offs for DVJ were available. Therefore, the tertile of the highest values, based on the total sample in the present study (all 154 players), in knee motion and side difference in frontal plane, and pKAM measured with DVJ were analyzed and used as a cut-off value.

Statistical methods

All statistical analyses were performed using IBM SPSS Statistics for Windows (Version 20.0-22.0. Armonk, NY: IBM Corp.). Mean and standard deviation (SD) or median and interquartile range (IQR) were calculated for descriptive statistics depending on normality of data. Statistical significance was defined as $P < 0.05$ for all analyses in all studies. Between-group comparisons were made using the Student's t -test (quantitative, normally distributed data), Mann-Whitney U test (ordinal data or non-normal distributions), chi-square test and Fisher's exact test (nominal data) as appropriate.

In study I, logistic regression analysis was used to study the association between factors related to the player and the ACL injury, and having returned to football or not. To reduce the number of variables in the final multiple logistic regression analyses, variables that were significant at a level of $P < 0.1$ in simple logistic regression analysis were selected and checked for multicollinearity using a variance inflation factor (VIF) of >5 using the linear regression method. No variable was excluded due to multicollinearity. The remaining 12 explanatory variables (age at survey, smoker, level of play before ACL injury, time between injury and ACLR, presence of articular cartilage injury, motivation (3 questions), most important reason for playing football before the ACL injury, personal standards, impulsiveness and adventure seeking) were then entered into a backwards stepwise multiple logistic regression model.

In study II, Paired-sample t -tests and the Wilcoxon signed ranks test for normal and non-normally distributed variables, respectively, were used to compare differences between limbs within players with ACLR and within controls.

In study III, multivariable Cox proportional hazards regression models were used to estimate associations between predictors (i.e., age, sex, injury side, activity performed at the time of first ACL injury, time from ACL injury to primary ACLR, presence of concomitant injuries) and the occurrence of additional ACLR (revision or contralateral) during the follow-up period. The final models were determined using a backwards procedure starting with the inclusion of all predictors, and performing stepwise deletion of the variables with the highest *P* values, until only significant variables remained. Several items were analysed separately using simple Cox regression models, including preoperative KOOS and EQ-5D due to low response rates. Graft type was analysed separately due to a skewed distribution. Hazard ratios (HRs) with 95% confidence intervals (CIs) and *P* values were included in the models. The statistical tests used are specified in Table 7.

Table 7. Statistical methods used in studies I-IV

Statistical methods	Study			
	I	II	III	IV
Student's <i>t</i> -test	x	x		x
Paired-sample <i>t</i> -test		x		
Mann-Whitney <i>U</i> test	x	x		x
Wilcoxon signed ranks test		x		
Chi-square test	x	x		x
Fisher's exact test	x	x		x
Logistic regression analysis	x			
Multivariable Cox proportional hazards regression models			x	

Sample-size calculation

In study I and IV, a sample-size calculation showed that 70 players in each group needed to be included to detect at least a 10% difference between groups in the questionnaire KOOS QoL (SD 21) [113] at an alpha level of 0.05 and with 80% power. In study II, a sample-size calculation showed that 73 players in each group needed to be included to detect at least a 10% difference in the one-leg hop for distance (SD 28) [77] at an alpha level of 0.05 and with 80% power.

Ethical considerations

The Regional Ethical Review Board in Linköping, Sweden approved all studies.

Study I Dnr 2012/24–31

Study II Dnr 2012/24–31 and 2013/75–32

Study III Dnr: 2013/321-31

Study IV Dnr: 2010/10-31 and 2012/425-32

The general ethical principles for medical research proposed in the Declaration of Helsinki were followed in all studies. Before entering the study, all players and patients received verbal and written information about the study. Oral or written informed consent was obtained from all players and patients in study I, II and IV by responding to the questionnaires. All patients in study III were informed when entering their data in the Swedish national ACL register that their data could be used in research. Study III was also approved by the board of the Swedish national ACL register.

RESULTS

Factors associated with playing football after ACLR (Study I)

There were 274 responders (60%), 182 of whom were included in the analyses. Ninety-four out of 182 (52%) had returned to football and were currently playing, while 88 (48%) had not returned after ACLR (Figure 1). At follow-up, the players who had sustained an ACL graft rupture ($n=15$) or a contralateral ACL injury ($n=20$), and those 36 females who had returned but were currently not playing, were not included in the analysis (Figure 8).

Figure 8. Flowchart of the female football players who responded to the questionnaires. Of the 254 football players, 35 (14%) had sustained a new ACL injury at follow-up.

Available data for the 186 non-responders (age at survey, age at ACLR, time from ACLR to follow-up, presence of concomitant injuries at ACLR) showed a difference only for the presence of meniscal injuries; the non-responders had fewer meniscus injuries (26% vs. 41%, $P = 0.002$).

The median follow-up after ACLR was 18 months (IQR 13). The current players had played football with the team for a median of 8 months (IQR 13). The most important reason for playing football among current players, before the ACL injury and after the ACLR was having fun (Figure 9).

Figure 9. The most important reasons for playing football among current players before the ACL injury and after the ACLR.

The reasons for not currently playing or not returning to football are presented in Table 8.

Table 8. Reasons for not returning or not currently playing football after ACLR (proportion of responses ranked by players as most important)

Reasons for not returning, n (%)	Had not returned to football n = 88	Returned to football, but not currently playing n = 36	Sustained an ACL graft rupture (n = 13) or contralateral ACL injury (n = 11) and not currently playing
Poor knee function	12 (14)	4 (11)	
Do not trust the knee	24 (28)	1 (3)	1 (4)
Fear getting a new injury	22 (25)	6 (17)	5 (21)
Change in team or coach	13 (15)	9 (25)	1 (4)
Family or work commitments	5 (6)	6 (17)	
Not fun to play anymore	2 (2)	4 (11)	
Had sustained a new injury	2 (2)	2 (6)	16 (67)
Other reasons	7 (8)	4 (11)	1 (4)
Total	87^a	36	24

^aMissing data from one player.

Of the 94 current players (information missing for two players), 54 (59%) played at the same level as before the ACL injury, 20 (22%) at a higher level and 18 (19%) at a lower level (Figure 10).

Figure 10. The current players' playing level compared with before the ACL injury.

Comparisons between current players and those who had not returned showed that current players were characterised by;

- Fewer non-smokers (1% vs. 8%, $P = 0.030$)
- Higher playing level (11% elite level vs. 2%, $P = 0.009$)
- Shorter time between injury and ACLR (median 140.5, IQR 138 vs. 158, IQR 129 days, $P = 0.047$)
- Considered the physiotherapist contact more important for knee function (88% vs. 70% rated the physiotherapist contact necessary for the current knee function) ($P = 0.001$)
- Higher motivation to return to football (median 10, 9, 10 vs. 9, 6 and 8 on the three motivation questions, $P < 0.001$)
- More often cited “to win” as the main reason for playing football before the ACL injury (22% vs. 8%, $P = 0.028$)
- Higher scores for the SSP personality trait “adventure seeking” (54.3 ± 8.5 vs. 51.4 ± 9.4 points, $P = 0.041$)
- Higher scores for the dimension “personal standard” on the SMPS (3.2 ± 1.0 vs. 2.7 ± 1.1 points, $P = 0.002$).

Logistic regression analysis showed that motivation (“How important was it for you to return to your previous activity level?” and “Did you think that it was possible for you to return to your previous activity level?”) and days between injury and ACLR were factors that were associated with returning to football (Figure 11).

Figure 11. Significant ($P < 0.05$) factors related to returning to football after ACLR. In the final step of backwards stepwise multiple logistic regression analysis, ACLR within one year increased the odds of playing football by 4.7–5.6-times (using >12 months as the reference). Every point increase in motivation (1–10 scale) was associated with 1.5-fold higher odds of having returned to football.

Functional performance in female football players with or without an ACL reconstructed knee (Study II)

Compared to controls, on clinical examination, players with ACLR had a higher proportion of;

- ≥ 3 mm side-to-side differences in anterior translation of the tibia in relation to the femur, measured with KT-1000, 39% vs. 4% ($P < 0.001$)
- Lachman graded as a soft endpoint, 22% vs. 0% ($P < 0.001$)
- Rotational stability graded as a positive pivot shift, 6% vs. 0% ($P = 0.029$)
- $\geq 10^\circ$ side-to-side differences in flexion, 21% vs. 0% ($P < 0.001$)
- $\geq 5^\circ$ side-to-side differences in extension, 30% vs. 12% ($P < 0.001$).

Within-group comparisons between limbs

The reconstructed and uninvolved limbs of players with ACLR did not differ in any of the tests. The controls had very small (less than 0.01 m) but statistically significant differences between dominant and non-dominant limbs on the SEBT anterior ($P = 0.042$), posteromedial ($P = 0.029$), and composite scores ($P = 0.013$), with better performance of the non-dominant limb.

Between-group comparisons

The only between-group differences were that players with ACLR;

- Performed worse than controls on the 5JT (mean 8.75 ± 1.05 vs. 9.09 ± 0.89 m, $P = 0.034$)
- Had significantly less valgus (medial) motion (median 0.028 m, IQR 0.049 vs. 0.045 m, IQR 0.043, $P = 0.004$)
- Had lower pKAM (median 69.2%, IQR 44.4 vs. 79.8%, IQR 44.8, $P = 0.043$).

The proportion of players with results classified outside recommended guidelines was 9–49% for players with ACLR and 10–44% for knee-healthy controls (all $P > 0.05$ for between-group differences). Only fourteen (18%) players with ACLR and 15 (19%) knee-healthy controls had results that met the recommended guidelines for all five tests ($P = 0.837$).

Predictors for additional ACLR (Study III)

There were low response rates for KOOS (68–69%) and EQ-5D (60–63%) and, therefore, these parameters were not included in the final Cox regression multivariable model. Simple Cox regression analyses showed that revision ACLR was significantly predicted by lower rating;

- In the KOOS symptoms subscale (more knee-related problems; HR 0.993)
- On the EQ-5D index (HR, 0.568)
- On EQ VAS (HR, 0.994) indicating worse health-related QoL.

This meant that every 10-point increase in the KOOS symptoms subscale or in the EQ VAS, was accompanied by a 7% or 6% decrease, respectively, in the rate of revision ACLR. Similarly, a change in the EQ-5D index from 0 to 1 decreased the rate of revision ACLR by 43%. On the contrary, higher ratings in the KOOS subscales pain, ADL, Sport/Rec, and QoL (indicating less knee-related problems) were associated with an increased rate of contralateral ACLR (HR, 1.006–1.010).

Significant predictors for revision and contralateral ACLR in the multivariable Cox model included;

- Younger age
- Short time between injury and ACLR
- Playing football at the time of injury.

Compared to the oldest age group (>35 years), the rates of revision and contralateral ACLR were over 4-fold higher in patients aged less than 16 years, and up to 3-fold higher in patients of 16–25 years. Compared with having primary ACLR >365 days after injury, the rate of revision and contralateral ACLR was 3-fold and 2-fold higher, respectively, when the primary ACLR was within 90 days after the injury, and 51–55% higher when the primary ACLR was within 91–365 days of injury. With football as the reference group, incurring the primary injury while playing other contact ball sports or other sports/recreation was associated with 21–39% lower rates of revision and contralateral ACLR (Figure 12).

Figure 12. Final Cox regression models with variables significantly ($P < 0.05$) associated with additional ACLR; age (reference is > 35 years), time between injury and ACLR (reference is > 365 days), and activity performed at primary ACL injury (reference is football).

Knee function, quality of life and activity level in female football players with an ACLR (Study I), and in patients with bilateral ACL injuries and unilateral ACLR (Study IV)

Comparisons between current players and those who had not returned to football (Study I)

There were significant differences favouring current female football players ($P < 0.001$) on the Tegner activity scale score, satisfaction with activity level and satisfaction with knee function; there were also significant differences on the KOOS (Figure 13), IKDC Subjective Knee Form, ACL-QoL and ACL-RSI scales (Table 9).

Figure 13. Knee injury and Osteoarthritis Outcome Score (KOOS) values given as means for current female football player^a ($n = 90$; 4 missing answers), players who had returned but currently not playing^b ($n = 31$; 5 missing answers), females who had not returned after ACLR^c ($n = 82$; 6 missing answers) (study I). KOOS values are also presented for patients with bilateral ACL injury^d ($n = 64$; 2 missing answers) and unilateral ACLR^e (initially $n = 182$; 2,5,3,8 and 6 missing answers in each subscale) (study IV).

Table 9. Current activity level and appraisal of knee function of female football players after ACLR (study I), and of patients with bilateral ACL injuries compared to patients with unilateral ACLR (study IV)

Current activity level and appraisal of knee function	Returned to football <i>n</i> = 94	Had not returned <i>n</i> = 88	Returned, but currently not playing <i>n</i> = 36	Returned vs. had not returned	Patients with bilateral injuries <i>n</i> = 66	Patients with unilateral ACLR <i>n</i> = 182	<i>P</i> Patients with bilateral injuries vs. unilateral ACLR
<i>Current activity level</i>							
Current activity level, Tegner activity scale (0–10), median (IQR)	9 (0)	3 (2)	3 (2)	< 0.001	4 (3.25)	4 (5) ^a	0.18
Satisfied with current activity level (1–10), median (IQR)	8 (2)	4 (4) ^b	6 (4) ^b	< 0.001	4 (5)	5 (5) ^c	0.14
<i>Appraisal of current knee function</i>							
Satisfaction with knee function (1–7), median (IQR)	2 (2)	4 (2) ^d	3 (2) ^d	< 0.001	3 (2.25)	3 (2) ^e	0.238
Delighted to pleased (1–2), <i>n</i> (%)	50 (53%)	17 (20%)	16 (46%)	< 0.001	24 (37%)	77 (44%)	0.314
Unhappy to terrible (6–7), <i>n</i> (%)	4 (4%)	20 (23%)	4 (11%)		12 (18%)	20 (11%)	
KOOS (0–100), mean ± SD							
Symptom	82 ± 15	72 ± 17	78 ± 20	< 0.001	74 ± 19	78 ± 19	0.14
Pain	90 ± 10	82 ± 13	86 ± 17	< 0.001	81 ± 16	86 ± 15	0.04
Activity in daily living (ADL)	96 ± 7	93 ± 9	94 ± 10	0.007	91 ± 10	92 ± 14	0.73
Sport/Recreation	78 ± 21	63 ± 22	75 ± 21	< 0.001	58 ± 27	70 ± 25	0.002
Quality of life	72 ± 18	54 ± 19	65 ± 21	< 0.001	53 ± 22	62 ± 23	0.003
ACL-QoL (1–10), mean ± SD	7.5 ± 1.5 ^f	5.7 ± 1.7 ^g	7.2 ± 1.6 ^e	< 0.001	5.8 ± 1.9 ^b	6.6 ± 2.0 ^h	0.008
IKDC (0–100), mean ± SD	84 ± 12 ^c	67 ± 15 ⁱ	77 ± 17 ⁱ	< 0.001			
ACL-RSI (1–10), mean ± SD	6.6 ± 1.9 ^c	3.9 ± 2.0 ^f	5.3 ± 2.1 ⁱ	< 0.001			

KOOS, Knee injury and Osteoarthritis Outcome score; IKDC, International Knee Documentation Committee Subjective Knee Form; ACL-QoL, Anterior Cruciate Ligament-Quality of Life; ACL-RSI, Anterior Cruciate Ligament-Return to Sport after Injury scale.

^aMissing data from 39. ^bMissing data from 2. ^cMissing data from 3. ^dMissing data from 1. ^eMissing data from 5. ^fMissing data from 4. ^gMissing data from 7.

^hMissing data from 10. Missing data for KOOS are presented in Figure 13.

Comparisons between patients with bilateral ACL injuries and patients with unilateral ACLR (Study IV)

Females were significantly younger than males when they suffered their first ACL injury (19.0 vs. 24.6 years, respectively, $P < 0.001$), and at the time of follow-up (25.8 vs. 32.0 years, $P < 0.001$). Twenty-eight (42%) patients were ≤ 18 years old when they sustained their first ACL injury, and 29 (44%) sustained their second injury within two years from either the first injury ($n=10$) or ACLR ($n=19$). There were no significant sex differences in scoring on the KOOS, Lysholm knee score, EQ-5D, ACL-QoL, Tegner activity scale, or in satisfaction with knee function and the level of activity ($P > 0.05$). Patients who had undergone unilateral ACLR were comparable to patients with bilateral ACL injuries in age and sex distribution ($P > 0.05$).

Patients with bilateral ACL injuries had a median Lysholm knee score of 82 (range 34-100, IQR 23). Fourteen (22%) patients had excellent (≥ 95) results and 10 (16%) had poor (< 65) results (Figure 14). The mean EQ-5D score of the overall health status was 0.77 ± 0.22 , and the mean EQ-5D VAS score was 75.5 ± 17.6 .

Figure 14. Lysholm knee score for patients with bilateral ACL injuries ($n=63$, 3 missing answers).

Patients who had undergone unilateral ACLR reported higher ACL-QoL, KOOS subscales pain, Sport/Rec, QoL and also in ACL-QoL ($P < 0.05$) compared to patients with bilateral ACL injuries (Table 9, Figure 13).

Tegner activity scale scores are presented in Table 9 and Figure 15. Compared to patients with unilateral ACLR, patients with bilateral ACL injuries had a higher Tegner activity scale score before the additional ACL injury (7, IQR 2 vs. 4, IQR 5, $P < 0.001$). Fifty-six (85%) patients were active in contact sports before the first injury, 46 (67%, two missing answers) before the second injury, and 12 (18%) at follow-up. Thirty-five (53%) patients were playing football at the first injury. Forty-one (62%)

patients sustained both ACL injuries while performing the same activity, 25 in football.

Compared to patients with bilateral ACL injuries, more patients with unilateral ACLR had returned to their previous activity at follow-up (43% vs. 23%, $P = 0.004$), and more often at the same activity level as prior to the ACL injury (28% vs. 12%, $P = 0.01$). Fewer patients with unilateral ACLR had changed their training habits because of their knee injury (77% vs. 92%, $P = 0.005$).

The most common reasons for not returning to pre-injury activities were reduced function of the knee (or knees), a sense of not trusting the knee (or knees) and fear of re-injury (Table 10).

Figure 15. Tegner activity scale scores for patients with bilateral ACL injuries and for patients with unilateral ACLR before any ACL injury (12 missing answers in unilateral ACLR group), before the second ACL injury (2 missing answers), and currently with bilateral ACL injuries or unilateral ACLR (39 missing answers). Levels 0-3 correspond to activities of daily living, levels 4-6 to recreational and individual sports, and levels 7-10 to competitive team sports.

Table 10. Reasons for not returning to previous activity after ACLR (proportion of responses ranked by patients as most important)

Reasons for not returning to previous activity, n (%)	Patients with bilateral ACL injuries <i>n</i> = 51 (of 66, 77%)	Patients with unilateral ACLR <i>n</i> = 103 (of 178 ^a , 57%)
Poor knee function	19 (38)	22 (22)
Do not trust the knee	11 (22)	27 (27)
Fear getting a new injury	10 (20)	22 (22)
Change in team or coach	1 (2)	5 (5)
Family or work commitments	8 (16)	13 (13)
Other reasons	1 (2)	11 (11)
Total	50^b	100^c

^aMissing data from 4 patients. ^bMissing data from 1 patients. ^cMissing data from 3 patients.

DISCUSSION

The main findings were that ACLR within one year and high motivation to RTS were important factors for returning to football after ACLR in females. After returning to football players with ACLR had functional performance that was equal to healthy controls, but many players, both with or without ACLR, had movement asymmetries. The rate of additional ACLR seemed to be increased in a selected group of young patients who desire a rapid return to strenuous sports (like football) after primary ACLR. Sustaining a contralateral ACL injury led to impaired knee function and activity level.

Return to sport (football) after ACLR

Undergoing ACLR within one year after injury was associated with a greater likelihood of returning to football after ACLR, but the risk for additional ACLR was also increased (study I and III). The return to football rate of 61% in a homogenous cohort of female football players (study I) was similar to previous studies that have included different sports, ages, sex, grafts, definitions of RTS, and have a more widespread follow-up period [10]. The return to football rate was also similar to other female football populations (46-67%) [33,191]. Notably, 14% of the female football players who responded to the questionnaires had sustained an additional ACL injury (study I), and 5 out of 77 (6%) had sustained a new knee injury before testing (study II). This suggests that returning to contact sports after ACLR increases the risk of sustaining additional knee injuries [26,165,218,229]. Similarly, in study IV, most patients with bilateral ACL injuries had a high pre-injury activity level, and more returned to their pre-injury activities (75%) before the second injury. Compared to patients with unilateral ACLR, patients with bilateral ACL injuries had a higher Tegner activity scale score before the additional ACL injury (study IV). Taken together, these results suggest that returning to a high activity level after ACL injury may be the most important risk factor for contralateral injury [189,206,229].

High motivation to return to football was another factor associated with RTS (study I). All participants had high motivation to RTS, although those who RTS had significantly higher motivation than those who did not return, a finding that supports previous research [12,69].

Reasons for return to football after ACLR

People may participate in sport for many reasons, including for health, for relaxation, to have fun, for socio-psychological well-being, performance, and for stress reduction. Reasons for participation may also be age and sex dependent [17]. While this thesis did not investigate the reason for RTS, in study II, female football players reported the

main reason why they were playing football. The main reported reason for playing football was to have fun. One comment added from a participant was; “I did not want to stop playing because of the ACL injury”. Motives for participation in sport predicted patient-reported outcomes 2 years after ACL injury [183]. Therefore assessing the reasons why patients play football may provide an indication about the likelihood of returning to football.

Reasons for not returning to sport after ACLR

The main reasons patients with bilateral ACL injuries, unilateral ACLR (study IV), and female football players (study I) did not returned to sports (football) were “reduced knee function,” “lack of trust in the knee” and “fear of new injury”. These findings are similar to a previous study [113]. The psychological component of returning to sport/football, especially the fear of re-injury, is probably underestimated in the rehabilitation process. Fear is a hindrance to RTS [10,214] and has a negative influence on the rehabilitation process [209]. Fear of re-injury may also be a risk factor for sustaining a new injury [207]. It is reasonable to speculate that patients who have had multiple ACL injuries might have heightened fear of re-injury. However, in this thesis, the proportion of patients with bilateral ACL injuries (study IV) who indicated fear of re-injury as a reason for not to returning to sport was similar to the proportion of patients with unilateral ACLR, and similar to a previous study [113].

Activity level typically decreases with age [7] – likely due to life events and lifestyle changes. In many cases, not returning to sport after ACL injury is unlikely to be due solely to the ACL injury. A follow-up study of male football players playing at the fourth-highest league in Sweden, found that the reasons for giving up football were age, lack of motivation and social factors in 78%, and due to injury 22% [55]. Twenty percent of patients with bilateral ACL injuries (study IV), reported that they did not return to previous activity because of reasons other than the ACL injuries. Two-thirds of female football players with ACLR who had returned to football, but were currently not playing reported other reasons than the knee (change in team or coach, family or work commitments, not fun to play anymore and other reasons) being behind their non-participation. Among those who had not returned to football, 31% reported that it was because of other reasons (study I). However, it is unclear whether patients who responded “not fun to play anymore or “change in team or coach” considered their knee or not when answering the questionnaire. This is because it may not be “fun to play anymore” if the player has problems with the ACL reconstructed knee.

Although RTS is important for many patients [20], requiring RTS before the outcome of treatment is deemed to be “successful” may be misleading. Not all patients with an ACL injury have the ambition to RTS, and some patients may be advised by physicians or physiotherapists not to RTS because of the high re-injury risk. Perhaps the question should be: how can we motivate young ACL-injured athletes *not* to return to

pivoting sports? Activity modifications and rehabilitation result in an acceptable activity level and good knee function after ACL injury [109] and most patients are satisfied [243].

Functional performance after ACLR and return to football

There were no deficiencies in the ACLR limb compared with the uninvolved limb on any of the functional performance tests in female football players with an ACLR. Furthermore, players with ACLR and controls performed similarly. Results at the group level indicate that the players with ACLR performed in line with recommended guidelines [77,140,172]. However, at the individual level, many players with ACLR *and* healthy controls had side-to-side differences and movement asymmetries (study II), which have been associated with an increased risk for primary [90] and secondary ACL injury [165]. Functional performance should be optimised to support safe RTS decisions. Therefore, outcome measurements are important. The validity of functional performance tests and PROM regarding safe RTS remains to be established and requires prospective research. When it is safe to RTS after ACLR is often unclear, and influenced by many factors. The definition of “safe” RTS is debated, but it might be reasonable to define safe as being when the chance for re-injury is the same as the chance for a primary injury.

High knee valgus motion and knee valgus angles may increase the strain on the ACL [62]. Therefore athletes are encouraged to avoid excessive valgus motion at landing or cutting to reduce the risk of knee injury [90]. Valgus motion is likely controlled by neuromuscular contribution of the entire limb kinetic chain [167]. In contrast with previous findings [57,111], controls in study II had greater knee valgus movement in the frontal plane (measured with DVJ) compared to players with ACLR (median difference of 0.017 m). Current postoperative rehabilitation programs emphasise the importance of landing with toes and knees pointed forward, and minimising knee valgus motion during take-off and landing. Players with ACLR may have practiced these landing techniques and could also have been aware of the purpose of the test, and therefore actively tried to avoid knee valgus motion. The tuck jump test is considered more demanding than the DVJ test because of its plyometric nature [85] and the groups did not differ for this test. However, almost half of the players had movement asymmetries on the tuck jump that scored outside recommended guidelines.

Different tests and measurement approaches might also explain the conflicting results. Previous studies have often used sophisticated laboratory equipment such as the Biodex balance system [167], force plates [48,145,201] and 3D motion analysis [48,57,111]. The tests used in study II may not have been sensitive enough to detect existing between-group differences. Myer et al [143] reported good correlation between 3D analysis and two-dimensional (2D) analysis in frontal knee motion meas-

urements, but 2D analyses in different settings may still have more sources of errors. Variations in camera placement in the frontal plane and landing technique (e.g., landing with hip rotation or a small distance between feet) could result in measurement errors in knee motion, although we tried to minimise such errors by standardisation of camera placements and data collection. However, the functional tests used in study II have been done in a clinical setting, and are much more accessible to the practitioner/clinician, much cheaper, and clinically applicable.

Only one previous study prospectively followed patients who had undergone ACLR to identify modifiable risk factors for new ACL injury, such as postural stability, and hip and knee control during landing [167]. In this study, advanced measurement equipment such as Biodex balance system and 3D motion analysis, were used. Recently, large cohorts with female handball and football players with and without ACLR have been prospectively followed to identify risk factors using both clinician-friendly evaluation tools (strength test, SEBT, knee joint laxity, generalised joint laxity and foot pronation) [152], and advanced equipment (3D motion analysis) [111,152]. Nilstad et al [152] and Krosshaug et al [111] did not find that valgus motion in a DVJ was predictive for a knee injury in female elite football and handball players without previous ACL injury and stated that DVJ is a poor screening test for ACL injuries. However, for players with a previous ACL injury, valgus motion in the knee was associated with an increased risk for injury [111]. In this thesis, only one tenth of the female football players were playing at the elite level and we are not aware of knee motion in frontal plane is predictive for a knee injury when playing at lower levels. Study II had a cross-sectional design. Therefore, we are not aware of whether results in the tests and results outside recommended guidelines predict an ACL injury and a prospective study is in progress. Prospective studies may help to identify modifiable risk factors for ACL injuries in female football players, especially ACLR players, and whether targeted rehabilitation interventions could be developed based on these factors.

Knee function and knee-related quality of life

Females who were currently playing football after ACLR had superior (and clinically relevant) self-reported knee function and knee-related quality of life compared to those who had not returned (study I). This supports previous research where good postoperative knee function favored returning to the preinjury level of sport [10]. Patients with unilateral ACLR reported superior knee function and knee-related quality of life compared to patients with bilateral ACL injuries (study IV). A common reason for a poor outcome in the KOOS is additional knee trauma [205], and the fact that patients in study IV who had had multiple knee injuries had worse self-reported outcomes may support this. The Lysholm knee scores of patients in study IV with bilateral ACL injury was also similar to previous research after ACL revision surgery [237]. Therefore, sustaining multiple ACL injuries seems to have a negative effect on the overall satisfaction with knee function and quality of life.

Patients with ACL injury have usually gone through a long rehabilitation, and may have expected to return to their previous activities. One-fifth reported that they had changed focus on work or studies, which could affect their lives. An additional knee trauma may be difficult to cope with. It is challenging to return to cutting and pivoting activities, which in most cases are team sports. In team sports, other factors than just participating in the sport (e.g. friendship and contributing to the team) may be important for the patients. Therefore, ACL injuries could affect patients both physically and mentally (study IV).

Predictors for additional ACLR

The main predictors for additional ACLR (study III) were younger age, undergoing primary ACLR within one year after injury, and sustaining ACL injury while playing football. An additional ACLR means that the person had sustained a new ACL injury (ipsi- or contralateral) and underwent a subsequent ACLR. We are not aware of graft failures and contralateral ACL injuries where no new ACLR was performed.

Younger people have a higher activity level, especially in contact sports [120,229]. The finding that young age predicted an additional ACLR is in line with previous reports [124,226]. It can also be argued that undergoing primary ACLR within one year is not a predictor *per se*, but rather, that early ACLR is most often performed in a selected sample of highly active young patients who desire a rapid return to strenuous sports. Players at the elite level or players who are more eager and motivated to RTS may be more likely to have early ACLR. In a systematic review, patients with an early ACLR (<3 months) had higher activity levels after ACLR [47]. Another predictor for additional ACLR was playing football at the injury occasion. It should be stressed that the available activity data in the current study only represents the activity performed at the occurrence of the primary injury and that no information was available regarding regular sports participation before or after the primary ACLR. Nonetheless, it is plausible that these patients represent an active subgroup of the cohort to a high degree and there is a high re-injury risk after ACLR in football players [33,165].

Methodological considerations

Study I

Because study I was not cross-sectional, it is not possible to draw conclusions regarding causal relationships between factors and returning to football. However, a hypothesis was that factors related to the player or to the ACL injury *per se* may have affected the likelihood of returning to football; accordingly, these were analysed in a logistic regression model. Behavioural factors (i.e. motivation, most important reasons for playing football before ACL injury and risk behaviour) were assessed retrospec-

tively and because of this, there is potential for recall bias. There is also a potential risk that the current players rated their motivation higher because they had already returned to football.

Another limitation was the response rate of 60%. This might be because many young people change address, may not have been interested to answer, or because of the response burden of completing many questionnaires. Most of the missing data were in the last questionnaires, SSP and SMPS. In addition, players who did not complete the survey had fewer meniscal injuries and may have had a different outcome than those who responded. Still, the response rate was similar or better than for other cross-sectional survey studies on ACLR and RTS [16,191].

To study two clearly defined groups (i.e. current players and those who never returned at all), players who had returned but were currently not playing were not included. The results only apply to those who returned and remained active at the time of follow-up, and this must be taken into consideration when interpreting the results.

Study II

Knee motion in DVJ has been analysed in many different ways: with 3D and 2D motion analysis; using clinic-based ACL injury prediction algorithm [141-143], measuring normalised knee separation distance in centimetres [154], in degrees [90,152,167], in newton meters (Nm) [90,143], grading jumps according to a scoring system [163] or with poor, reduced or good control [153], and by dichotomising knee valgus motion as the midpoint of patella moving inwards and ending up medial to the hallux [57]. This leads to problems when reporting absolute scores and cut-off values for movement asymmetries. No reference values for high knee valgus motion in the frontal plane and pKAM are available, except in 3D kinetic analyses, with knee abduction load measured in Nm [143]. Three dimensional motion analysis is often considered as the gold standard, but the method is often too expensive and time consuming to be used in clinical practice [132]. A clinic-based assessment tool based on 2D analysis (results based on a nomogram) has been developed, and was used in study II [143]. The nomogram for this assessment has been published as a figure, although the formula in Excel was obtained for this thesis through personal communication.

While 2D analyses have some limitations, there are also many advantages. These include being low-tech, low cost, having a low time requirement, and being applicable in a large setting. The tests were performed in different places on different surfaces and conditions, which could have influenced performance and absolute scores. However, the study purpose was to compare limbs and players with ACLR to controls, all tested in the same conditions. The test leader (AF) was not blinded to group identity, but to minimise measurement errors, the tests were done by the same experienced test leader (AF), and all video analyses were performed by the same experienced, blinded assessor.

A strength of study II is the homogeneous cohort of female football players, and controls recruited from the same football teams as the players with ACLR. Most previous studies include a general population, combining different sports, ages and sexes [151]. However, the results from the present study cannot be generalised to other populations than female football players.

Study III

In study III, several limitations of using registry data must be acknowledged. The true rate of new ACL injury to the ipsi- or contralateral knee is unclear, since only surgically treated ACL injuries are reported in the register. While a second ACL injury is unquestionably a negative outcome, undergoing an additional ACLR could represent a favorable outcome for some patients. It is plausible that young and active patients are more frequently offered additional ACLR, while older patients who are active at a recreational level may instead be recommended non-surgical treatment. Therefore, patient selection for surgery could be one explanation for why younger and more active patients had an increased rate of additional ACLR.

There are also several possible important predictors for additional ACLR that were not controlled for. The Swedish national ACL register does not include data on potentially important predictors like insufficient rehabilitation, premature RTS, high activity level, technical failure at the primary ACLR, biological issues and smoking (insufficient data).

The register is estimated to include more than 90% of all ACLRs in Sweden. However, some patients could have been lost to follow-up for reasons such as moving out of the country, and it is possible that an additional ACLR was not reported in The Swedish national ACL register for some patients. Therefore, similar to other studies, the rate of additional ACLR may have been underestimated [124].

There was a low response rate to the preoperative KOOS and EQ-5D questionnaires. Because of this, these variables were not included in the final Cox regression model. It would have been valuable to also analyse KOOS and EQ-5D postoperatively, as these could arguably be more important predictors for additional ACLR. However, these data were not included, again due to low response rate (41–51%), and the uncertainty of whether patients completed the questionnaires before or after a possible additional ACLR.

Study IV

In study IV, patients had to recall their activity and activity level retrospectively, which could be up to 12 years prior to the study. Therefore, recall error cannot be ruled

out. However, ACL injuries often occur in sport and therefore it is likely that patients accurately remember their activity.

There is no questionnaire developed for bilateral ACL injuries and that was the reason why two questionnaires were completed via telephone interview. However, many questions assess function, for example, the EQ-5D, the QoL, ADL and sport participation subscales in the KOOS, and are not side-specific. There are also several possible confounding variables for PROMs that were not controlled for, including rehabilitation, smoking, concomitant injuries, and surgical factors.

The cohort studied was relatively small and heterogeneous – some patients had graft ruptures, some had ACL revision surgery, and some had associated injuries in addition to their ACL injury. Having associated injuries can lower self-reported outcomes for patients with unilateral ACL injury [138,158], although other studies have not shown any difference in self-reported outcomes between patients with isolated or combined ACL injuries [109,205]. The purpose of study IV was to describe the characteristics of patients with bilateral ACL injuries, irrespective of whether they were treated surgically or not, and we did not analyze subgroups because of the limited sample.

Clinical implications

Clinicians should be aware of the importance of players' motivation for their return to football, because factors other than knee function could determine whether they resume playing after ACL injury. The questions about motivation used in study I could be useful during rehabilitation, both before and after ACLR, to better understand the player's motivation level. It may be beneficial to discuss the goals with the patient before ACLR is performed. However, clinicians should also be aware of the increased risk for additional ACLR in young patients who return to strenuous sports after primary surgery. It may be important to take this into account prior to ACLR, during post-operative rehabilitation and when discussing return to sports/activity with these patients.

In the young female football players, clinicians should evaluate side-to-side differences and movement asymmetries. Knee-healthy controls had side-to-side differences and movement asymmetries to the same degree as the ACLR players. This may need to be taken into consideration because young female football players are a high risk group of sustaining an ACL injury. Maybe the results from study II could give information about potential factors that might increase the risk for sustaining an additional ACL injury because it will be linked to a prospective study

Sustaining a contralateral ACL injury may be associated with a subsequent change in activity participation, decreased knee function and reduced knee-related quality of life. The results from study IV might be used in the rehabilitation phase to inform and guide patients with bilateral ACL injuries to have realistic expectations of knee function and activity level. Explicit patient information about realistic goals for ACLR seems to be necessary to prevent dissatisfaction, despite a successful reconstruction from the surgeons' point of view [60].

Future research

Study I investigated factors that may be associated with returning to football after ACLR in females, but the non-prospective design of the study limited the conclusions that could be drawn regarding causal relationships between these factors and the ability to return to football. In the future, there is a need for prospective studies to determine causal relationships between demographic, personality and psychological factors, ACL-injury- and football-related factors and returning to football. Understanding relationships between these factors and returning to football might help improve the rehabilitation approach and enhance the possibility of returning to football for players who wish to RTS. There is also a need to investigate factors that are associated with "safe" RTS, in both female and male football players, and in other sports than football.

The tests used in study II could be repeated under fatigue, in males and in other sports than football in future studies. Other tests should also be evaluated that are: more sport-specific with unanticipated movements, and more endurance-demanding. The evaluation should emphasise quality of movement and body compensations. If the ongoing prospective study of the females in study II could discriminate players at risk for sustaining an additional ACL injury, a prevention program could be developed to address the identified risk factors. The next step is a randomised controlled intervention trial.

The Swedish national ACL register did not include data on several potentially important predictors for subsequent ACLR, including RTS and activity level, rehabilitation factors and injury mechanism. These predictors may be assessed in future studies. It may also be valuable to analyse KOOS and EQ-5D post-operatively, as these could arguably be more important predictors for additional ACLR.

Future studies that focus on patients with bilateral ACL injuries should incorporate a qualitative design, to help characterise this patient group. More research on a more homogenous group of patients with bilateral ACL injury is also needed.

CONCLUSIONS

- Undergoing ACLR within one year after injury was positively associated with a player's return to football after ACLR, but also an increased risk for additional ACLR.
- High motivation to RTS was positively associated with female players' return to football after ACLR.
- Female football players 6-36 months after ACLR, had no differences between the ACLR limb and the uninvolved limb in functional tests.
- Overall, female football players 6-36 months after ACLR performed in line with recommended guidelines suggested in the literature regarding functional performance, and similarly to knee-healthy controls. However, many individual players with ACLR and controls had side-to-side differences that have in previous studies been associated with an increased risk for primary and secondary ACL injury.
- Younger age, having ACLR early after the primary injury, and sustaining the primary injury while playing football are key predictors for revision and contralateral ACLR. This suggests an increased rate of additional ACLR in a selected group of young patients who likely desire a rapid return to strenuous sports after primary surgery.
- Sustaining a contralateral ACL injury decreased knee function, quality of life and activity level compared to having a unilateral ACLR.

SAMMANFATTNING

Bakgrund: En främre korsbandsskada är en allvarlig och vanlig knäskada, speciellt inom idrotter med hög belastning på knäleden såsom fotboll. I fotboll har kvinnor 2-4 gånger högre risk jämfört med män att ådra sig en främre korsbandskada. Efter en främre korsbandsrekonstruktion är ett vanligt mål att kunna återgå till idrott, dock återgår bara runt två tredjedelar av patienterna. Patienter som är under 20 år och återgår till idrott efter korsbandsrekonstruktion kan ha 30-40 gånger högre risk att ådra sig ytterligare en främre korsbandsskada jämfört med en knäfrisk person.

Syfte: Det övergripande syftet med avhandlingen var att öka kunskapen om kvinnliga fotbollsspelare med ett främre korsbandsrekonstruerat knä och personer med bilaterala främre korsbandsskador samt att identifiera faktorer som ökar sannolikheten för att genomgå en ytterligare främre korsbandsrekonstruktion i samma och/eller i motsatt knä.

Metod: Avhandlingen består av fyra studier. Studie I och II var tvärsnittsstudier bestående av kvinnor som ådrog sig en primär främre korsbandsskada under fotbollsspel och genomgick en rekonstruktion för 6–36 månader sedan. I studie I inkluderades 182 kvinnor som fyllde i ett batteri av frågeformulär i median 18 månader (IQR 13) sedan rekonstruktionen. Av dessa återgick 94 (52%) till fotbollsspel och var aktiva spelare, och 88 (48%) hade inte återgått till fotboll. I studie II, ingick 77 av de 94 aktiva fotbollsspelande kvinnor (från studie I) med ett främre korsbandsrekonstruerat knä och 77 knäfriska fotbollsspelande kvinnor. Ett testbatteri användes för att utvärdera dynamisk balans (the Star excursion balance test) och hoppförmåga (enbenshopp, femhoppstest och sidohopp). Rörelseasymmetrier i nedre extremiteten och i bålen bedömdes med tvåbensfallhopp (Drop vertical jump) och upphopp med knäuppslagningar (Tuck jump) genom att använda tvådimensionell videoanalys. Studie III, var en kohortstudie bestående av alla patienter med en primär främre korsbandsrekonstruktion (n=22,429) registrerade i Svenska korsbandsregistret mellan januari 2005 och februari 2013. Data uthämtades från registret för att identifiera faktorer som kunde öka sannolikheten för att genomgå ytterligare en främre korsbandsrekonstruktion såsom; ålder vid primär främre korsbandsrekonstruktion, kön, aktivitet vid skadetillfället, primär skada i höger eller vänster knä, tid mellan skada och primär rekonstruktion, kombinerade brosk- eller meniskskador, graft-typ, Knee injury and Osteoarthritis Outcome Score och Euroqol Index Five Dimensions mätt pre-operativt. Studie IV var en tvärsnittstudie och patientrapporterad knäfunktion, livskvalitet och aktivitetsnivå hos 66 personer med bilaterala främre korsbandsskador undersöktes och jämfördes med 182 personer med unilateral främre korsbandsrekonstruktion.

Resultat: Faktorer som associerade med återgång till fotboll hos kvinnor var; kort tid mellan skada och rekonstruktion (0–3 månader, OR 5.6; 3–12 månader OR 4.7 jämfört med referensgrupp >12 månader) och hög motivation (studie I).

Det korsbandsrekonstruerade benet skiljde sig inte från det icke rekonstruerade benet i något av funktionstesterna och kvinnor med ett främre korsbandsrekonstruerat knä skiljde sig minimalt från de knäfriska kontrollerna. I de olika testerna hade 9-49% av spelarna sidoskillnader och rörelseasymmetrier och endast en femtedel klassades som godkända i samtliga tester. Samma utfall sågs i båda grupperna (studie II). Faktorer som ökade sannolikheten för att genomgå en revision och/eller en kontralateral rekonstruktion var ung ålder (fyrfaldigt ökad för patienter <16 år jämfört med >35 år), att genomgå rekonstruktion tidigt efter första främre korsbandsskadan (två till trefaldigt ökad vid rekonstruktion <3 månader jämfört med >12 månader) och att första främre korsbandsskadan hände vid fotbollsspel (studie III). Personer med bilaterala främre korsbandsskador rapporterade sämre knäfunktion och livskvalitet jämfört med personer med en unilaterala främre korsbandsrekonstruktion. De hade en hög aktivitetsnivå före första och andra främre korsbandsskadan, men sänkt aktivitetsnivå efter deras andra främre korsbandsskada vid uppföljningstillfället (studie IV).

Slutsatser: Kvinnliga fotbollsspelare, som återgick till fotbollsspel efter en främre korsbandsrekonstruktion, hade en hög motivation och hade genomgått sin främre korsbandsrekonstruktion inom ett år efter skadan. Deras funktion var liknande som hos knäfriska kontroller, men rörelseasymmetrier fanns i stor utsträckning i båda grupperna. Detta har i tidigare studier visat sig associera med en ökad risk för en primär och en sekundär främre korsbandsskada. Andelen som genomgår ytterligare en främre korsbandsrekonstruktion verkar vara högre i den grupp av unga patienter som önskar en snabb återgång till idrotter med hög belastning på knäleden såsom fotboll efter sin primära främre korsbandsrekonstruktion. Att ådra sig bilaterala främre korsbandsskador ledde till nedsatt knäfunktion och aktivitetsnivå.

Nyckelord: fotboll, främre korsband, funktionell prestation, knä, kontralateral, patientrapporterat utfallsmått, rekonstruktion, revision, åter till idrott

ISBN: 978-91-7685-736-6

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to all my colleagues, friends, and relatives who have contributed to this work. It would not have been completed without your support.

I would especially like to thank:

Joanna Kvist, my main supervisor, for your valuable well-balanced guidance, sharp important feedback and support in pushing this work forward in an inspiring way. Joanna and Martin Hägglund have been the perfect mix of supervisors! Joanna has taught me stringency and has also told me: “It is good with holidays. You have time to work then :-)”.

Martin Hägglund, my co-supervisor, for your excellent support during this work. You produce a lot of excellent scientific papers on a very important topic – football and injuries!

Henrik Magnusson, my co-author, for valuable statistical help and advice.

Magnus Forssblad, my co-author, I look forward to continued collaboration in the future.

All the **PhD students, former PhD students (now PhDs) and researchers** at the Division of Physiotherapy at Linköping University, for support, friendship and valuable and stimulating discussions. Special thanks to the administrative staff, especially **Åsa Fahlstedt** for excellent support and ”dog talks”. Thanks also to **Karolina Kristenson** and **Håkan Gauffin** for valuable discussions.

Isabella Manzoni, for analyzing all the films in study II.

Clare Ardern, for language comments and for stimulating, interesting discussions.

All my colleagues at the department of Physiotherapy, Region Jönköping County for being good friends and supporting me at all times. Special thanks to **Kristin Gustafsson**, **Jenny Walmborg**, **Samuel Anfors**, and **Elizabeth Häggquist**. And, of course, my bosses, **Marianne Svensson** and **Annelie Winström** for the opportunity to complete my PhD.

Other colleagues at Region Jönköping County, **Ann-Sofi Kammerlind**, **Bo Rolander**, **Anneli Ohlsson**, **Peter Öhling**, **Daniel Urberg** and all staff at the Medical Library, especially **Mikael Wallin**, for your valuable help!

All the physiotherapists and other staff, which allowed access to their physiotherapist clinics for testing and help with various things, **Marianne Thorwid, Karna Karlsson, Mia Forsberg, Camilla Italiener, Christina Mikkelsen, Åsa Lönnqvist, Annica Näsmark, Maria Wiker, Petra Nilsson, Annica Svensson, Håkan Nilsson, Timmy Gustavsson, Dale Reese, Simon Bakkioui, Kjell Svensson, Sören Brodin, Ulrika Blomé, Carina Zakrisson, Kristina Bälter Sandell, Nane Andersson, Charlotte Häger, Hjördis Durango, Ola Rhen, Ove Lind, Anders Bergström, and Kristina Davidsson.**

All the participants in the studies. This thesis could not been done without you!

Cecilia and Mia Båge, for your excellent work with the cover page and, of course, the photo models and (former) football players with ACL reconstructed knee(s) **Henny Yngve, Evelina Kimmehed, Ellen Bertilsson** and **Mikael Eriksson**. And of course, **Roger Wandebby**, who took the photo of Mikael.

All my **friends and family** for always believing in me, your wonderful support and many valuable comments of my work.

The studies were mainly supported financially by Futurum—the Academy for Healthcare, Region Jönköping County, the Medical Research Council of South-east Sweden, the Faculty of Health Sciences at Linköping University, Swedish Research Council for Sport Science (CIF), and the Swedish Football Association.

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