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# **CRUCIATE LIGAMENT INJURY – CRUNCHING THE NUMBERS**

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# CRUCIATE LIGAMENT INJURY – CRUNCHING THE NUMBERS FOR DOCTORAL DEGREE (Ph.D.)

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*“Nothing in life is to be feared, it is only to be understood.  
Now is the time to understand more, so that we may fear less.”*

– Marie Curie

*“Your assumptions are your windows on the world.  
Scrub them off every once in a while, or the light won’t come in.”*

– Isaac Asimov

## ABSTRACT

Cruciate Ligament (CL) injury is a serious injury that occurs primarily during activities like soccer, handball, floorball, alpine skiing, etc. Patients are generally young and the injury often results in early discontinuation of activity and an early onset of osteoarthritis (OA). The optimal treatment of CL injury is under continuous debate, where surgical reconstruction is recommended for patients engaged in high-level sports. Non-surgical treatment is considered to have a satisfactory outcome in the general population. CL injuries are one of the most studied topics within the field of sports medicine. Over 20,000 articles have been published, however none of these studies have hitherto used a national register-based approach.

The overall aim of this thesis was to study the incidence, treatment and long-term effects of patients with CL injury in Sweden using a register-based approach. The thesis includes four studies, each with a specific aim. The first aim was to calculate the incidence of CL injuries in the general population. Earlier studies have focused on patients at risk or on the reported cases in a smaller geographical setting. Thus, the incidence in the general population has been unknown. For a long time, an argument for CL reconstruction (CL-R) has been that it prevents development of post traumatic OA, however, studies investigating this have presented conflicting results. Therefore, the second aim of this thesis was to study if this argument could be proven using a register-based approach. The third aim was to study what impact socioeconomic status (SES) has on the choice of treatment for these injuries. For other conditions, higher SES has been associated with a higher access to and utilization of surgical treatments, but its effect on patients with CL injury has never been studied. The fourth aim was to study how choice of treatment for a CL injury influenced changes in SES. This approach to create a new alternative outcome for symptomatic surgical procedures is essential in the process to develop new tools and methods for personalized medicine.

This thesis shows that the incidence of CL injury in Sweden is 78 per 100,000 inhabitants. More than 50% of the patients are younger than 30 years and 60% are males. Overall, 36% are treated with surgical reconstruction and this option was more common among younger patients. Preventing post-traumatic OA is not a valid argument for CL-R. On the contrary patients going through surgical reconstruction had a 22% increased risk of developing symptomatic OA compared with those treated non-operatively. Ten percent of the patients developed symptomatic OA, and a concomitant meniscus injury increased this risk threefold. Even though CL-R is done with the aim to create a stable knee, SES had a big impact on which treatment the patient was admitted to. Patients with university education had a 29% increased likelihood of undergoing CL-R compared with those who had not graduated from high-school. The choice of treatment did not significantly affect the salary of a patient five years after injury. However, this thesis presents a multivariate model for an alternative outcome for symptomatic surgery where individual variables, such as socioeconomic outcome variables, are considered. This sets the foundation for future studies about symptomatic surgery, and the creation of decision tools to offer a more personalized treatment.

## LIST OF SCIENTIFIC PAPERS

This thesis is based on the following original articles. The papers will be referred to in the text by their Roman numerals (I-IV).

- I. Nordenvall R, Bahmanyar S, Adami J, Stenros C, Wredmark T, Felländer-Tsai L.  
**A Population-Based Nationwide Study of Cruciate Ligament Injury in Sweden, 2001-2009: Incidence, Treatment, and Sex Differences.**  
*The American Journal of Sports Medicine*, 2012 Aug; 40(8), 1808-13
- II. Nordenvall R, Bahmanyar S, Adami J, Mattila VM, Felländer-Tsai L.  
**Cruciate Ligament Reconstruction and Risk of Knee Osteoarthritis: The Association between Cruciate Ligament Injury and Post-Traumatic Osteoarthritis. A Population-Based Nationwide Study in Sweden, 1987– 2009.** *PLOS one*, August 2014, Volume 9, Issue 8, e104681
- III. Nordenvall R, Marcano AI, Adami J, Palme M, Mattila VM, Bahmanyar S, Felländer-Tsai L.  
**The Impact of Socioeconomic Status on Choice of Treatment for Patients with Cruciate Ligament Injuries in The Knee.**  
*The American Journal of Sports Medicine*, 2016 Nov 11; E-pub ahead of print
- IV. Nordenvall R, Marcano AI, P Karlsson, Gerdin M, Adami J, Palme M, Mattila VM, Bahmanyar S, Felländer-Tsai L.  
**The Socioeconomic Impact of Treatment for Cruciate Ligament Injuries – A Population-Based Cohort Study of Patients on the Workforce**  
*Manuscript*

## LIST OF ABBREVIATIONS

ACL	Anterior Cruciate Ligament
ACL-R	Anterior Cruciate Ligament Reconstruction
CI	Confidence Interval
CL	Cruciate Ligament
CL-R	Cruciate Ligament Reconstruction
EC	Ethical Committee
HOM	Health Outcomes Measurement
HR	Hazard Ratio
ICD	International Classification of Diseases
LISA	The Longitudinal Integration database for Health Insurance and Labor Market Studies
NPR	National Patient Register
OA	Osteoarthritis
OR	Odds Ratio
PCL	Posterior Cruciate Ligament
PIN	Personal Identification Number
RCT	Randomized Controlled Trials
TPR	Total Population Register
SES	Socioeconomic Status





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# 1 FOREWORD

Except for the things we all hold dearest, like our family and friends, I like three things more than others. First of all, sports, second medicine, third data. I was extremely lucky to be able to combine all three interests while working with this thesis.

My father was 30 years old when he injured his anterior cruciate ligament. He went through reconstructive surgery and later developed post-traumatic knee osteoarthritis. The pain and limitations that followed woke my interest to find out more about cruciate ligament injuries and osteoarthritis. Could my father's osteoarthritis have been prevented so that he could continue playing soccer and tennis with me? This question remained with me all through medical school. Finally, when I got the chance to plan my own thesis, I was determined to find out more about cruciate ligament injuries, how these can be treated and why.

My fascination for data and how the information bank of national registers can enlighten us and give the answers to all our questions, has grown over time. With this thesis, I was able to study the national registers in detail and learn techniques and methods that make me confident to say that, using the national records, everything can be measured –if you ask the right questions.

With this thesis, I want to learn about patients with cruciate ligament injuries and present new facts about how they are treated and why. But, I also want to contribute to the implementation of new, more reliable and effective ways of using our nationwide registers in Sweden. Thus, register studies can serve its purpose to mirror and enhance the health of the population.



*My father's knee osteoarthritis made me want to study if it could have been prevented so that he could continue playing soccer and tennis with me*

## 2 PREAMBLE

### 2.1 HOW WOULD YOU TREAT THE FOLLOWING PATIENTS?

When a patient is diagnosed with a cruciate ligament (CL) injury an orthopedic surgeon is faced with a decision, to plan for CL reconstruction (CL-R) or to wait and see how the patient responds to physiotherapy. When evaluating what treatment regime should be offered to a patient, many aspects need to be considered. It is easy to say that what should be treated is the subjective problem that the CL-deficient knee is causing to the patient. But, is it possible to say whom will be satisfied with a CL-deficient knee (so-called “copers”) and whom will need a CL-R (so-called “non-copers”) at an early stage? If so, you could save the patients that eventually will need a CL-R a lot of time by planning for an immediate reconstruction, as well as prevent development of secondary meniscus injuries that could originate as a result of an unstable knee.

Below I present four different patients that I have met and followed. Imagine that you meet them for the first time, six weeks after a knee trauma and with a diagnosed CL injury. Then ask yourself, how would you treat them? Would you plan for immediate surgery or would you start with physiotherapy with a reevaluation after a few weeks?

Sara is a 15-year-old female who plays soccer 2-3 times a week. Her MRI shows a ruptured ACL and no meniscus or cartilage injuries. Lachman’s test is 2+ and pivot-shift is inconclusive. Sara loves to play soccer and wishes to be back to practice as soon as possible.

Christopher is a 20-year-old male who plays soccer in the second division on a professional level. His MRI shows a ACL rupture with no meniscus or cartilage injuries. Lachman’s test is 2+ and pivot-shift negative. Christopher wants to return to the soccer field as soon as possible since a few clubs from the first division have shown interest in him.

Patrick is a 32-year-old male who plays floorball with his colleagues every week. His MRI shows a ruptured ACL with horizontal ruptures in the medial meniscus. Lachman is 3+ and pivot-shift is positive. Patrick likes to play floorball and wants to continue exercising since he lost 5 kilos the last months. He aims to lose another 5 kilos before the summer.

Thomas is a 56-year-old male, he is going skiing 5-6 weeks per year and plays tennis and squash every week. His MRI shows a ruptured ACL, an injured medial meniscus and a cartilage thickness of 4 mm. Lachman’s test is 3+ and pivot-shift positive. Thomas loves skiing and is planning to go to Canada this autumn to ski the Rocky Mountains.

There is no obvious right or wrong, and surely experienced orthopedic surgeons around the world would have different opinions about the answers. But this example highlights that the treatment decision for a CL injury is not easy and evidence is incomplete. The choice of treatment often ultimately relies on experience. With a register based approach, this thesis is intended to discover new knowledge that can help physicians and patients find answers to their questions and give them tools to make better decisions.

### 3 INTRODUCTION

The common theme of this thesis is the epidemiology of CL injuries. However, this thesis also serves as an example of how registers can be used to answer a multitude of questions. The Personal Identification Number (PIN) and the evolution of electronic health registers in Sweden have created unique resources where almost any answer can be found as long as you ask the right questions.

For over a century, the search for the optimal treatment for a CL injury has been the holy grail within the field of sports medicine. Over 20,000 scientific articles have been published upon this topic, including observational studies as well as Randomized Controlled Trials (RCT). Along with several orthopedic treatments, many studies focus on different types of surgery, such as drilling techniques, types of grafts or screws or positioning of the grafts. Few studies try to answer the question of whether to do surgery, to whom and why. However, before this thesis was initiated, no one had ever tried to use nationwide registers to answer the most essential questions: 1) Who are the patients and how many are they? 2) How should they be treated for best long-term results? 3) What factors influence the treatment they receive? and 4) What long-term effects does the choice of treatment have on the rest of the patient's life? This thesis consists of four epidemiological studies trying to answer the questions presented above using different Swedish national registers.

The first paper presents the descriptive epidemiological data for all patients diagnosed with a CL injury. The second paper answers if a common argument for CL-R is true, namely that it prevents the development of osteoarthritis. The third and fourth studies take the socioeconomic aspects of CL injuries into account. Study three describes the effect that socioeconomic factors have on the choice of treatment and study four analyses the impact that this choice has on the development of such factors.

While studies one to three answer questions important to the search for the so-called holy grail of sports medicine, study four is of a different character. This study represents a first step in creating a model that can be used to study the impact of all treatments on socioeconomic status (SES). Choices of treatments are of extra importance within the field of orthopaedics, where symptomatic surgery is common, death is not a relevant outcome and solid outcome measures are difficult to define.

Since this thesis includes four register-based studies and the International Classification of Diseases (ICD) -codes used in these registers do not allow to distinguish between an anterior cruciate ligament (ACL) injury and a posterior cruciate ligament (PCL) injury, both injuries were considered as one entity. However, since isolated PCL injuries are rare, the results presented in this thesis can be safely extrapolated to ACL injuries in general.

## 4 BACKGROUND

### 4.1 THE CRUCIATE LIGAMENTS

#### 4.1.1 History

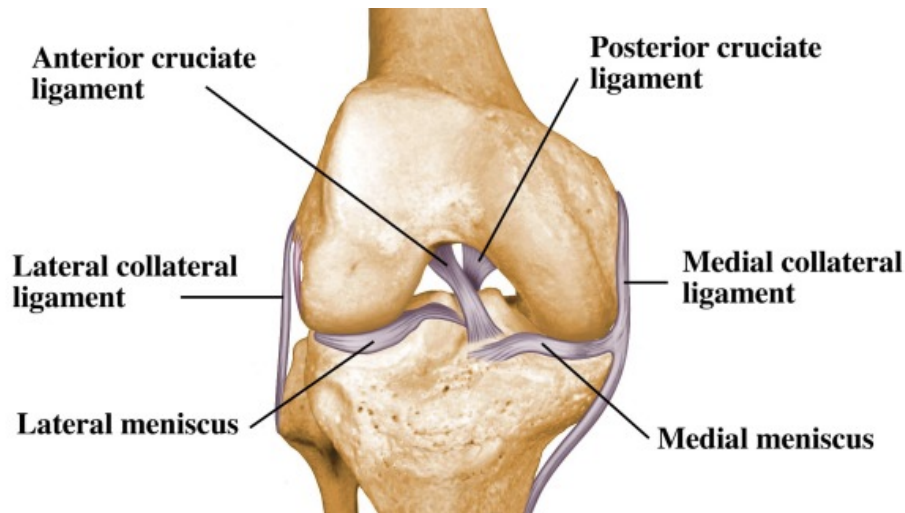
The CL is said to be mentioned in the Smith Papyrus dated to 3000 BC (1). However, since this Papyrus consists of 48 trauma cases –starting with the head and working downwards and never reaching below the chest– it is unclear how well understood the CL was in ancient Egypt (2). Instead, Hippocrates might be the first one to indirectly describe the CL, when in 400 BC he wrote: “Owing to their configuration, the bones at the knee are indeed frequently dislocated, but they are easily reduced, for no great inflammation follows, nor any constriction of the joint” (3). However, it is clear that Hippocrates might not have fully understood the importance of the CL. This was instead described by Claudius Galenus, better known as Galen of Pergamon. He was a prominent Greek physician active during the second century in the Roman Empire. Galen was in charge of treating the gladiators and became therefore the first sports medicine doctor. He acknowledged the importance of a stable knee and described the anatomy of the CL which he named “Genu Cruciatum”. He wrote: “The knee-joint, however, has several other ligaments besides the capsular. One is deep down, cruciate, comparable to that hidden in the hip-joint but twofold in the knee” (4). After that, as with all science, nothing interesting happened until the renaissance, when in 1533 Andreas Vesalius performed the first anatomical dissections since ancient Greek and gave a detailed description of the knee and its ligaments. Then, after another 300 years of silence, W. and E. Weber Göttingen described the biomechanics of the knee joint motion and ever since the CL has never gone out of fashion. In 1856 James Stark published the first description of a CL injury in “Two Cases of Rupture of the Cruciate Ligament of the Knee-Joint”. In 1875 Georges C. Noulis described the clinical examination used to diagnose CL injuries that was later named by John Lachman. Four years later, Paul Segond described the classical symptoms of an acute knee injury and the avulsion fracture of the lateral tibial condyle of the knee, often seen on the x-ray of the CL-injured knee. The CL and its function had finally been described in detail and thus the search for sports medicine’s holy grail began.

#### 4.1.2 Anatomy

The knee-joint is a free movable joint where the end of the bone is covered with articular cartilage, allowing gliding with minimal friction, and is stabilized by ligaments and muscles (5). The Cruciate Ligament (CL) comprises two ligaments, the Anterior CL (ACL) and the Posterior CL (PCL), and is the primary restraint against anterior and posterior tibial translation and hyperextension of the knee (Figure 1). The ACL originates from the posterior part of the medial surface of the lateral femoral condyle and inserts in a wide depressed area in front of and lateral to the anterior tibial spine. The PCL originates from the posterior part of the lateral surface of the medial femoral condyle and inserts into the depression behind the intraarticular upper surface of the tibia. The ACL is 31-38 mm long and 8 mm thick and has a tensile strength of 1725-2195 Newton (6,7). The ACL is not a single chord but consists of



two bundles, the anteromedial and the posterolateral bundle, all built up of a collection of fascicles that fan out over a broader area (8). The PCL is broader and stronger than the ACL and has a tensile strength of 2000 N. The CLs receive nerve fibers from the posterior articular branches of the tibial nerve and have, apart from its stabilizing purpose, also an important role as a proprioceptive sensor (9).



*Figure 1: The anatomy of the ligaments and joint capsule of the knee.  
From Physiopedia (<http://www.physio-pedia.com/Knee>)*

#### **4.1.3 Injury**

The injury mechanism for CL injury is complex and not fully understood (10). In short, ACL rupture is believed to be a result of hyperextension and PCL rupture of hyperflexion. CL injuries almost always consist of ruptures of the ACL. Isolated PCL injuries are uncommon, accounting for an estimated 3% of all acute knee injuries, with an incidence of 1,8 per 100.000 inhabitants in the general population (11,12). Bilateral injuries of the CLs, also represent a minority. Only three cases of simultaneous bilateral injury have been reported and data from the Swedish Cruciate Ligament Register show that less than 2% of the patients underwent bilateral reconstruction (13,14). Combinations of valgus-external rotation or flexion-internal rotation may also be responsible for ACL injuries (15). 70% of all ACL injuries occur during sporting activities and primarily in activities with knee-pivoting movements such as soccer, floorball, team handball, basketball and alpine skiing (16). Isolated ACL injuries are practically nonexistent, but the concomitant injury could be less or more severe. In best cases, an ACL injury is combined only with a bone marrow lesion or a minor cortical depression. A concomitant meniscus injury occurs in between 36-68% of all injuries and an injury of the collateral ligament and/or a more severe cartilage injury, in about a third of all ACL injuries (17).

CL injuries among children are rare and account for less than 5% of all CL injuries and rarely occur in children under the age of 9 years (18). Children's knees are very different from the knees of adults because of growth plates and an increased knee laxity. The growth plates fuse

around 13,5 years for females and 15,5 years for males, after that the incidence of CL injury increases dramatically (19).

#### 4.1.4 Incidence

For a long time, the incidence of CL injuries was unknown. Many studies have described the incidence in subpopulations such as athletes, but the general population has remained somewhat unstudied due to lack of population-based studies. For over 20 years, researchers referred to a Danish study reporting a yearly incidence of around 30/100,000 inhabitants (20). Afterwards, a Swedish hospital-based study of 159 patients reported a yearly incidence of 81 per 100,000 inhabitants aged 10 to 64 years, and after that numerous studies have confirmed this number (21). Baseline epidemiologic data including all patients with CL injury, treated both operatively and non-operatively, are crucial to be able to validate and judge the generalizability of results from procedure registers.

Many risk factors for getting a CL injury have been described. Of course, exposure to activities that include knee-pivoting movements confers the highest risk, but also gender has been shown to have a big effect. Female patients have been shown to have an increased risk for CL injury, ranging between 2.4 and 9.7 times greater than that for male patients (22–26). Other risk factors include environmental (e.g. the surface on which the activity is taking place), anatomical (e.g. the dimensions of the intercondylar notch) and hormonal (e.g. the day of the menstrual cycle).

#### 4.1.5 Diagnosis

At the time of injury, rapid hemarthrosis develops and the patient is prone to seek emergency care. Diagnosis is made by clinical investigation, magnetic resonance imaging (MRI), or arthroscopy (27).

When a patient presents at the emergency ward with a knee-trauma and possible CL injury the following investigations are performed:

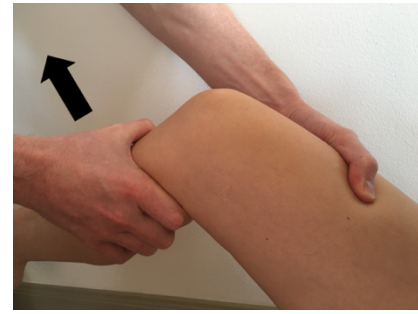
##### 4.1.5.1 Clinical investigation

First an inspection of the knee is performed to look for cuts, swelling, bruising or deformations. Usually a CL-injured knee has a significant swelling because of the hemarthrosis. After inspection, passive and active range of motion is evaluated where it is important to identify any knee locking that can occur as a result of a concomitant meniscus injury. Palpation around the joint for tenderness, warmth and swelling follows, where a medial meniscus injury could be suspected if the joint line on the inner knee is tender. Finally, the stability of the knee is tested and the Lachman's test is recognized as



Figure 2: A swollen knee is the result of the rapid hemarthrosis

reliable, sensitive and usually superior to other clinical tests when diagnosing an ACL injury (28,29). The test was named after the orthopedic surgeon John Lachman and is performed with the patient positioned supine (Figure 3). The knee is flexed at 20–30 degrees and one hand is placed behind the tibia and the other on the patient's thigh. The tibia is pulled forward and the translational movement of the tibia compared to the femur is assessed. In an ACL-deficient knee there is no firm endpoint of the movement and there is more than 2 mm anterior translation of the tibia compared to the uninjured knee (30).



*Figure 3: Lachman's test*

It must be pointed out that in the acute phase, pain and swelling may preclude a conclusive clinical examination mandating follow up and reassessment of the patient.

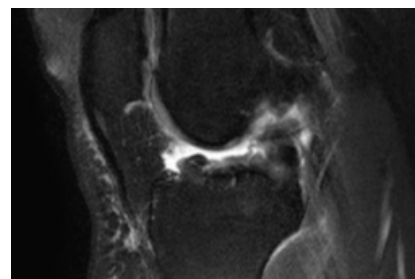
#### *4.1.5.2 Imaging*

In the acute stage an X-ray of the knee is performed to rule out any major fractures. Apart from swelling, other signs could be seen on the X-ray that indicate ACL injury. Most famous is the Segond fracture which is an avulsion fracture involving the lateral aspect of the tibial plateau (Figure 4) (31). The arcuate sign represents another avulsion fracture, associated with ACL injury, occurring at the proximal fibula at the site of insertion of the arcuate ligament (32). Another sign of ACL injury is the deep lateral femoral notch sign which is a depression on the lateral femoral condyle at the terminal sulcus (33). If there is a complete rupture of the ACL, the anterior tibial translocation sign could be seen, which refers to a subluxation of the tibia relative to the femur of more than 7 mm (34).



*Figure 4: Segond fracture*

A thorough patient history, combined with a clinical examination, is often enough to make the diagnosis. However, most hospitals have guidelines recommending a subacute (within two weeks) MRI if a patient presents with acute knee effusion after trauma. A MRI investigation of a CL-injured knee can visualize both primary and secondary signs of the injury (Figure 5). Primary signs refer to the ligament itself while secondary signs are closely related to the CL injury. Primary signs are fiber discontinuity, increased signal on T2 or a change in the expected course of the CL, while secondary signs include bone contusions, meniscus injuries, as well as signs that could also be seen on the X-ray (35).



*Figure 5: Complete rupture of the CL*

#### 4.1.6 Treatment

When an adult patient (the management of pediatric ACL tears differs) is diagnosed with a CL injury, broadly speaking, there are two possible treatments: operative or non-operative (36). A torn ACL will not heal by itself and has a 40-100% failure rate even after surgical repair using sutures (37). In best case, a torn or partially torn ACL could heal against the PCL preserving some mechanical stability and proprioception. Non-operative treatment aims to build up the muscles stabilizing the knee joint as well as the proprioception and is performed in five steps. All five steps could be followed regardless of whether later surgical treatment is planned or not (38).

- 1) **Reduce swelling:** In the acute stage, the first step is to reduce swelling using the established PRICE-principles (Protection, Rest, Ice, Compression and Elevation).
- 2) **Regain full range of motion:** The next step is to perform exercises aiming to regain full range of motion, especially focusing on extension. A patient should start using his/her knee a few days after injury and can usually walk with full weight-bearing after 1 to 2 weeks (39).
- 3) **Build up strength:** After 2 to 3 weeks, the swelling has been reduced and full range of motion has been established. By then, aggressive rehabilitation should be performed to build up strength and endurance. To protect the ACL-deficient knee-joint from tibial translocation, the hamstring muscles should be trained to the same strength as the quadriceps muscle, which normally is 30% stronger (40).
- 4) **Build up proprioception:** When the muscles stabilizing the knee have regained almost full strength, balancing exercises aiming to increase proprioception could be started.
- 5) **Evaluate the effect:** When a patient has undergone the first four steps, it is time to evaluate the effect of the training, what remaining symptoms the patient has and what activities the patient can undertake. The result of this evaluation will decide if the patient should go through a CL-R or if nonoperative treatment has had satisfying results.

##### 4.1.6.1 CL reconstruction

Optimal treatment of a CL injury is under continuous debate despite all advances ranging from surgical methods to new rehabilitation protocols (41). The purpose of CL-R is to restore kinematics and counteract knee instability, aiming to make it possible for the patient to return to a desired activity level. It must be remembered though, that even if CL-R improves stability, it does not recreate the original kinematics and that anatomical stability is not the same as subjective stability (42). CL-R is a common procedure today and usually the choice of treatment for patients engaged in high-level sports (43,44).

**History:** The first ACL repair was performed by Mayo Robson in 1895 who, using an open technique, sutured a ruptured ACL in a 41 year old miner from Leeds (45). Hey Groves was the first one to perform an ACL reconstruction using an iliotibial band graft. The Swedish

orthopedic surgeon, and pioneer within this field, Ivar Palmer, published already in 1937 the first femoral drill guide for ACL reconstruction (ACL-R) which is very similar to the drill guide used today. He also performed the first anatomical double-bundle reconstruction with good results over 50 years before this technique was introduced (45). Ivar Palmer stated two ideas: 1) ACL injuries need to be diagnosed fast, which is still unquestioned; and 2) they need to be surgically repaired, which is still under debate. Over the years, the surgical techniques have changed and evolved. Since all attempts to reinsert or suture the ACL have failed, surgical reconstruction using a graft has become the only surgical possibility (46,47). Different graft choices have been used. Artificial grafts have been tried and failed (48). Willis Campbell introduced the patellar tendon as a graft in 1939, which was the golden standard in Sweden until studies showed that hamstring grafts had similar outcome but less donor-site morbidity in the late 90's (49). The arthroscopic technique was introduced in the 1970's and since David Dandy performed the first arthroscopic ACL-R in 1982, this technique has continued to be used (50).

**Timing:** The optimal timing for performing ACL-R differs between different patients. For patients who are elite athletes, with great demands on their knee function, ACL-R is usually performed as soon as the swelling has receded, the patient has regained a full range of motion and has a good control of the quadriceps (51). For patients who are not engaged in high-level sports, studies have shown that structured rehabilitation, with delayed ACL-R as an option, has had as good outcomes as immediate ACL-R (52,53). However, a disadvantage of this option is that an unstable knee is more vulnerable to new trauma and risk for concomitant injuries, especially meniscal tears.

**Techniques:** Today in Sweden, ACL-R is almost exclusively done arthroscopically using hamstring autografts (14). Allografts have historically been used successfully but remain only as an alternative to autografts due to the higher costs of this procedure and the risks of transmission of disease. Different fixation methods and bio-absorbable implants are being introduced, although metal fixation is still the most common choice.

**Complications:** Complications after a CL-R are rather uncommon, having satisfactory rates as high as 80-90%. Such complications can be divided into two categories: 1) those associated with the surgery itself, and 2) those associated with the reconstruction (54). Complications associated with the surgery itself are mainly infection and thrombosis. An infection after CL-R is a rare but severe complication, and septic arthritis occurs after 0,5-1% of all operations (55). As is common after all surgeries that result in immobilization, especially in the lower limbs, there is an increased risk for blood clots. Deep venous thrombosis occurs after about 1 to 2% of all operations, of which 1 out of 20 result in a pulmonary embolism (56). Among the complications associated with the reconstruction of the CL, knee-pain is rather common, occurring after about 20% of all surgeries (49). Another complication associated with CL-R is knee-stiffness or loss of motion, which occurs in up to 10% of all reconstructions, but is dependent on the quality of the rehabilitation (57,58). The

last complication associated with CL-R is failure of the graft, which occurs after 10-15% of the surgeries (59).

#### **4.1.7 Long-term effects**

The natural history of the CL-deficient knee is yet to be fully understood. However, it is clear that an injured knee, in many cases, results in an individual not being able to engage in sports to the extent that he or she wants, while also being predisposed to an early onset of osteoarthritis (OA) (60). Among clinicians in Sweden, there is a general belief that an isolated CL injury, by itself, would not have any major long-term negative effects. Instead, it is believed that the concomitant injuries at the time of trauma (i.e. meniscus, cartilage or subchondral injuries) or the secondary meniscus and cartilage injuries resulting from an unstable knee, are what truly cause the development of OA. This is supported by studies presenting meniscus injury as the biggest risk-factor for developing OA (61–64). However, studies answering if CL-R protects the knee from the development of secondary meniscal tears and/or osteoarthritis are still lacking. Results from a meta-analysis and two systematic reviews show a prevalence of OA after CL injury ranging between 0 to 48% (62,65,66). For patients diagnosed with a meniscal injury the prevalence of OA is higher (67,68).

##### *4.1.7.1 Osteoarthritis*

Osteoarthritis could be the world's oldest known disease. Typical joint changes have been identified in dinosaurs living 50 to 70 million years ago, and is also a common finding among Egyptian mummies (69,70). However, since Hippocrates, all joint pain was diagnosed as gout, and OA was not recognized until the 18<sup>th</sup> century. Today, OA is pushing to be on the top 10 of the global disease burden list, with a prevalence of about 5% in patients over 26 years and 12% in patients over 60 years (71–73). The symptoms of OA are pain, morning stiffness and loss of function. OA is diagnosed by clinical investigation and radiography. There is no way of reversing the pathologic process in the joint. Instead, treatment regime focuses on relieving the symptoms, primarily with analgesics, physiotherapy, weight loss and ultimately joint replacement.

## **4.2 SOCIOECONOMIC STATUS AND SYMPTOMATIC SURGERY**

Socioeconomic status is a way to measure an individual's access to important resources such as money, material goods, networks of people, power, education, and healthcare (74). The influence that SES has on healthcare has been widely recognized (75). Higher SES has been associated with a higher access to and utilization of surgical and pharmacological treatments as well as better outcomes after treatment (76–80). Education is probably the best single indicator representing SES (81,82). However, if the individual in focus is young and has not finished his/her education, the education of the individual's parents is a suitable substitute. Money is also a common indicator to measure SES, but it can take many shapes. For example, salary is interesting if one wants to study an individual's possibility to or success at work. But, an individual's disposable income might be a better indicator of how much money a person has access to (i.e. wealth). However, most families consist of several members, each

with different resources which are shared among all. Thus, the family's disposable income might be a good way to capture wealth.

The analysis of socioeconomic data as exposures and/or outcomes for orthopedic conditions has not been thoroughly undertaken. This is probably due to the fact that such variables are deemed to be secondary to clinical outcomes and not even thought of as causal. This conception is faulty, especially in orthopedics, where the return to optimal physical capability often translates into productivity. Therefore, an indicator for SES, for example salary, can be regarded as a surrogate variable indicating treatment success, in cases where treatment is sought for controlling symptomatology.

Some conditions, more common in the field of orthopedics, are in great need of more evidence and new outcome measurements. These are conditions where: i) death is not a relevant outcome; ii) there is an existing debate exists about the results of surgical treatment compared to conservative treatment; and iii) indication for surgery includes relative or subjective symptomatology. Surgical treatment for these conditions are referred to as symptomatic surgery.

For these conditions studies have shown that there is a great disparity between how various orthopedists choose to treat the exact same injury (83). The variable that had the strongest association with non-surgical treatment was experience, where younger surgeons with less experience more often choose a more aggressive treatment including surgery.

The burden of musculoskeletal diseases has been stated to account for as much as 9.6 to 28.9% of all years lived with disability and affecting especially low-income countries (84,85). This burden has an economic aspect represented by direct, indirect and intangible costs (i.e. expenditure for medical care, costs resulting from loss of function and decrease in quality of life respectively) (86). An important indirect cost of musculoskeletal injury is loss of productivity. For this reason, it is reasonable to argue that returning to a productive life could be a relative indication for aggressive treatment in specific musculoskeletal conditions. It is therefore interesting to study an alternative outcome such as the change in SES after orthopedic treatments, especially in those where the lack of evidence ignites debates about its indications.

The effects of medical treatment and surgery transcend the limits of healthcare, where the benefits or harm of a particular measure could extend to the economy, welfare, lifestyles and society. Conditions treated with symptomatic surgery are of particular interest. Creating new covariates and outcome variables are essential to understand if symptomatic surgery has a place, and if so, who would benefit from this surgery. Recognizing this fact and the importance of personalized medicine, socioeconomic variables can be used in order to be able to reach better and individualized decisions. Ultimately, this will contribute to create a clinical decision-making aid that includes a wide variety of outcomes adapted to each individual patient. The advantages of such an approach is that both patients and clinicians can have clear expectations from each different treatment option, which would in turn, be

translated to better patient satisfaction. Additionally, preemptive steps can be taken to improve risks or conditions that could worsen outcomes.

### **4.3 PERSONALIZED MEDICINE**

All treatments are not for everyone. In almost all cases, there are subgroups of patients where the effect of a specific treatment is greater or smaller. In personalized medicine, patients are divided into different groups where the medical decisions, practices, interventions and products are tailored to the individual patient based on their predicted risk or response to diseases (87). In a tax financed public healthcare system, where the resources are scarce, it is important that expensive treatments are prioritized those where the treatment has a positive effect. To help the clinician decide which treatment is the right decision for each specific case, decision-making tools need to be created. For symptomatic surgery, the goal is to relieve the patients of his/her symptoms. However, this outcome is hard to study and an alternative, clearer outcome is missing, and therefore additional, alternative outcomes need to be defined and studied.

### **4.4 REGISTER-BASED RESEARCH**

The definition of register-based research is research, based on data from records kept by government agencies or other organizations. Apart from the patient registers including health data, Sweden also collects social, demographic and environmental data, as well as biobanks with blood samples from all inhabitants and hundreds of quality registers for specific diseases. Because of the PIN, a unique identifier that is assigned to all Swedish citizens, the data can be traced to individuals and linked between the registers, allowing researchers to construct extensive databases including a wide variety of healthcare related data. Sweden has a longtime tradition of keeping national registers. This tradition started in 1686 when the Swedish church began to register members in local church books that enabled the Swedish state to follow its population, enroll people in the army and collect taxes (88). The Swedish registers have evolved and grown over time and are today a gold-mine for researchers aiming to confirm or dismiss their hypotheses.

This unique database can lead you into the false assumption that everything can be measured. This might be true if you can find the right questions to ask, but register-based research also comes with a few challenges. The biggest challenge is that, when working with register data, you only have the data that is included in the registers and you must work with the quality that this data has. If the data is not gathered systematically, and the rate and method of data collection are inconsistent, or where the way to diagnose and register the disease in the healthcare records has changed over time, misclassification of the data and bias may be introduced. The size of the registers can help us with this problem since we always can include many people and accept that effect measures are biased toward the null (89). Even if we can compensate for random exposure and misclassification, and adjust for measurable confounders, some flaws, like missing data, can never be taken care of.



The access to data has opened a new field where new methods and concepts are developed, aiming to use healthcare data to create new outcomes measuring quality, which can be used to improve, govern and reimburse healthcare. Even if this has a good intent, creation of Health Outcomes Measurements (HOM) is hard and should be treated with the highest of respect. Two conclusions when aiming to create a HOM are:

1. No single measurement for outcome can measure quality. There are two ways to work with this. Either you can choose one indicator that is the predominant goal of the treatment and respect the fact that all details are lost, or use a quality indicator with a shotgun approach, where you hope that all your outcomes together give a fair picture of the overall quality.

Since every different register has its unique flaws, many different data-sources can be used to minimize the risk for bias.

# AIMS

## 4.5 STUDY I

Very few studies focusing on CL injuries are register-based studies, therefore the incidence of CL injury in the general population and baseline characteristics of patients with CL injury is unknown. Such epidemiological data are needed to be able to validate and judge the generalizability of the large amount of clinical studies performed. The Aim of **Study I**: *To study the incidence and characteristics of patients diagnosed with cruciate ligament injury in Sweden.*

## 4.6 STUDY II

The end stage after a CL injury is often OA, which due to its severe consequences, is something everyone aims to prevent. Many studies have investigated if CL-R protects from the development of OA, but the consensus of all these studies remains inconclusive. Therefore, prevention of the development of posttraumatic OA is still an argument for CL-R. The Aim of **Study II**: *To study the association between CL injury and development of post-traumatic osteoarthritis in the knee in patients treated operatively with CL reconstruction compared with patients treated non-operatively.*

## 4.7 STUDY III

For many orthopedic conditions, as well as CL injury, the indication for performing surgery is subjective and is negotiated between the clinician and the patients depending on the patient's symptoms and/or expectations about how the injury will affect life. For these conditions, it is important to understand which are the factors that influence the treatment decision. The Aim of **Study III**: *To evaluate the association between SES and choice of treatment in patients with a cruciate ligament injury.*

## 4.8 STUDY IV

For symptomatic surgery, there is no obvious outcome measure except for the patient's experience of less symptoms / better function, which is hard to measure. However, many surgical treatments aim to relieve the patient's symptoms and in many cases, make it possible for the patient to return to work. The Aim of **Study IV**:

*To investigate how the choice of treatment, for patients diagnosed with a CL injury, is associated with patients' future SES.*

## **5 MATERIAL AND METHODS**

### **5.1 PERSONAL IDENTIFICATION NUMBER**

This year (2017), the personal identification number (PIN) celebrates its 70<sup>th</sup> birthday. It was created in 1947 and registered in local parish registers to include information on date and place of birth, sex, and address. It made Sweden the first country in the world to assign all inhabitants a unique identifier nationwide. In 1991 the responsibility for PIN was moved to the National Tax Office (90).

Every person who is registered in Sweden is assigned a PIN. Newborns are given a PIN usually within the first 24 hours of life and immigrants who become permanent residents or intend to stay in Sweden for at least one year are also given a PIN. Immigrants who do not fulfill these conditions are given a coordination number if they use the Swedish welfare system. These coordination numbers are not included in the healthcare registers and therefore immigrants who are not permanent residents or citizens are not included in register-based studies.

The PIN is built up by ten numbers and a separator. The first six indicates a person's date of birth, the separator is a (-) or a (+) depending if the person is over or under 100 years old. Then follows four numbers. The first two were, until 1990, an indication of which county the individual was born in, but since 1990 these two numbers are assigned randomly. The third number indicates the person's sex, with an odd number for males and an even number for females. The last number is a control-number, a construct of the previous nine numbers, which purpose is to make it harder to register a false PIN.

### **5.2 DATA SOURCES**

Sweden has over 50 national registers, over 100 quality registers, over 450 biobanks and accountable research databases. In this thesis four national registers have been used: The Swedish Patient Register, The Total Population Register, The Multi-Generation Register and The Longitudinal Integration database for Health Insurance and Labor Market Studies (LISA).

#### **5.2.1 Swedish Patient Register**

The Swedish Patient Register, or the National Patient Register (NPR), was established by the National Board of Health and Welfare in 1964 (91). It contains documentation of all individual hospital discharges, each record corresponding to one hospital-episode. Every record includes a national registration number, the date of hospital admission and discharge, age, sex, geographical location of the hospital, clinical ward, and up to 8 discharge diagnoses and surgical procedures. For inpatient visits, the register has been 100% complete since 1987. The outpatient register was started in 2001 and includes information on specialist care, and since 2004, it has been mandatory for all publicly financed healthcare providers to register the ICD codes for all diseases. The diagnoses are coded per the World Health Organization's

International Classification of Diseases (ICD-7 until 1968, ICD-8 from 1969-1986, ICD-9 from 1987-1996, and ICD-10 thereafter).

### **5.2.2 Total Population Register**

Statistics Sweden established the Total Population Register (TPR) in 1968. This happened as part of a big digitalization of the local population registers.(92) The register contains information on all citizens births, deaths, place of residence, civil status, migration, and citizenship. The local tax offices report to the National Tax Board and the register is updated every day.

### **5.2.3 Multi-Generation Register**

The first version of the register, The Second Generation Register, was established in 1994 and replaced by the Multi-Generation Register in 2000 (93). The Multi-Generation Register is a part of the TPR and allows for identification of family members by linking all Swedish residents to their parents. The register contains information of all individuals who, during any period, have been registered as Swedish citizens, since 1961. These individuals are called index-persons and the register contains these person's PIN, and the PIN of biological or adoptive parents. The registry allows linkage between index persons and parents if the parents have a valid PIN, i.e. if they were citizen of Sweden after 1947. Immigrated index persons can be linked to their parents if they came to Sweden before they had turned 18 years old and immigrated together with their parents.

### **5.2.4 Longitudinal Integration Database for Health Insurance and Labor Market Studies**

The first version of the Longitudinal Integration database for Health Insurance and Labor Market Studies was called LOUISE and was established in the mid 1990's (94). The version used today is called LISA and was created in 2003 with the aim to follow and evaluate sick leave absence for Swedish citizens. The register contains information on all sorts of income, employment and education for all Swedish citizens, aged 16 years or older, since 1990. The income variables include, for example, salary, return on equity and social security, and a weighted variable where the total income of a whole family is included. It includes information on what is the highest education an individual has achieved as well as employment variables including what type of work the person is doing as well as absence from work.

## **5.3 STUDY POPULATIONS AND DESIGNS**

### **5.3.1 Defining Cruciate Ligament Injury and Surgery**

Patients with a CL injury were identified using the ICD-9 and ICD-10 coding system. Since the ICD-codes do not allow to distinguish between ACL and PCL injury, both injuries and potential surgical treatments were treated as one. The following ICD-codes were used to define CL injury:

- ICD-9
  - 844C – cruciate ligament in knee (**Study I, II, III, IV**)
- ICD-10
  - S835 – distortion engaging the cruciate ligament in the knee (**Study I, II, III, IV**)
  - M235 – chronic instability in the knee joint (**Study I, II, III, IV**)
  - S837 – Injury to multiple structures of knee (**Study II**)

Patients who underwent CL-R were identified using the Swedish version of Classification of Surgical Procedures (NOMESCO): The following codes were used to define CL-R:

- 8573 – reconstruction of ligament in knee (**Study I, II, III, IV**)
- NGE41 – arthroscopic or endoscopic reconstruction of ligament in the knee without foreign material (**Study I, II, III, IV**)
- NGE42 – open reconstruction of ligament in the knee without foreign material (**Study I, II, III, IV**)
- NGE49 – reconstruction of ligament in the knee without foreign material, unspecified (**Study II, III, IV**)
- NGE51 – arthroscopic or endoscopic reconstruction of ligament in the knee with foreign material (**Study II, III, IV**)
- NGE52 – open reconstruction of ligament in the knee with foreign material (**Study II, III, IV**)

### **5.3.2 Defining Symptomatic Osteoarthritis in the Knee**

The NPR contains complete information from inpatient care since 1987 and information from specialist outpatient care since 2001. Symptomatic OA was defined as registered OA diagnosis or a registered surgical procedure due to knee OA, in either inpatient or outpatient care. The following codes were used to define symptomatic OA:

- OA: M170- M179 and corresponding ICD-9 codes
- Operations due to knee OA: 8191, 8423–8428, NGB09-NGB99, NGC09-NGC99, NGG09-NGG99, NGK59, NGN49; NGU09, NGH2.

### **5.3.3 Defining Meniscus Injury and Surgery**

Meniscus injury was defined as a registered diagnosis of meniscus injury and meniscus surgery as a registered surgical procedure equivalent to meniscus injury. For patients under the age of 35 the meniscus injury was classified as acute. The following ICD-codes were used to define meniscus injury:

- Meniscus injury: ICD-10: M232, M233, S832, S837 and corresponding ICD-9 codes
- Meniscus surgery: NGD

### 5.3.4 Overview of Study I

#### 5.3.4.1 Study population

All patients with at registered CL injury were included in the study. Data were collected from 1987 when the NPR was complete with inpatient visits. However, a big increase in registered cases was seen in 2001 when the NPR also included outpatient-visits. In 2001, there was a pool of registered cases that were interpreted to be prevalent cases from previous years. From 2002 and onwards the number of cases stabilized and these cases were interpreted to be incident cases and were all included in the study (Figure 6).

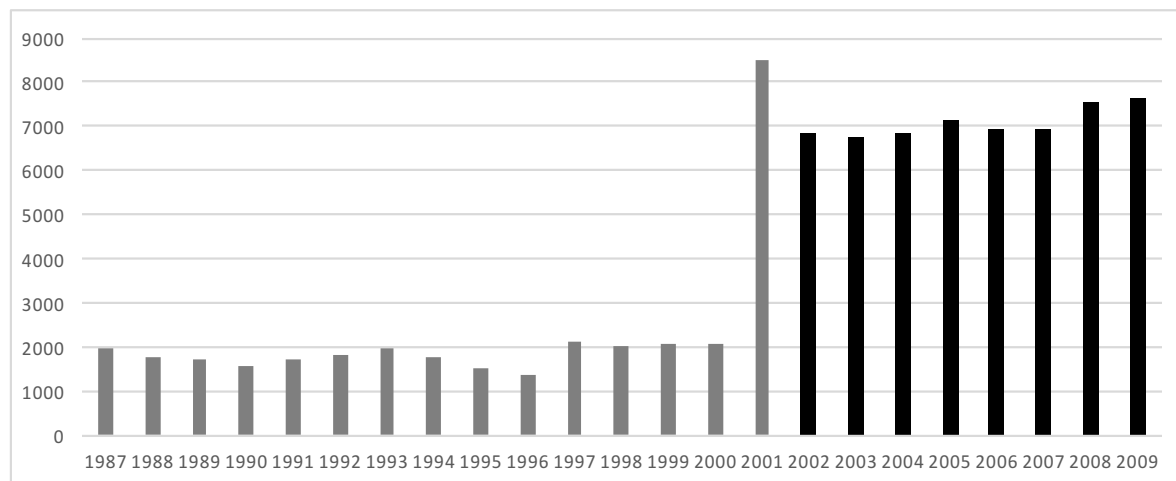


Figure 6: Incident and prevalent cases of CL injury in NPR

#### 5.3.4.2 Study design

This study is a national, register-based, descriptive epidemiology, cohort study.

### 5.3.5 Overview of Study II

#### 5.3.5.1 Study population

In this study, all patients aged 15-60 years with a registered CL-injury in the NPR between 1987 and 2009, were included. The age limits were used to exclude patients younger than 15 years old at diagnosis and exclude patients over 60 years. Younger patients were excluded since the consensus regarding treatments and outcomes of CL injury among children with open epiphysis widely differ from treatment of adult patients. Older patients were excluded since CL injury among older patients are rare and potentially misclassified. Patients that had a preexisting OA diagnosis or surgical procedure, that had been registered before the first registered CL injury, were also excluded.

The follow-up started at the date of the first registered CL injury and ended at the date of the first of following events: registered diagnosis of knee OA, registered operation due to knee OA, emigration, death or December 31st 2009. All patients with a follow-up shorter than two years were excluded since OA prevention trials need a follow up time of at least two years.

### 5.3.5.2 Study design

This study is a national, register-based cohort study.

### 5.3.5.3 Exposure, outcome and covariates

The exposure in this study was CL-R and the outcome was symptomatic knee OA, both were categorized as dichotomous variables. Four covariates, sex, age-group, year of injury and acute meniscus injury were included in the model. Meniscus injury was included as a confounding factor, independent of whether the date of the meniscus injury/surgery was before or after the first date of the CL injury.

## 5.3.6 Overview of Study III

### 5.3.6.1 Study population

All patients with a registered CL injury in the NPR between 2002-2009 were included in the study (Figure 7). Patients with surgery recording errors (i.e. CL-R dates prior to injury) were excluded.

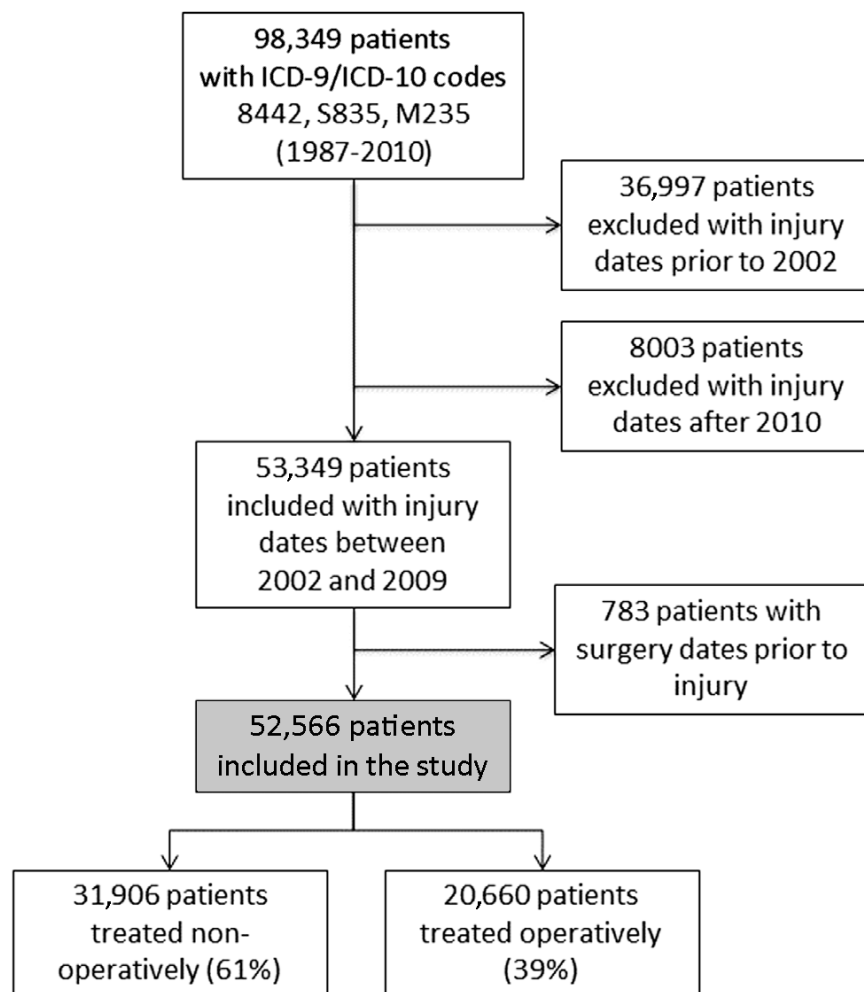


Figure 7: Flow of patients through Study III

### 5.3.6.2 *Study design*

This study is a national, register-based cohort study.

### 5.3.6.3 *Exposure, outcome and covariates*

The exposure in this study was SES for which two different indicators were used, (1) education (2) household income. To determine the educational level of the patient the number of total years of education was calculated using 5 different categories: 5, postgraduate/professional training or standard college/university graduation; 4, partial college/university education; 3, high school graduation (12 years); 2, vocational schooling (10th or 11th grade); and 1, junior high school (including 9th grade) or less. The highest achieved educational level of the patient (or the patient's parents for those 25 and younger) was used. For income, the patient's total household disposable income per consumption unit was used. This was categorized in quartiles by year of injury. A weight system is used to allow comparisons of the household income between different households with different compositions of household-members (95). In this weight system, a single adult and first adult in a cohabiting relationship weights 1.0, a second adult in a cohabiting relationship weights 0.51, a household member older than 14 years of age weights 0.5 and a household member younger than 14 years weights 0.3. The outcome was CL-R which was categorized as a dichotomous variable. The two covariates sex and categories of age (<10, 11-20, 21-30, 31-40, 41-50, >50 years) were included in the study.

## 5.3.7 **Overview of Study IV**

### 5.3.7.1 *Study population*

All patients with a diagnosed CL injury, with at least a five-year follow-up, that were part of the workforce at the time of injury were included in the study. This population was defined by first including patients with a CL injury registered between 2002 and 2011. All patients with surgery dates more than two years after injury or with surgery recording errors were excluded to create comparable groups. Being part of the workforce was defined by excluding patients under the age of 16 and all patients who were retired or students at the time of injury. Patients over the age of 60 were excluded because injuries in this older population are rare and are potentially misclassified and are seldom subjected to surgical treatment for CL injuries. Follow-up was from date of CL injury and ended after 5 calendar years, emigration, death or December 31st 2010, whichever came first. All patients with a follow-up shorter than five years were excluded. Finally, all patients who had missing data needed for calculating the outcome (i.e. no reported baseline disposable salary, and/or no reported salary at 5 years after the year of injury) were excluded. A total of 18,507 patients were included in our analysis (Figure 8).



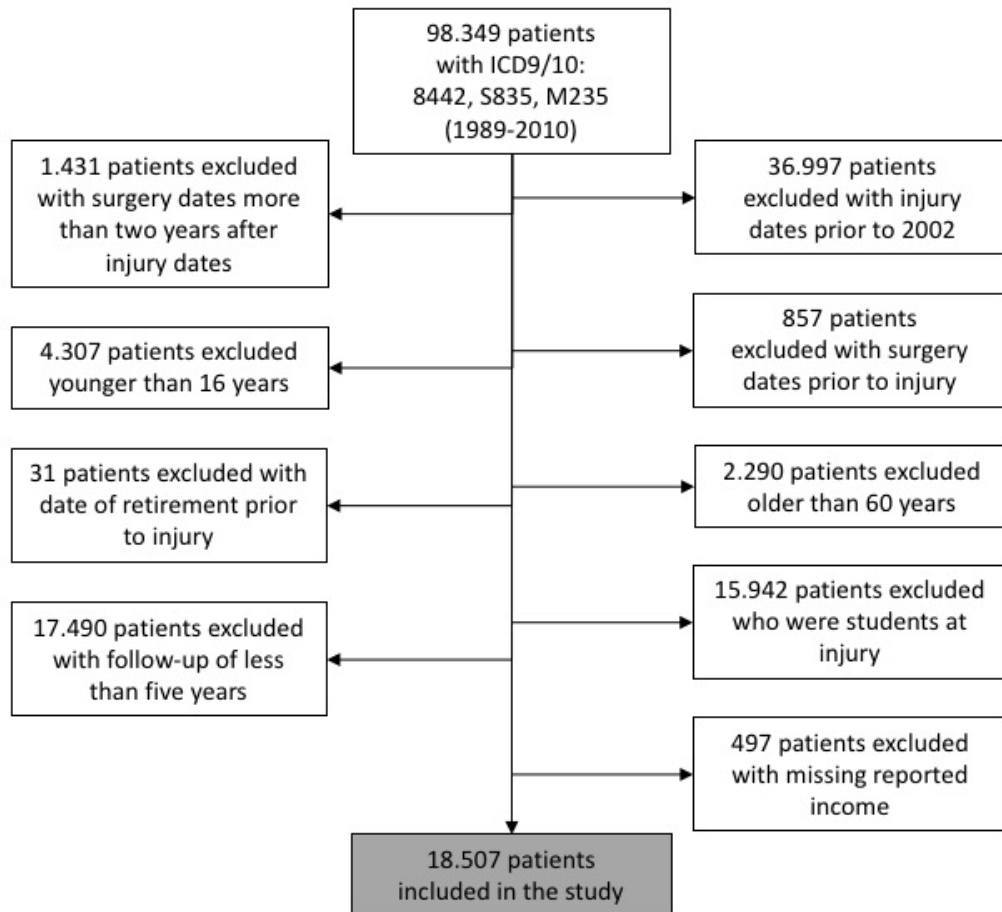


Figure 8: Flow of patients through *Study IV*

### 5.3.7.2 Study design

This study is a national, register-based cohort study.

### 5.3.7.3 Exposure, outcome and covariates

The exposure in this study was CL-R and was categorized as a dichotomous variable. The outcome was the change of salary calculated as the salary reported five years after the year of injury divided with the baseline salary (the salary reported the year before injury). To allow for calculations, the salary for individuals with reported zero or negative salary at baseline were converted to the highest salary of the three years prior to injury or 1 SEK, whichever was highest. Those with reported zero or negative salary at 5 years after the year of injury were converted to 1 SEK. In total nine covariates were included in the study. The year of injury was included to adjust for inflation and pre-injury salary was included as an effective strategy to analyze change (96). To control for and study possible confounding and effect modifications, the covariates, age, sex, residence area, comorbidities, meniscus injury and SES were included (Figure 9). Age was categorized into five groups (<20, 21-30, 31-40, 41-50, >50 years). Type of work was classified into 10 groups based on the International Standard Classification of Occupations (ISCO-88) (1, legislators, senior officials and

managers; 2, professionals; 3, technicians and associate professionals; 4, clerks; 5, service workers and shop and market sales workers; 6, skilled agricultural, forestry and fishery workers; 7, craft and related trades workers; 8, plant and machine operators and assemblers; 9, elementary occupations; and 0, armed forces occupations) (97). Highest achieved educational level of the patient was included as a primary SES indicator and region of residence (large city, medium urban region and small rural region) as a secondary SES indicator. Since meniscus injury is often presented in combination with CL injuries in more severe knee injuries, the existence or not of meniscus injuries was included in the model. The last covariate was patient comorbidities prevalent at any time between three years before injury and final follow-up and was calculated using an adaptation of the method initially described by Elixhauser et al (98).

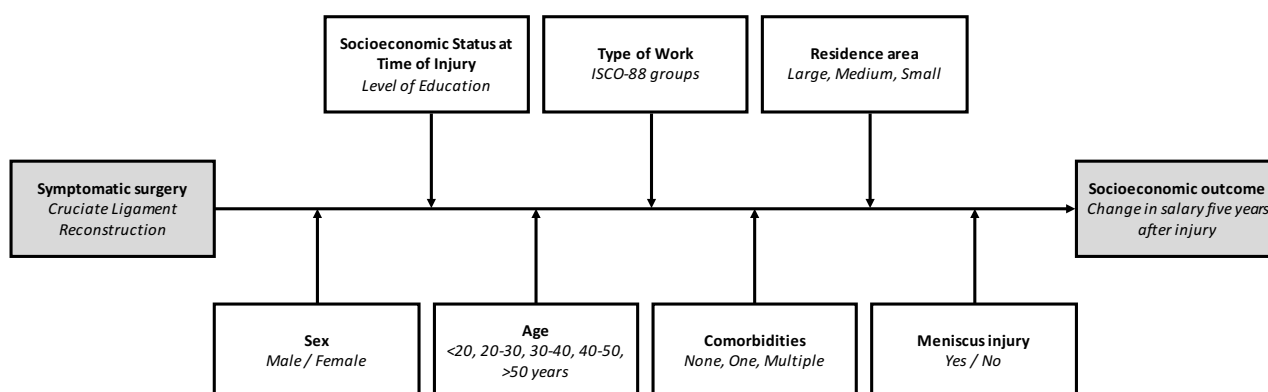


Figure 9: The statistical model for change of SES as outcome

## 5.4 STATISTICAL ANALYSIS

Statistical analysis within the field of epidemiology is usually used to describe the association between an exposure and an outcome. In this thesis, this has been done by 1) formulating the hypothesis, 2) defining the exposure, outcomes and covariates. 3) collecting data from individuals in the national registers, 4) analyze the data. The conclusions in this thesis have been made based on the results of these analysis and the patterns of associations described.

The specific calculation that is performed or the model that is chosen depends on many different factors, for example if the variable is continuous, categorical or binary, if there is variation over time or how the variables are distributed. In this thesis, several statistical models were used.

### 5.4.1.1 Statistical tests

A statistical test is used to make inferences about the data by providing a tool that can quantify the possibility that the observed pattern is real or due to chance. In **Study I** age- and sex-specific incidence rates were calculated. To calculate the significance of the results (level was set at  $p < 0,05$ ) a Student t test was used for the comparisons of continuous variables and a Chi<sup>2</sup> test for the categorical variables when comparing means of the groups. Confidence

intervals for estimated incidences were calculated assuming a Poisson distribution for the number of newly diagnosed patients.

#### *5.4.1.2 Kaplan-Meier*

A Kaplan-Meier analysis is usually used as survival analysis (i.e. to calculate the fraction of patients alive after a treatment.) It is a non-parametric statistic which means that it does not make any assumptions about the distribution of the data. In **Study I** a Kaplan-Meier estimate was computed to describe the probability of being operated with CL-R. A statistical test (the log rank test) was used to compare the survival curves.

#### *5.4.1.3 Regression models*

A regression model is used to calculate the relationship between and among different variables. The model got its name from Francis Galto who used the technique, in the 19<sup>th</sup> century, to describe the relationships between the height of the fathers to the height of their sons. The model showed that sons of tall fathers tended to regress in height down to the normal average, thereof the name regression. A generalized linear model is a more flexible model than an ordinary linear regression. In an ordinary linear regression a constant change in a predictor results in a constant change in the response variable. This does not work if the data is not normally distributed or if the outcome is binary. In this thesis the following regression models were used.

#### **Poisson regression model**

The Poisson regression model is a generalized linear model. The Poisson regression model assumes that the outcome variable has a Poisson distribution and is useful, for example, when the outcome is a binary variable and independent of time. It is also a model that is fast to run on big data-sets in the analysis software.

In **Study I** the Poisson regression model was used to estimate the risks of surgery associated with sex, age, residential county, and year of diagnosis.

In **Study III** univariate and multivariate Poisson regression models were used to estimate relative risks and 95% confidence intervals (CIs) for the association between household income or education and CL-R.

#### **Cox proportional hazard model**

As the Poisson model, the Cox proportional hazard model is a survival model, but it differs in how it handles the time for an event to occur. The model allows to study the impact that the different covariates included have on every specific time to the event studied. For this model to work, data needs to fulfill the proportional hazard assumptions (99). This means that the relative effect of a covariate over the outcome (baseline) should be continuous over time. For example, if CL-R has the potential to decrease the risk of developing symptomatic OA with 50%, this decrease in risk of 50% needs to be constant over time for the proportional hazard

assumption to hold. If the proportional assumption does not hold, the follow-up needs to be divided into smaller strata where the assumptions do hold.

In **Study II** a Cox proportional hazard model was used to estimate the association between CL-R and the development of symptomatic knee OA. The result was presented as hazard ratios (HR) with 95% CI and CL-R was treated as a time-varying covariate. Previous studies have described that the time from CL injury to CL-R might influence the outcome, therefore a stratified analysis was performed for this covariate categorized to: less than 3 months, 3 months to one year or over 1 year (100). Tests showed that the proportional hazard assumptions did not hold, thus, the follow-up was stratified and hazard ratios estimated for those with a follow up of 2–4,9 years, 5–9,9 years, and over 10 years.

#### 5.4.1.4 ANCOVA

ANCOVA stands for analysis of covariance and is a generalized linear model that blends an analysis of variance ANOVA with a regression. ANCOVA can analyze if the population means of an outcome (a dependent variable) differ depending on the exposure (an independent variable) and at the same time statistically controlling for the effects of covariates that are not of primary interest. This is useful when not only wanting to study the effect of an exposure on an outcome, but also to see how that effect differs depending on different covariates. Something that is necessary when constructing a decision-making tool.

In **Study IV** an analysis of covariance (ANCOVA), with a logarithmic transformation of the dependent variable (outcome) and using least square means, was used to estimate the association between CL treatment and change in salary five years after injury. The categorical covariates sex, age groups, region of residence, type of work, meniscus injury, comorbidities, level of education, year of injury, and the continuous covariate income the year before injury, as well as the interactions between CL-R and all categorical covariates (except year of injury) were treated as independent variables and included in the model to account for interactions.

#### 5.4.1.5 Interactions

An interaction happens in situations with three or more variables, where the simultaneous effect of two variables (for example covariates) has an effect on a third variable (for example an outcome) that is not additive. This has an impact when constructing the statistical model. In this thesis interactions have been included in two of the studies.

In **Study II** an interaction between the exposure (CL-R) and one of the covariates (meniscus injury) was included into the full models since the interaction was significant.

In **Study IV** interactions between CL-reconstruction and the categorical covariates sex, age groups, region of residence, type of work, meniscus injury, comorbidities and level of education were included based on clinical knowledge and kept in the model regardless of significance. The interactions were included to internally stratify the model and study the magnitude of the effect modification that these covariates have on the exposure. Including

several interactions and presenting stratified results is the first step in creating a personalized decision-making tool, which is of importance when evaluating which patients will benefit from surgical treatment.

#### *5.4.1.6 Software*

SAS version 9.2, 9.3 and 9.4 (SAS Institute) was used for statistical analyses.

## **6 ETHICAL STATEMENT**

When performing any type of research, the researcher must value the potential benefits of the results against the potential harm to the subjects. Before a research project is started approval from an ethical committee (EC) is required in parallel to critical thinking. If the potential benefits exceed the potential harms and the researcher presents a solid strategy for how they will minimize the risks for the subjects, the EC might approve of the research. Members of the EC are usually appointed by academic or research institutions or by the government (101). The regional EC in Stockholm has evaluated and approved of all studies in this thesis. Dnr 2005/302-31/4 (Amendment 1: Dnr 2010/1713-32; Amendment 2: Dnr 2011/932-32; Amendment 3: Dnr 2013/1363-32/4)

### **6.1 INFORMED CONSENT**

Informed consent is essential in medical research and the right for study participants to decline participation in research is governed by international directives and Swedish law (102). Usually the EC demands that the researcher has personal consent from the subjects. However, since all studies in this thesis are register-based studies, none of the studies deviates from clinical routine or involves direct contact with the study participants, therefore no personal consent is needed (101).

### **6.2 PRIVACY AND DATA SECURITY**

One of the benefits with register-based research is that the collecting of data is the result of routine healthcare and in this thesis, no extra data collection was performed. All data in this thesis were pseudonymized. Pseudonymization differs from anonymization by the fact that there is a key stored that can be used to find the identity of the individuals in a dataset. This was important to be able to link the subjects between different datasets. These keys were not accessible but held by The National Board of Health and Welfare and Sweden Statistics.

Register-based research imposes very few risks on the study participants, but the risks that do exist are significant. First, data can be mishandled and accessed by non-researchers. This was prevented by safe storage of data on firewall protected servers and encryption of the files. Second, there is a risk for backward identification, which is when individuals are identified by combining detailed data. This was prevented by only presenting results in an aggregated form.

## 7 RESULTS

### 7.1 STUDY I

56,659 incident cases of CL injury were registered in the NPR between 2002 and 2009. The annual incidence in the general population during this period was 78 per 100,000 inhabitants (95% CI, 77.1-78.4). The mean age at diagnosis was 32 years. The risk for CL injury and the annual incidence differed between different sexes, age-groups and residential area. Male patients had a 44% higher risk of CL injury than female patients (RR=1,44, 95% CI 1,41-1,46). There was a big difference between different age groups. Men had their highest risk of injury between 21 and 30 years of age, while females were injured earlier with their high-risk period from ages 11 to 20 years (Table 1).

	All		Males		Females	
	RR	95% CI	RR	95% CI	RR	95% CI
≤10 years	0.01	0.1-0.02	0.01	0.01-0.01	0.02	0.02-0.03
11-20 years	0.83	0.81-0.85	0.59	0.57-0.61	1.35	1.3-1.4
21-30 years	1		1		1	
31-40 years	0.83	0.81-0.84	0.79	0.76-0.81	0.91	0.87-0.95
41-50 years	0.58	0.56-0.59	0.48	0.47-0.5	0.79	0.76-0.82
>50 years	0.12	0.12-0.13	0.1	0.09-0.01	0.18	0.17-0.19

\* The models are adjusted for sex and residential place

Table 1: Relative risk (RR) \*of CL injury and 95 % confidence interval (CI) among different age groups, stratified by sex

The patient group with the highest incidence were men aged 21-30 years with an annual incidence of 225 per 100,000 inhabitants. Females had their highest incidence aged 11 to 20 years with 144 per 100,000 inhabitants (Figure 10).

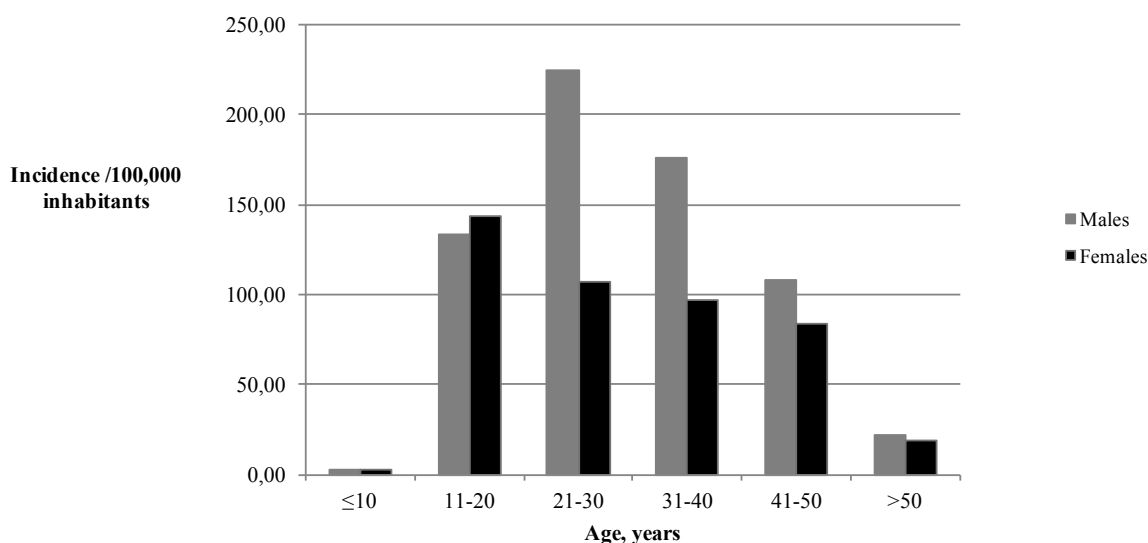


Figure 10: Age and sex specific incidence of CL injury in Sweden, 2002-2009

Thirty-six percent of the patients were treated surgically and there was no difference between men and women. Patients treated surgically were younger with a mean age of 27 years compared with those treated conservatively where the mean age was 35. Forty-eight percent of the patients under 30 were treated surgically compared with 26% of those older than 30.

Most patients treated surgically were operated during the first year after diagnosis. During the first six months, the probability of surgery was 22% for males and 24% for females (Figure 11).

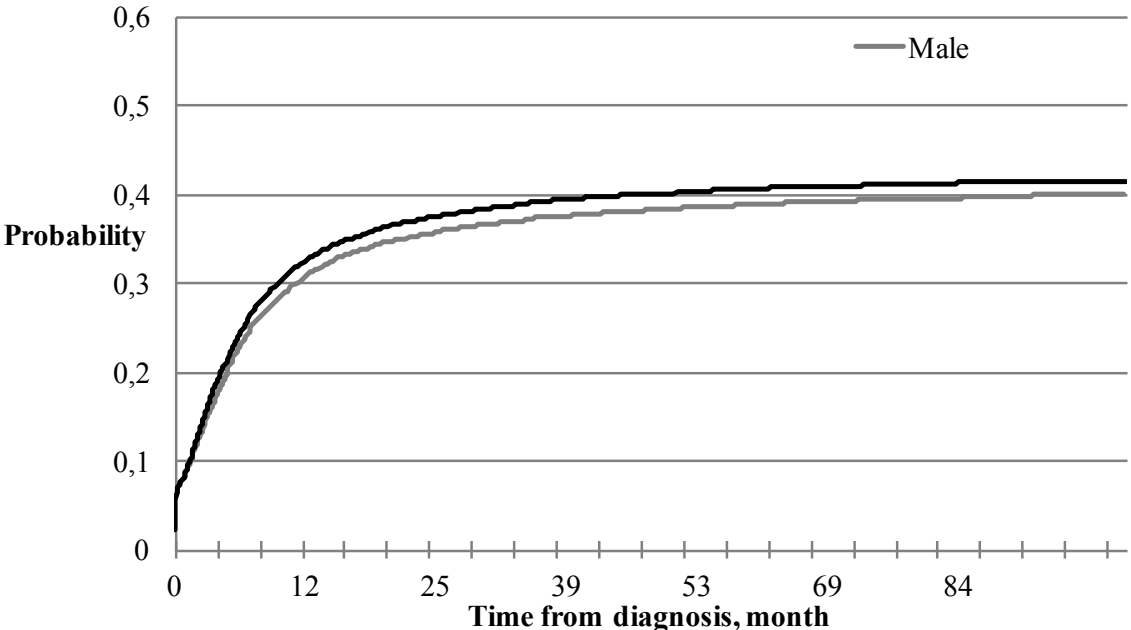


Figure 11: Cumulative Incidence function for operation among 33,778 males and 22,881 female patients with CL injury

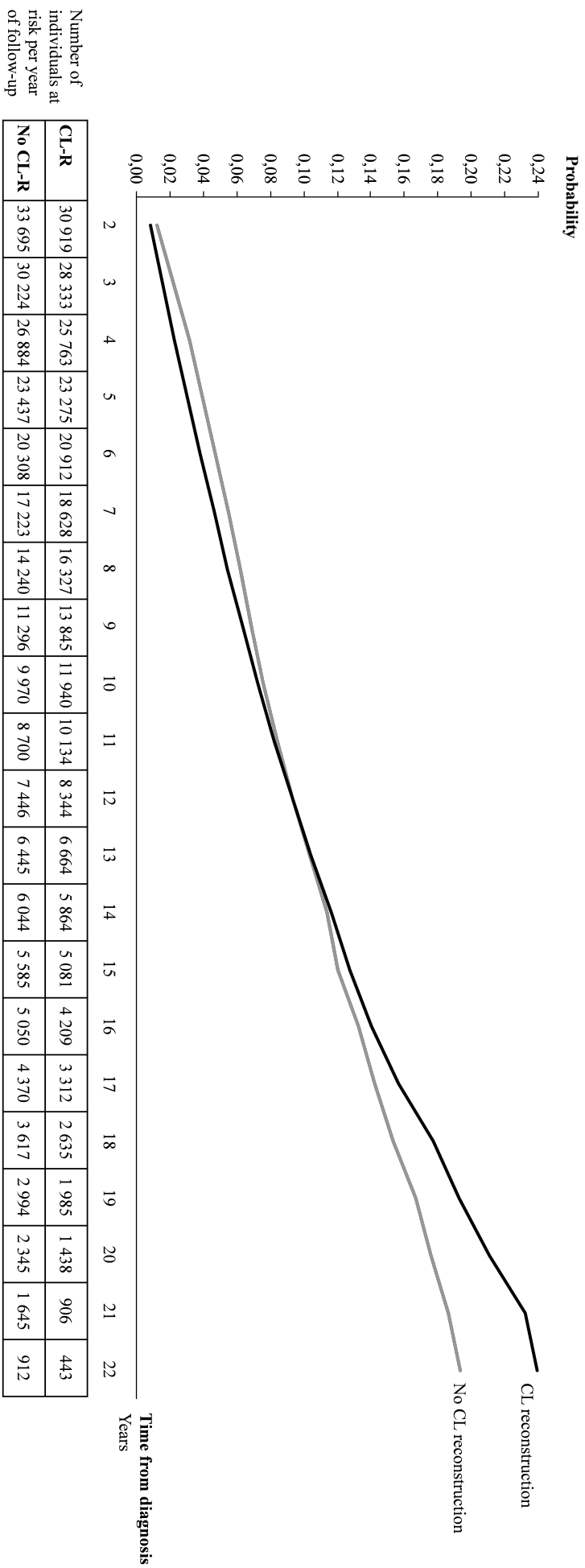


## 7.2 STUDY II

64,614 patients aged 15-60 years were included in the study. After 10 years of follow-up, approximately 10% of the cohort had developed symptomatic OA. At the end of follow-up, 24% of those treated surgically and 19% of those treated non-operatively had developed symptomatic OA. There was no difference in the risk of developing symptomatic OA between males and females. Having an acute meniscus injury increased threefold the risk of developing symptomatic OA. Overall patients treated surgically had a higher risk of developing symptomatic OA compared with those treated non-operatively (HR=1,22, 95%CI 1,14–1,30) (Table 2). This difference in risk was first seen after five years of follow-up, after which it increased over time (Figure 12).

	Number of events	Model 1*
<b>Overall</b>		
No CL-R	2199	Reference
CL-R	2115	1.26 (1.18-1.34)
- No meniscal injury	780	1.21 (1.10-1.33)
- Meniscal injury	1335	1.22 (1.12-1.33)
- Meniscal injury without surgery	263	1.29 (1,07-1,57)
- Meniscal injury with surgery	1072	1,17 (1,061,29)
<b>Follow up 2-4,9 years</b>		
No CL-R	925	Reference
CL-R	630	1.05 (0.95-1.16)
- No meniscal injury	261	1.04 (0.89-1.22)
- Meniscal injury	369	1,01 (0.85-1.18)
- Meniscal injury without surgery	73	0.94 (0.70-1.26)
- Meniscal injury with surgery	296	0.97 (0.83-1.12)
<b>Follow up 5-9,9 years</b>		
No CL-R	638	Reference
CL-R	731	1.29 (1.16-1.44)
- No meniscal injury	263	1.12 (0.94-1.33)
- Meniscal injury	468	1.10 (0.94-1.29)
- Meniscal injury without surgery	82	1.55 (1.12-2.15)
- Meniscal injury with surgery	386	1.21 (1.04-1.41)
<b>Follow up &gt;10 years</b>		
No CL-R	636	Reference
CL-R	754	1.43 (1.28-1.60)
- No meniscal injury	256	1.42 (1.20-1.70)
- Meniscal injury	498	1.41 (1.22-1.63)
- Meniscal injury without surgery	108	1.63 (1.18-2.23)
- Meniscal injury with surgery	390	1.42 (1.21-1.67)
* Adjusted for sex, age-group and calender		

Table 2: Hazard ratio (HR) and 95% confidence interval (CI) for the association between crucial ligament reconstruction and knee osteoarthritis, according to meniscal injury and follow-up



*Figure 12: Cumulative incidence for osteoarthritis in the knee among 33,695 patients with CL diagnosis treated non-operatively and 30,919 patients with CL diagnosis treated surgically in Sweden 1987–2009.*

### 7.3 STUDY III

52,566 patients were included in the study. The higher SES a patient had, the higher the likelihood that the patients would undergo surgery. The highest educated patients had a 29% increased chance to undergo CL-R compared with those with the lowest education (RR, 1.29; 95% CI, 1.19-1.39). Similar results were found when studying income, where the highest quartile of disposable household income had a 16% higher likelihood of undergoing CL-R than those in the lowest quartile (RR, 1.16; 95% CI, 1.11-1.20) (Table 3).

SES	Crude			p-value	Model 1 <sup>***</sup>			p-value
Education Level*	RR	(95% CI)			RR	(95% CI)		
1	1	<i>(Reference)</i>		<i>Reference</i>	1	<i>(Reference)</i>		<i>Reference</i>
2	1.35	1.25	1.46	<0.001	1.05	0.97	1.14	0.194
3	1.88	1.74	2.03	<0.001	1.17	1.09	1.27	<0.001
4	1.88	1.74	2.03	<0.001	1.25	1.15	1.35	<0.001
5	1.94	1.80	2.09	<0.001	1.29	1.19	1.39	<0.001
Income Quartile**	RR	(95% CI)			RR	(95% CI)		
Q1	1	<i>(Reference)</i>		<i>Reference</i>	1	<i>(Reference)</i>		<i>Reference</i>
Q2	0.94	0.90	0.98	0.002	1.03	0.99	1.08	0.107
Q3	0.94	0.91	0.98	0.004	1.04	1	1.08	0.061
Q4	1.08	1.04	1.12	<0.001	1.16	1.11	1.20	<0.001
* Education level: 1, junior high school or less; 2, partial high school education; 3, high school graduation; 4, partial college/university education; 5, post-graduate/professional training or college/university graduation.								
** Household income quartiles: 1, <25%; 2, ≥25% <50%; 3, ≥50% <75%; 4, ≥75%.								
*** Model 1 included sex and categories of age.								

*Table 3: Relative risks for surgical treatment of CL injuries as determined by SES*

In those cases where patients were treated surgically, those with higher SES were operated quicker. Patients with the highest education had a mean delay to CL-R on 221 days compared with 261 days among those with the lowest education.

## 7.4 STUDY IV

18,507 patients who were diagnosed with a CL-injury, had a five-year follow-up and were part of the workforce at the time of injury. Patients who were treated with CL-R had a 73% higher increase in salary compared with those treated non-surgically, however this point estimate was non-significant (RR 1,73 95% CI 0,88-3,42). The stratified analysis of all the covariates showed that almost all subgroups showed a positive effect from surgery, although most were nonsignificant. However, among four groups the association was significant 1) among patients between 20 and 30 years, those in the CL-R group had a twice as high change in salary 2) among skilled agricultural, forestry or fishery workers, the patients in the CL-R group had a five times higher change in salary than those in the no CL-R group 3) among patients with none or one comorbidity, those in the CL-R group had a more than twice as high change in salary than those in the no CL-R group.

	No CL-R		CL-R	
	RR	95% CI	RR	95% CI
<b>Sex</b>				
Male	1 (Reference)	-	1.94	(0.98-3.86)
Female	1 (Reference)	-	1.55	(0.78-3.1)
<b>Age group</b>				
<20 years	1 (Reference)	-	1.4	(0.49-4.03)
20-30 years	1 (Reference)	-	2.08	(1.04-4.15)
30-40 years	1 (Reference)	-	1.87	(0.94-3.62)
40-50 years	1 (Reference)	-	1.6	(0.79-3.24)
>50 years	1 (Reference)	-	1.81	(0.78-4.19)
<b>Residence area</b>				
Large	1 (Reference)	-	1.58	(0.83-3.02)
Medium	1 (Reference)	-	1.67	(0.88-3.18)
Small	1 (Reference)	-	1.63	(0.8-3.34)
<b>Education Level</b>				
Junior high school	1 (Reference)	-	1.67	(0.82-3.38)
Partial high school	1 (Reference)	-	1.3	(0.67-2.55)
High school graduation	1 (Reference)	-	1.18	(0.68-2.29)
Partial university education	1 (Reference)	-	1.13	(0.56-2.28)
University graduation	1 (Reference)	-	1.14	(0.57-2.3)
<b>Type of work</b>				
Legislators, senior officials and managers	1 (Reference)	-	0.94	(0.41-2.13)
Professionals	1 (Reference)	-	1.58	(0.76-3.26)
Technicians and associate professionals	1 (Reference)	-	1.22	(0.6-2.46)
Clerks	1 (Reference)	-	1.21	(0.56-2.59)
Service workers and shop and market sales workers	1 (Reference)	-	1.67	(0.82-3.4)
Skilled agricultural and fishery workers	1 (Reference)	-	5.25	(1.37-20.09)
Craft and related trades workers	1 (Reference)	-	1.33	(0.64-2.75)
Plant and machine operators and assemblers	1 (Reference)	-	1.39	(0.67-2.89)
Elementary occupations	1 (Reference)	-	1.65	(0.73-3.75)
Armed forces	1 (Reference)	-	1.61	(0.33-7.85)
<b>Meniscus injury</b>				
Yes	1 (Reference)	-	1.58	(0.8-3.13)
No	1 (Reference)	-	1.9	(0.95-3.8)
<b>Comorbidities</b>				
None	1 (Reference)	-	1.72	(1.12-2.64)
One	1 (Reference)	-	2.32	(1.15-4.68)
Multiple	1 (Reference)	-	1.31	(0.27-6.27)
* Relative risk of income change five years after the year of injury				
Adjusted for sex, age groups, region of residence, type of work, meniscus injury, comorbidities, level of education, year of injury, income the year before injury.				

Table 4: Marginal stratification by covariates and their effects on income change among groups.

## 8 METHODOLOGICAL DISCUSSION

### 8.1 INTERNAL VALIDITY

Internal validity describes to what extent a conclusion based on an analysis is warranted. Three things, random error, bias and confounding can affect the internal validity. If bias and confounding are controlled for and the random error is low, it is likely that the associations found in a study are true and the internal validity is high.

#### 8.1.1 Selection Bias

Selection bias occurs when data for analysis are selected in a way that makes the sample not representative for the population intended to be studied (103). This bias need to be addressed for all studies in this thesis since a common limitation to all studies is that patients with CL injuries, who never seek medical care or seek medical care but do not get the correct diagnosis for their injury, are not included in the patient sample analyzed. However, most patients are likely to visit a healthcare provider, and given the right diagnosis. With an increased access to MRI, most clinics routinely send a patient with an acute effusion of the knee joint to MRI investigation. Sweden has had a dramatic increase in the accessibility of MRI in ten years, from a moderate accessibility in 1999, to around 50,000 MRI examinations of the knee in 2009. However, the availability is different in rural and urban areas (104).

In **Study II** there is a risk for selection bias since patients are included from 1987-2009, and outpatient visits where not recorded until 2001. That means that patients included between 1987 and 2000 will be different (more severe cases, with a higher rate of surgery and a higher complication rate) than patients included after 2001, and therefore not representative for all patients with a CL injury. Stratified analysis per inclusion years was performed to control for this risk of selection bias.

#### 8.1.2 Information Bias

Information bias occurs if the exposure, covariate or outcome variables are measured, classified or categorized in a way that results in different accuracy of information between comparison groups (103).

Information bias is usually an issue that needs to be addressed in register-based studies since the registry information does not include information about criteria or diagnostic methods. However, any misclassification should most likely be random and therefore any relationship biased “toward the null.”

For all studies in this thesis a main limitation is that the ICD-10 classification does not allow for a distinction between the ACL and isolated PCL injury. This limitation should not have a major impact on the results given that isolated PCL injuries only accounts for 3% of all CL injuries (11). It is also a limitation that bilateral injuries cannot be identified. However,

bilateral injuries are uncommon, and data from the Swedish Cruciate Ligament Register show that only 2% of patients underwent bilateral reconstruction (14).

Another risk for information bias in this thesis is that it is impossible to study the severity of the knee injury. A CL injury is not a dichotomous injury. An injury includes different levels of severity, which is not described in the register. This is especially a limitation in **Study II** where patients with more severe injuries might be more likely to undergo CL-R as well as having an increased risk to develop symptomatic OA. One way to adjust for this is to include a registered meniscus injury as a covariate. However, this covariate is also a subject for information bias where, meniscus injury, like CL injury, is not a dichotomy. It is a continuous variable ranging from traumatic lesions to degenerative injuries.

### 8.1.3 Confounding

When studying the relationship between an exposure and an outcome it is important to be aware of other variables that correlates with both the outcome and the exposure. Depending on the direction of this association, a variable can be either a confounder, a mediator or a collider (Figure 13). It is therefore important to understand the relationship that the variable has with the outcome and the exposure to know how to handle that variable in the statistical analysis.

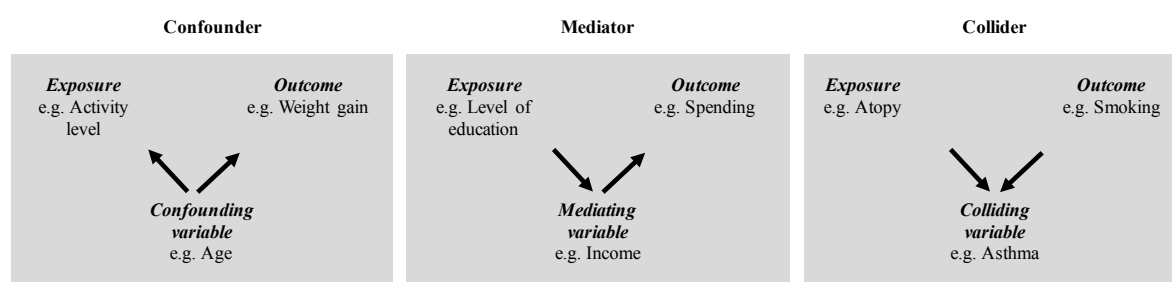


Figure 13: Examples of a confounding, mediating and colliding variable

Confounding is a phenomenon that occurs when a variable is the common cause of both the outcome and the exposure. This becomes a problem if the confounding variable cannot be measured and therefore not controlled for by either restricting or stratifying the data or by including the confounding variable in the model.

#### 8.1.3.1 Physical activity

Physical activity is a confounding factor that is of importance in **Study II** and **Study III**. Since it is not recorded in the registers it is not possible to include it in the statistical models.

In **Study II** physical activity could be associated with both CL-R (people who are physically active usually have higher demands on their knee and therefore undergo surgery to a higher extent) and development of OA (physically active patients put their knee under more stress and are therefore more prone to develop OA) (105,106). However, studies have also shown that moderate physical activity protects against development of OA, which makes it hard to estimate the impact of physical activity as a confounding factor (107).

In **Study III** physical activity could be associated with both SES (people with lower SES are reported to be less physically active) and CL-R (108). However, this confounding might have a relative little effect in this study since patients who get a CL injury are usually physically active (16).

#### *8.1.3.2 Associated traumatic injuries*

Associated traumatic injuries are factors that might be of importance in **Study IV** and is not included in the statistical models. The confounding occurs since associated traumatic injuries, such as fractures, concussion and internal hemorrhage is a result of a more severe trauma. A more severe trauma is associated with an increased risk for more severe knee injuries, which in turn is associated with an increased risk for CL-R. Associated traumatic injuries might also be associated with a more negative effect on the future income. If this confounding is strong the positive effect of increased income associated with CL-R might be underestimated.

## **8.2 EXTERNAL VALIDITY**

External validity describes to what extent the results found in a study can be generalized to other populations and situations. In population-based studies the external validity is generally high for the country where the study has taken place. The results are usually also generalizable for countries with similar healthcare systems and guidelines to Sweden, e.g. the Scandinavian countries. For **Study I** and **II** the results might also be generalizable in countries outside Scandinavia. However, for **Study III and Study IV** this is probably not the fact, mainly due to too big differences in how the healthcare system is financed.

One thing that can affect the external validity in population-based studies is if the data included in the study are restricted to only include a subset of the population. This becomes a factor in **Study IV** where the cohort is restricted to people who are part of the workforce. This makes it hard to generalize the results to all patients with a CL injury. By restricting the analysis to only include the workforce, the effects of treatment on income is not applicable for patients who are either students or retired and excludes a large portion of the younger population in whom CL injuries are common.

## **8.3 VALIDATION OF THE REGISTER**

The NPR has been well-scrutinized achieving a validation of as high as 95% (91). However, this validation has not been made specifically for CL injuries. To validate the NPR regarding CL injuries, the Swedish Cruciate Ligament Register can be used (109). This national quality register, established in 2005, is a surgical register that includes patients undergoing CL reconstruction (110). It has an estimated national coverage of 90% of all patients subjected to surgery of the CL, of which only a minority are PCLs. The results presented in this thesis for patients undergoing CL-R are coherent with the Swedish Cruciate Ligament Register validating this patient-group. To validate the NPR for patients not undergoing CL-R other non-register-based studies can be used. Another Swedish study, including patients aged 10 to 64 years diagnosed with a CL injury in a hospital in southern Sweden, presented an incidence

of CL injury of 81 per 100,000 inhabitants, which is similar to the results presented in this thesis (21).

#### **8.4 DEFINITIONS OF CL INJURY AND CL RECONSTRUCTION**

In the four studies presented in this thesis, different definitions for CL injury and CL-R have been used. In **Study II**, the ICD-10 code S837 (Injury to multiple structures of knee), was used to define some CL injuries. This was done with the purpose of finding as many CL injuries as possible, since the outcome studied was rare. However, few patients receive only the ICD-10 code S837 without also receiving the specific ICD-10 code for CL injury S835 (Distortion engaging the cruciate ligament in the knee), thus very few CL injuries were added by including the S837 ICD-10 code. Given that knowledge, the ICD-10 code S837 was not included in **Study I, III** or **IV**. Regarding CL-R the codes for reconstruction with foreign material (NGE49, NGE51, NGE52) were added in **Study II, III, IV** to make sure to include all CL-R. However, this surgical technique is very uncommon and therefore the results in **Study I** were not affected by not including these codes.



## **9 GENERAL DISCUSSION**

### **9.1 STUDY I**

This was the first population-based nationwide study reporting the incidence and characteristics of patients with a CL injury. This study defines the incidence of CL injury in the general population and the proportion that undergoes CL-R. It also describes the characteristics of the patients as well as the sex differences, where male patients were more likely to sustain a CL injury, but female patients were injured at an earlier age. Earlier studies that have been published had either not been specific for CL injury or been based on few and local observations (20,21,111). This type of baseline epidemiological studies are essential to have a result that can be used to validate and judge the generalizability of results from other studies.

### **9.2 STUDY II**

This study was the first register-based study aiming to study if CL-R prevents the development of OA. It also explains the natural process of the CL-deficient knee and risk factors to develop OA. The study presents an association between CL-R and development of OA and found that 10% of the patients develop OA within 10 years, with acute meniscus injury as the most important risk factor.

Before and after this study, new studies with conflicting results keep on being published, trying to answer if CL-R prevents development of OA (112,113). Since OA is a multifactorial disease, this question might not have an easy answer and since no study, except for a large multicenter randomized study with perfect design, can adjust for all factors, causality might be very hard to prove.

Does the question need an answer? Much has happened since this study was published. At that time, preventing OA could still be an argument for performing CL-R, today however this has changed. In Sweden, CL-R has become a symptomatic treatment offered for those with high demands and subjective instability. If CL-R is indicated for those with subjective symptoms and high demands, and preventing development for OA is not an argument for CL-R, then, perhaps, we can allow ourselves to leave this question unanswered.

### **9.3 STUDY III**

This study was the first register-based study to analyze the association between SES and treatment for a CL injury. The study showed a clear association between high SES and CL-R, an association which is hard to explain by any biases or confounding variables not included. These results are similar to a previous study where the odds of ACL surgery were higher among patients with a higher SES (114).

All Swedish citizens are, by law, entitled to the same quality of healthcare (115). Therefore, unmotivated differences in treatment between different socioeconomic groups are a big challenge. One potential explanation to our findings are that patients with a higher SES have

more demands and higher expectations on healthcare. Another explanation is that SES might influence the patient-physician communication. Higher health literacy and communication skills among patients with higher SES have been linked to disparities in healthcare (116–120). Another factor that may also explain why patients with a high SES are treated operatively more often is the negative effect that surgical treatment has on the time to return to work. Patients who perform intellectual work (often of high SES) may need to miss only 1 week of work or school after cruciate ligament reconstruction. In contrast, patients who perform manual labor (often of low SES) may need to miss 12 weeks of work after CL-R.

When hard guidelines regarding treatments are lacking, it is important to understand on what grounds the choice of treatment is taken. This study demonstrates that SES has an impact on choice of treatment.

#### **9.4 STUDY IV**

This study is the first of its kind using a multivariate approach where SES worked as alternative outcome when evaluating symptomatic surgery. In the study seven covariates were included which are important patient-characteristics when evaluating if a patient should receive surgical treatment for a musculoskeletal condition. This study showed a trend that CL-R was associated with a more positive change in income compared with conservative treatment which was stronger in different subpopulations. For example, if the patient was aged 20-30 years, had no higher education and worked with manual labor the positive effects of CL-R were greater than if the patient was 40-50 years, had a university education and worked in an office. The study design makes it hard to compare these results to studies showing that CL-R is cost effective (121,122). These studies analyze the cost of CL-R in general while individual socioeconomic consequences to the patients were considered.

The reason that only few of the results in this study were statistically significant might be a result of the fact that CL injury is not severely detrimental to socioeconomic outcome. However, the effects that were found can perhaps be explained by surgical treatment enabling rapid restoration of physical capabilities required for physical jobs why education as well as type of job were included as covariates. The results demonstrated that choice of treatment has very little effect on patients who are highly educated and work as legislators, senior officials and managers. This indicates that these patients may be protected or more resistant to the negative consequences of a CL injury and treatment and that a CL injury is not severe enough to impact their capability to gain salary. The same theory can also partly explain why patients with lower levels of education who are treated non-operatively have a greater effect of surgery. Lower level of education could reduce the different options a person has when applying for a job and makes a patient more susceptible to the negative physical effects of an untreated CL injury. In a similar way, young patients (between 20-30 years) seemed to benefit from surgical treatment. One might speculate that this population may also be more susceptible to the negative physical effects of an untreated CL injury since it represents an early stage in career development and of transitioning from studies to the workforce.

For symptomatic surgery, alternative outcomes are of great importance when evaluating the pros and cons of these, often expensive treatments. The statistical modeling done in this study, including seven important covariates when studying a socioeconomic outcome, is the first step in creating a personalized decision-making tool. This can be of great importance when evaluating what patients, if any, will benefit from symptomatic surgery. In a tax-financed health-care sector where the resources are scarce, new methods to offer personalized treatment options are a must to achieve maximal cost-effectiveness, something that of course also will benefit the patient receiving the treatment. The inclusion of socioeconomic covariates into the model demonstrates the possibility of evaluating different factors presenting in patient's lifestyles that can contribute to the observed outcome.

## 10 CONCLUSIONS

- **Study I** defines the incidence of CL injury in the general population as 78 per 100,000 inhabitants. It presents patients characteristics, where the mean age is 32 years and half of those injured are under 30 years. It demonstrates sex differences, in which men are more likely to sustain a CL injury, although female patients are injured at an earlier age. It presents how the patients are treated, where 36% undergo CL-R, a treatment that are more common if the patient is younger.
- **Study II** describes the risk to develop symptomatic OA after a CL injury, where 10% develop symptomatic OA within 10 years of injury. It presents meniscus injury as the most important risk-factor, where an acute meniscus injury three-folds the risk to develop symptomatic OA, independent of treatment. It provides evidence that CL-R in the general population does not seem to have a protective effect on long term OA in either men or women.
- **Study III** provides a population-based validation that having a higher SES as determined by the household income and/or level of education increases the likelihood of undergoing operative treatment after a CL injury with up to 29%.
- **Study IV** presents a new way to evaluate symptomatic surgery using SES as an alternative outcome and including seven patient-characteristics as covariates that serve as support for the decision-making process, guiding the physician about which patients would benefit the most from surgical procedures.

## 11 FUTURE RESEARCH AND CONSIDERATIONS

This thesis, along with science in general, generates more questions than it provides answers. It opens new areas of inquiry and presents results that make us ask ourselves why? Two of the studies gave some “clear answers”. The incidence of CL-injury in the general population has now been defined and the chance to be treated with CL-R increases if you have a higher SES. Even though it is a known phenomenon that patients with higher SES receive more expensive and advanced treatments, the issue of inequalities within the Swedish healthcare sector is a challenge. Action and policy work is needed, in parallel to research, to minimize unmotivated and unjust differences in healthcare.

I failed to answer if my father’s CL-R prevented or caused his early onset of OA. Since OA is a multifactorial disease this question might never receive a straight answer, and maybe it should not have one. Because, luckily, things have changed in Sweden, and the choice of treatment today, is based on the patient’s symptomology and not to prevent OA. In other countries, where the invisible hand of financial interests of the care giver might be more pronounced, the argument that CL-R prevents OA might still be valid and require further research.

### 11.1 HEALTH OUTCOMES MEASUREMENTS

This thesis presents new interesting Health Outcomes Measurement (HOM) that can be used to study and to evaluate the treatment of patients with CL injury. Maybe, the development of posttraumatic, symptomatic OA, the impact of SES on treatment and the change of salary five years after injury will be measured for patients with CL injury on a regular basis in the future.

During the last years, the development of new HOMs and the use of these in clinical practice has increased rapidly in Sweden and around the world. Billions of Swedish kronor, assigned to the Swedish healthcare sector, have gone to the creation of new measurements using the healthcare registers. Relevant information, presented in a structured way, fed back to healthcare providers can be a valuable tool. This information can help healthcare providers to assess their work and provide answers to questions like “How are we doing compared to others?” and “Have the new method and guidelines implemented had a positive effect?”. Being able to answer such questions can help to inspire, implement and evaluate improvements in healthcare, thus, benefit both patients, providers as well as the society as a whole.

However, the recording and use of HOMs is a powerful tool that also can have strong adverse effects. An accurate interpretation of results from national or local registers requires an interpreter with deep knowledge of the specific medical field, the validity of the registers, the context in which the measurements are produced as well as the setting in which the results are presented. Therefore, a strong case can be made for using the results for local quality improvement, but a similar strong case can be made *against* using the HOMs directly in regulatory or reimbursement settings where the results are used automatically and without interpretation.

Unfortunately, many cases of misuse of HOMs can be observed and there is a strong trend towards using HOMs outside the scope of local quality improvement, even as far as including them directly into incentive models. The use of HOMs in incentives models is associated with a number of risks:

- **Loss of perspective and crowding out effect**

Almost no outcome is so good that it should be the goal regardless of the situation. Therefore focusing on one specific outcome can create new unintentional adverse effects. One example: Let's say that short-term survival is the one outcome that is prioritized and measured for neonatal intensive care units. This might result in the unintentional effect that children with a non-existing chance for a longtime survival unintentionally are kept alive for a short period of time with severe suffering for the child as well as the family. This is an example of an adverse effect that is inhumane for the child and parent and a drain of resources from other more prioritized patients. This scenario is in line with previous research that has shown that unsuccessful pay for performance schemes can lead to crowding out effects whereby the "real" quality for the patient is reduced compared to baseline while the "documented quality" is improved simultaneously (123).

- **Demotivation**

People who choose to work within the field of healthcare are often intrinsically motivated by the possibility to treat, cure and care for those in need. Misuse of HOMs might have a negative effect on this driver of intrinsic motivation and thereby resulting in demotivated doctors and nurses. In general rewards are not considered to decrease intrinsic motivation (124). Especially verbal praise is considered to produce an increase in intrinsic motivation. However, negative effect can be expected when tangible rewards are given to individuals simply for doing a task.

- **Unfair punishments**

Since HOMs often are based on the data reported to the national registers, deep knowledge of how different variables are coded and registered are needed when interpreting the results. For example: Let's say that an obstetric delivery unit in a hospital implements new guidelines on how to diagnose and treat vaginal lacerations. A natural and positive result of this will be that more lacerations are diagnosed and registered. Later, when studying the rate of lacerations per clinic, the clinic with newly implemented guidelines might falsely stand out as having a high rate of lacerations. For an interpreter lacking deep knowledge of this matter, it might look like the unit performs worse than other comparable clinics and the unit discussed might be unfairly penalized.

- **Corruption of the registers**

Measuring the complication-rate using the national registers is a common HOM. If a healthcare unit is evaluated based on these results there is a risk that the unit reevaluates the definition of a complication and how it should be diagnosed, coded and registered. This incentive-driven change of routines and diagnostics might corrupt

the data in the registers and make it harder to use the data in research and evaluations.

The risks stated above share similarities with general problems associated with incentive plans (125). In Kohn's words: "Excellence pulls in one direction; rewards pull in another. Tell people that their income will depend on their productivity or performance rating, and they will focus on the numbers. Sometimes they will manipulate the schedule for completing tasks or even engage in patently unethical and illegal behavior."

## **11.2 DECISION-MAKING TOOLS FOR PERSONALIZED MEDICINE**

Symptomatic surgery is a billion-dollar business and new techniques with the aim to relieve pain and disability from the musculoskeletal system are continuously developed. In this thesis, a multivariate approach was tested, that can be used to study the effect symptomatic surgery has on a new alternative outcome, SES. The model includes seven covariates that can be used to create guidelines and personalized decision-making tools. More research is needed to further develop and refine this model so that it can be used to evaluate other musculoskeletal conditions and facilitate the development of guidelines and decision-making tools that can be used in clinical practice.





# 12 POPULÄRVETENSKAPLIG SAMMANFATTNING

## 12.1 BAKGRUND

Korsbandsskada är en allvarlig skada som ofta drabbar yngre individer i samband med idrottsutövande. De idrotter där skadan är mest vanligt förekommande är fotboll, handboll, innebandy, alpin skidåkning och basket. Personer som får en korsbandsskada tvingas inte sällan avsluta en idrottskarriär i förtid. Skadan ger livslånga besvär och ofta leder den till tidig utveckling av knäartros, oavsett hur den behandlas. En korsbandsskada kan antingen behandlas kirurgiskt, då man skapar ett nytt korsband, eller utan kirurgi då man genom strukturerad sjukgymnastik arbetar för att träna upp stabiliteten i knät.

Korsbandsskador är ett av ortopedins mest studerade områden, men trots att över 20,000 vetenskapliga artiklar publicerats till dags dato har det saknats kunskap om hur vanlig skadan är, vilka faktorer som påverkar valet av behandling samt evidens som ger tydlig vägledning om vilka patienter som ska opereras och vilka som kan behandlas icke-operativt. Denna avhandling syftar till att besvara dessa frågor och samtidigt visa hur de nationella register som finns i Sverige kan användas för att i slutändan hjälpa hälso- och sjukvårdspersonal och patienter att fatta beslut om vilken behandling som är bäst varje enskild individ.

## 12.2 METODER

Sverige har en tradition av att samla in data och på ett strukturerat sätt lagra information om dess invånare. Detta har lett till att det idag finns över 50 nationella register som innehåller information om allt från våra individuella skolresultat till vilka sjukdomar vi drabbats av. Dessa register, där en hel svensk population följts under årtionden, utgör en guldgruva för forskare som vill studera trender och orsakssamband. Denna avhandling syftar till, att med hjälp av dessa register, studera olika aspekter av korsbandsskador. I avhandlingen används framför allt register från hälso- och sjukvården, samt de register som beskriver individers socioekonomiska status som utbildningsnivå, lön och sjukfrånvaro.

Genom att använda och utveckla olika statistiska modeller samt skapa sätt att med hjälp av data beskriva förlopp och effekter har denna avhandling försökt besvara följande fyra övergripande frågeställningar:

1. Hur många drabbas av korsbandsskada i Sverige, vad karakteriserar dessa individer och vilken behandling får de?
2. Ett vanligt argument till att operera patienter med korsbandsskada har varit att man skyddar knät mot att utveckla knä-artros. Är detta argument sant?
3. Det är ett välkänt fenomen att patienter med högre inkomst och utbildning erhåller dyrare och mer avancerade behandlingar inom svensk hälso- och sjukvård. Stämmer detta även för patienter som drabbas av en korsbandsskada?
4. Inom ortopedin syftar många behandlingar till att återställa funktioner i rörelseapparaten samt ta bort eller minska smärta. Lyckade behandlingar bör därför kunna göra det möjligt för patienter att återgå till arbete. Kan man genom att använda

de register som finns mäta detta och stämmer detta påstående för patienter som genomgår kirurgisk behandling av korsbandsskada?

### **12.3 RESULTAT**

I denna avhandling presenteras för första gången hur vanligt förekommande korsbandsskada är i Sverige. Varje år skadar sig ca. 8000 personer i Sverige. Sextio procent av dessa är män och hälften är under 30 år. Trettiosex procent av patienterna opereras och de som opereras är klart yngre än de som ej erhåller kirurgisk behandling. Resultaten visar också att argumentet att kirurgisk behandling förebygger utveckling av knäartros inte stämmer. Istället visar resultaten ett omvänt samband där risken att utveckla artros är 22% högre hos de som genomgår kirurgisk behandling efter 10 år jämfört med de som ej opereras. Att utveckla knäartros är dock vanligt och efter 10 år har 10% fått diagnosen. Att ha en meniskskada ökar dock risken avsevärt.

I denna avhandling redovisas att patienter med högre utbildning och inkomst genom går kirurgisk behandling för korsbandsskada i högre utsträckning än de med låg utbildning. Resultaten antyder att det finns en tendens att de som opereras får en bättre löneutveckling än de som ej opereras, men resultaten är ej statistiskt säkerställda.

### **12.4 DISKUSSION**

Antalet som drabbas av en korsbandsskada varje år var klart fler än vad som var känt tidigare. Att man nu har en god förståelse om hur hela patientgruppen som får en korsbandsskada ser ut är nödvändigt för att utvärdera och designa studier för att kunna svara på hur dessa skador bäst ska behandlas. Målsättningen med behandling bör vara att till bästa mån återställa knäfunktionen så att den som får sin skada kan vara fysiskt aktiv på önskad nivå. Önskvärt vore om man lyckades identifiera vilka patienter som bör opereras för att skydda knät mot efterföljande skador då det är tydligt att kirurgisk behandling ej har en allmänt skyddande effekt för alla patienter.

I ett land med offentligt finansierad sjukvård ska alla invånare enligt hälso- och sjukvårdslagen ha rätt till en likvärdig vård. Att mer välutbildade patienter erbjuds mer avancerade behandlingar är ett problem vilket delvis skulle kunna bero på att patienter med högre utbildningsnivå ställer högre krav på hälso- och sjukvårdssystemet. Det kan även vara så att patienter med lägre socioekonomisk status ej har råd att vara borta från arbetet en längre tid, vilket blir en konsekvens av kirurgisk behandling. Dock visar denna avhandling snarare en omvänd effekt där de som opererades hade en bättre inkomstutveckling än de som ej opererades.

Denna avhandling visar att möjligheterna att använda de svenska nationella registren för att svara på svåra och komplexa ortopediska frågeställningar är stora. Att man kan skapa nya utfallsmått för tidigare svårstuderade tillstånd och behandlingar öppnar oanade möjligheter att på sikt kunna utveckla verktyg för hälso- och sjukvårdspersonal och patienter att avgöra mer exakt vilken behandling som är bäst för var enskild patient.

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