NORWEGIAN SCHOOL OF SPORT SCIENCES

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Prevalence of radiographic and symptomatic knee OA 10 years after ACL injury

Between patients treated surgical or non-surgical

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Abstract

Background: Following an Anterior Cruciate Ligament (ACL) injury, there is an 3-4 times increased chance of developing post-traumatic osteoarthritis (PTOA). After an ACL injury, the treatment options are typically an ACL Reconstruction (ACLR) with rehabilitation or rehabilitation-alone. Earlier studies have shown no difference between these two groups regarding pain, symptoms, or radiographic Osteoarthritis (OA). But more high-quality research surrounding the prevalence of symptomatic and radiographic OA is warranted.

Objective: Investigate the differences in prevalence of symptomatic and radiographic knee OA in those treated with ACLR and those treated with rehabilitation alone, 10 years after an ACL injury.

Material and Methods: The data used is derived from the Norwegian part of the Delaware-Oslo ACL Cohort study. Of the 123 eligible for the 10-year follow up, 84.5% (n=104) agreed to participate. The primary outcome measures were x-rays of the knee diagnosing tibial-femoral joint (TFJ) and patella-femoral joint (PFJ) OA using the Kellgren & Lawrence grading. The prevalence of symptomatic OA was decided by applying three different models based on a combination of knee pain, Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire subscale scores, and radiographic OA.

Results: There was no significant difference between the two groups of ACLR and rehabilitation-alone regarding the prevalence of radiographic OA and symptomatic OA. A low prevalence of radiographic OA was observed in both groups. The prevalence in the ACLR group was 11.9% TFJ OA and 10.2% PFJ OA in the injured knee. The prevalence in the rehab-alone group was 0% TFJ OA and 4.3% PFJ OA in the injured knee. The highest prevalence of symptomatic OA was observed when applying the third model, where there was a prevalence of 13.2% symptomatic TFJ OA and 14.7% PFJ symptomatic OA in the ACLR group, and a prevalence of 26% symptomatic TFJ OA and 17.4% PFJ symptomatic OA in the rehabilitation alone group.

Conclusion: Following 10 years post ACL injury, there were no significant differences between the ACLR group and rehabilitation alone group regarding the prevalence of radiographic and symptomatic OA.

Content

Foreword

This master thesis was written as a part of the master graduate study at the Norwegian school of sport sciences.

I would like to give a big appreciation and thanks to my supervisor May Arna Risberg for all the help and guidance. Your knowledge is endless, and I am grateful for the time you spent trying to share some of it with me.

I would also like to thank Marie Pedersen and Anouk Urhausen for helping with the data collection and data plotting. You guys were always ready to give advice and support.

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Introduction 1.0

The incidence of ACL injuries is approximately 5/10.000 new cases in the general population each year (van Meer, Meuffels et al. 2015). ACL injuries are frequent sports-related injuries and are often treated with surgery (Montalvo, Schneider et al. 2019). The number of ACLR performed in Norway in 2019 was 1924 (kvalitetsregistre 2020). An ACL injury is often associated with an earlier onset of knee OA. If there is a combination of ACL, and meniscus injury, there is a four to six times greater risk of developing knee OA (Muthuri, McWilliams et al. 2011, Whittaker, Woodhouse et al. 2015, Risberg, Oiestad et al. 2016, Poulsen, Goncalves et al. 2019). The prevalence of knee OA 10 years after an ACL injury is 8-80%, and there is a four times bigger chance of developing knee OA (Muthuri, McWilliams et al. 2011, Ajuied, Wong et al. 2014, Barenius, Ponzer et al. 2014, Whittaker, Woodhouse et al. 2015, Kastelein, Luijsterburg et al. 2016, Belk, Kraeutler et al. 2018, Chen, Wang et al. 2019, Hamrin Senorski, Sundemo et al. 2019, Lie, Risberg et al. 2019).

This master thesis is a part of the Delaware-Oslo ACL Cohort, which began in 2006 and is a prospective cohort study on athletes in nonprofessional pivoting sports with ACL rupture. This master thesis will include 10 years follow-up data from the Delaware-Oslo ACL cohort study. The purpose of the Delaware-Oslo ACL Cohort study is to assess outcomes and prognostic factors among both surgically and rehabilitation-treated patients. Professor May Arna Risberg is the primary investigator of the Norway part of this study, and she is my main supervisor through the process of this master project.

Background 2.0

Following an ACL injury, you will typically face the treatment options between ACLR with rehabilitation or rehabilitation-alone. The rehabilitation is similar regardless of the chosen treatment option, but the rehabilitation following an ACLR is often more substantial and more prolonged. A randomized controlled trial found that rehabilitation and early ACLR did not provide better patient-reported outcome (PRO) scores than rehabilitation-only with an optional delayed ACLR (Frobell, Roos et al. 2010).

At the five-year follow-up, there were no statistically significant differences in pain, symptoms, return to pre-injury activity level, radiographic OA, or number of meniscus surgery between the ACLR plus rehabilitation or the rehabilitation-alone groups (Frobell, Roos et al. 2013).

Studies have shown an increased risk regarding the prevalence of knee OA in this ACL injury cohort 10 years after injury. Previous studies show 3-4 times higher risk of knee OA in the ACLR knee compared to the contralateral knee, more than 10 years after surgery (Barenius, Ponzer et al. 2014, Chen, Wang et al. 2019). Harris et al. (2017) investigated the prevalence of TFJ OA between two groups, ACLR plus rehabilitation and rehabilitation-alone, 10-14 years post-surgery. The results showed a slightly higher prevalence of knee OA in the ACLR group with 41%, compared to 30.9% in the rehabilitation-alone group.

Knee OA, which develops after a knee injury, is often referred to as PTOA. It is also referred to as secondary knee OA, whereas primary knee OA is non-traumatic (Swärd, Kostogiannis et al. 2010). Primary knee OA often develops in older adults, while PTOA tends to develop in younger adults because of injury in their youth (Whittaker, Woodhouse et al. 2015). Since knee OA can develop in younger people, it cannot be explained solely by biological aging as a risk factor (Ackerman, Kemp et al. 2017). Associated risk factors for developing knee OA are age, high BMI, previous injury, and quadriceps weakness (Barenius, Ponzer et al. 2014, van Meer, Meuffels et al. 2015, Øiestad, Juhl et al. 2015, Huang, Ong et al. 2020).

Knee OA is often being diagnosed by radiographic imaging, focusing on the narrowing of the joint space and the presence of osteophytes. However, this way of diagnosing represents a challenge as these x-rays' findings are signs are of late-stage joint degradation. But the development of OA starts much earlier than we can detect radiographically. Especially following a traumatic injury, like an ACL injury, because of a cascade of biomechanical events and processes (Harkey, Luc et al. 2015).

When diagnosing knee OA with only imaging, there is a possibility of not identifying the people with symptomatic knee OA. As pointed out by Lohmander et al. (2004) where 75% had knee symptoms and pain, but only 50% of the participants had radiographic

knee OA. This is also exemplified by Skou et al. (2014), where findings between clinical symptomatic OA and radiographic knee OA were lower in agreement with younger than with older patients. Meaning a higher number of younger patients had clinical symptomatic knee OA but were not diagnosed by radiographic imaging in this study.

Patients with symptomatic knee PTOA often present themselves with different characteristics than primary knee OA. These other characteristics involve younger age, lower BMI, greater physical activity, and longer-lasting symptoms (PM Holm 2018). The main clinical sign of symptomatic knee OA is knee pain. Knee OA pain can be a result of several pathological conditions such as allodynia, hyperalgesia, and central sensitization (Bihlet, Byrjalsen et al. 2018). The correlation between knee pain and previous injury is relatively high, as demonstrated by Whittaker et al. (2015), where evidence of young athletes with a history of a knee injury had more pain illustrated by a lower KOOS score (Roos, Roos et al. 1998). Participants with ACL injuries scored a mean of 9.43 (95% Confidence Interval (CI); 5.21 to 13.65) lower on the KOOS symptoms subscale and questionnaire compared to the uninjured participants (Whittaker, Woodhouse et al. 2015). The KOOS questionnaire was developed to evaluate people with knee injuries and used clinically to diagnose symptomatic knee OA (Barenius, Ponzer et al. 2014, Wasserstein, Huston et al. 2015).

There is no consensus for the definition of symptomatic OA when diagnosing using only clinical and PROs (Wasserstein, Huston et al. 2015). However, the most frequent clinical criteria used are the European League Against Rheumatism (EULAR), the American College of Rheumatology (ACR) and the National Institute for Health and Care Excellence (NICE) (Altman, Asch et al. 1986, Zhang, Doherty et al. 2010, National Clinical Guideline 2014).

It is essential to help practitioners with tools and knowledge about symptomatic PTOA, so that correct and more effective treatment is initiated early on (Skou, Thomsen et al. 2014). More research is warranted to help practitioners diagnose symptomatic knee PTOA in primary care without relying on radiographic or magnetic resonance imaging (MRI) imaging. Studies focusing on detecting the true prevalence of PTOA following ACL injuries are also warranted.

Objective 3.0

Main objective:

The main objective of this study is to investigate the differences in the prevalence of symptomatic and radiographic knee OA in those treated with ACL reconstruction and in those treated with rehabilitation-alone, 10 years after an ACL injury.

Hypothesis:

There is no difference in the prevalence of symptomatic OA and X-ray diagnosed knee OA between ACL injured treated with ACLR plus rehabilitation or rehabilitation alone.

4.0 Theory

4.1 ACL

The ACL consists of a tightly packed collagen fiber group that is aligned parallel to help the stability of the musculoskeletal joints (Woo, Abramowitch et al. 2006). The ACL originates from the intercondylaris area anterior of the tibia, between the two front ends of the meniscus. From here it extends backward upward to the intercondylar fossa of the femur (Woo, Abramowitch et al. 2006, Bojsen-Møller 2011). There are two bundles of collagen fibers in the ACL, one anterior medial and one posterolateral. The primary job of these two bundles together is to prevent all excessive backsliding of the femur in relation to the tibia and restrain rotational moments in the knee (Woo, Abramowitch et al. 2006, Bojsen-Møller 2011). In an ACL deficient knee, there may be instability and therefore diminish the ability to do pivoting and cutting maneuvers as you do in pivoting sports (Petersen, Taheri et al. 2014, Brukner 2017).

4.2 ACL Injuries

The incidence of ACL injuries is 5/10.000 new cases each year or 69/100.000 person-years (van Meer, Meuffels et al. 2015, Lie, Risberg et al. 2019, Matthewson, Kooner et al. 2019). Proposed external risk factors for ACL injuries include shoe/surface, type of competition, weather, lower extremity alignment and neuromuscular control. Some of the internal risk factors are related biomechanical factors (Dai, Herman et al. 2012, Alentorn-Geli, Mendiguchía et al. 2014). Newer research also suggests a genetic component as a risk factor for an ACL injury (Magnusson, Turkiewicz et al. 2020).

An ACL injury can be disabling and affect your quality of life (Filbay, Culvenor et al. 2015) (Just imagine having to give up playing your favorite sport for the rest of your life, or your dream of becoming the next LeBron James because of an ACL injury). The percentage of people who did not return to their previous level of sport is 35%, and only 55% return to competitive sport following an ACLR (Ardern, Taylor et al. 2014). Over the past two decades, there has been an increase in ACLR in children and

adolescents, indicating more ACL injuries (Kay, Memon et al. 2018). It seems that what kind of sports you are playing is a significant factor in the likelihood of getting an ACL injury. Specifically in sports like soccer, handball, floorball, and basketball where there is a lot of loading of the knee with a change of direction and pivoting. The chances of getting an ACLR are four times higher for those who compete in pivoting level 1 sports compared to those who did not (Johnsen, Guddal et al. 2016). There is also an economical backside to ACL injuries and surgery. According to Herzog et al. (2017), the median cost of an ACL surgery in the USA was $14,692 in 2013. So, ACL injuries bring an economic burden on society as well.

4.3 Treatment options

After getting an ACL injury, you typically have two choices, ACLR with rehabilitation or rehabilitation alone, but the most optimal treatment method is still unclear. One reason for choosing ACLR is that it can possibly limit excessive torsional loading of the menisci by reestablishing rotational stability. The lesser torsional load can shelter the damage on the menisci, cartilage, and ACL and thereby help to prevent or slow down the degenerative changes in the knee (Ajuied, Wong et al. 2014). In addition, studies have shown that knee-joint stability after an ACLR poses a better knee function than the non-surgery treatment (Smith, Postle et al. 2014, Krause, Freudenthaler et al. 2018). Systematic reviews have assessed the outcomes of these two main treatment options, ACLR or rehabilitation alone (Smith, Postle et al. 2014, Monk, Davies et al. 2016, Krause, Freudenthaler et al. 2018). The findings in these systematic reviews showed that no treatment was superior to the other, and they also emphasized the poor quality of the included studies.

Van Melick et al. (2016) proposed that those who do not choose ACLR should be prescribed a rehabilitation program that focuses on gaining full range of motion in the injured knee joint and strengthening the quadriceps muscle. This should be done by using closed and open chain exercises along with neuromuscular training (van Melick, van Cingel et al. 2016). The same rehabilitation program should also be prescribed postoperatively to those who undergo ACLR.

A sizeable Swedish randomized controlled trial by Frobell et al. (2010) called the Knee Anterior Cruciate Ligament, Nonsurgical versus Surgical treatment (KANON-study), compared two groups of participants with ACL injuries to investigate the optimal management. Authors behind the study randomly assigned active young adults with an ACL injury into two groups of either early ACLR and rehabilitation or rehabilitation-alone with the option of delayed ACLR. The conclusion was no difference in PROs after two years, represented by a KOOS score with only a 0.2 (95% CI: -6,5 – 6.8) difference. After five years, a follow-up for the same cohort compared PROs and radiographic images of the injured knee between the same two groups (Frobell, Roos et al. 2013). The KOOS score between the two intervention groups was not statistically significant, with a 2.0-point (95% CI: -8.5 – 4.5) difference favoring the rehabilitation-alone. The radiographic images, graded by the Kellgren & Lawrence scale, also showed no statistically significant difference between the two groups. The ACLR and rehabilitation group showed that 10 (11%) had developed TFJ radiographic OA and 20 (23%) had PFJ OA. The rehabilitation alone group showed three individuals (12%) with TFJ radiographic OA, and two individuals (8%) with PFJ radiographic OA.

Regarding the cohort this master thesis is based on, Grindem et al. (2014) discovered that there were no significant differences between the ACLR and rehabilitation alone groups regarding to knee function at two years follow-up. Overall, there seemed to be very few differences in the clinical course between the surgery and non-surgery groups in this cohort after two years.

There are different findings in the literature regarding the preventative outcome with ACLR or rehabilitation alone regarding developing knee OA. Older studies found that ACL reconstruction increased the risk of osteophytes, but no difference in joint narrow space (Swärd, Kostogiannis et al. 2010). The follow-up in this study was 12-14 years after ACLR, and there was no information about meniscus injury or type of treatment for the meniscus injury. Ajuied et al. (2014) reported that a relative risk of developing moderate or severe knee OA was 4,89 (CI 2,35 – 10,15) in the non-surgery group consisting of 120 ACL injured people. In the ACLR group, of 465 operated people, the relative risk was 3.89 (CI 2,72 – 5,57). A more extensive systematic review by Lie et al. (2019) discovered the prevalence of knee OA in patients with an ACL injury treated

surgically or non-surgically, varied from 23-80% and 8-68%. Since there is an overlap, there is no absolute way to say that one treatment favors the other. It is noteworthy that only 210 (4%) participants were treated non-surgically compared to the 4709 (96%) treated surgically, which is a much smaller group of rehabilitation alone participants to compare statistically.

A recent systematic review and meta-analysis by Lien-Iversen (2020) focused on ACLR and if it could reduce knee OA and meniscal injury after an ACL rupture. The systematic review included only studies with at least a 10-year follow-up. Of the five studies included, the results revealed a higher risk of knee OA in the surgery group than in the non-surgery group. However, it showed less knee laxity and a lower risk of secondary meniscus surgery in the ACLR group. These results should be taken with a grain of salt as there were some methodical challenges. Within the five studies included, there were three different methods to diagnose knee OA via radiographic imaging.

The overall findings concluded that ACLR is not superior to conservative treatment of ACL injury. Nevertheless, findings suggest that ACLR can restore normal function in the ACL deficient knee in the form of reduced knee laxity and reduce the risk of secondary meniscus injury (Ajuied, Wong et al. 2014, Smith, Postle et al. 2014, Krause, Freudenthaler et al. 2018).

4.4 Pathogenesis of OA

In short, OA is a degenerative joint disease. But what happens on a cellular level?

Beforehand it was thought that the “itis” (inflammation) did not play a part in the development of OA (Fu, Robbins et al. 2018). But nowadays, there is a clear understanding that inflammation does in fact play an essential role in the progress of OA, and it is not just a “wear-and-tear” disease as generally described (Hunter and Bierma-Zeinstra 2019). A normal healthy joint consists of two bones where each has a layer of articular cartilage (AC), which allows the bones to glide against each other smoothly and without friction. In the knee, which is also a synovial joint, the synovium that along with the AC forms the inner lining of the joint space. On the surface of the

synovium, there are type A cells that clear cellular debris. The debris is a product of articular matrix turnover. Lubricin and hyaluronic acid that construct segments of synovial fluid acts as a lubricin for the joint (Scanzello and Goldring 2012, Jørgensen, Kjær et al. 2017). One of the main problems of OA is the gradual loss of AC, which results in a narrowing of the joint space, that in return adds more friction between the two articulating surfaces. The narrowing of the joint and more friction can generate inflammation, and thereby pain through the nerve endings in the joint space (Li, Chen et al. 2015, Hunter and Bierma-Zeinstra 2019). Maintaining a healthy AC is the chondrocyte´s job. A chondrocyte is a specialized cell that is responsible for maintaining everything AC-related. The chondrocytes produce and are embedded in the extracellular matrix, which contains type II collagen, a protein that provides structural support, and proteoglycans (Flugsrud, Nordsletten et al. 2010, Jørgensen, Kjær et al. 2017). Together this extracellular matrix gives the cartilage elasticity and high tensile strength. When a joint is loaded, force is distributed onto the joint surface, and as a result, reducing pressure on the AC.

Chondrocytes maintain a delicate balance between catabolic activity (breaking down old cartilage) and anabolic activity (construct new cartilage). If damage occurs to the cartilage the chondrocyte tries to repair the cartilage by producing fewer proteoglycans and more type I collagen. A different collagen type is produced, and when it interact with proteoglycans it causes a decrease in elasticity in the cartilage and allowing it to breakdown (see figure 2) (Li, Chen et al. 2015). Eventually, the chondrocytes can undergo apoptosis (programmed cell death) as a result of working overtime to repair the cartilage (see figure 1) (Flugsrud, Nordsletten et al. 2010, Li, Chen et al. 2015). The effect of this is softening and weakening of the cartilage, continuous loss of elasticity and chondrocytes start to exfoliate off in the synovial space. Here the type A cells, as mentioned in the beginning, tries to remove the cellular debris. This chain of events will recruit and activate macrophages and lymphocytes, which produce proinflammatory cytokines. This will ultimately cause inflammation of the synovium, also called synovitis (Hunter, McDougall et al. 2009, Scanzello and Goldring 2012).

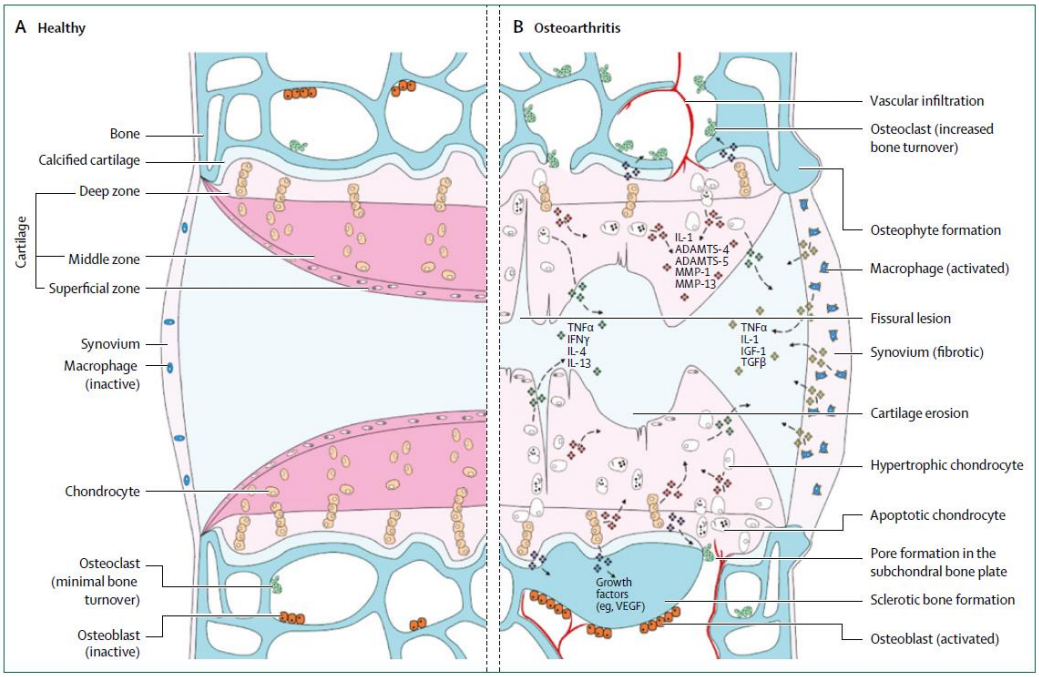

Figure 1: *structural changes in the development of osteoarthritis (Hunter 2019 Written consent to use this picture was secured)*

In the case of PTOA, the degenerative changes can develop after the initial injury or trauma, like an ACL injury, and thereby cause a traumatic bone marrow lesion and start the activation of proinflammatory cytokines (Dare and Rodeo 2014, Harkey, Luc et al. 2015, Li, Chen et al. 2015, van Meer, Meuffels et al. 2015). In a nonhealthy joint, the balance between breaking down and producing cartilage is disrupted, and the balance tips so breaking down exceeds the amount produced over time. This is illustrated in figure 2 (Bay-Jensen, Hoegh-Madsen et al. 2010).

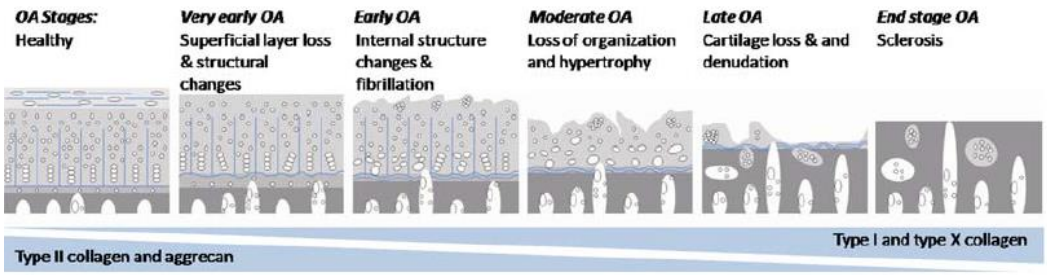

Figure 2: *The balance between producing Type II collagen and aggrecan in a healthy joint and the lack of type II in a non-healthy joint. Which instead produce type I and type X collagen (Bay-Jensen, Hoegh-Madsen et al. 2010). Written consent to use this picture was secured.*

Eventually, the cartilage will erode and causing the joint space to be narrowing, and in the end, it will be bone rubbing against bone. In the late stages of OA, the bone will grow outward and form osteophytes on the edges of the joint (Hunter, McDougall et al. 2009, Fu, Robbins et al. 2018, Hunter and Bierma-Zeinstra 2019). So even if the development of PTOA starts with initial trauma, narrowing of joint space and osteophytes is only detectable in the late stages via radiographic images. This makes a 10-year follow-up of this prolonged condition interesting.

4.5 Risk factors for knee OA

When looking at the risk factors of getting knee OA, you can divide them into two categories: non-modifiable and modifiable. The non-modifiable is challenging to impact, but the modifiable risk factors can be influenced in the clinical practice (Johnson and Hunter 2014).

4.5.1 Non-modifiable risk factors

Age is a strong predictor of OA, and as age increases, the prevalence of OA is also increasing (Hunter and Bierma-Zeinstra 2019). The exact reason is yet unknown, but a combination of biomechanical and biological changes might be an explanation (Johnson and Hunter 2014).

Former knee injury is also a risk factor with strong or moderate evidence (Muthuri, McWilliams et al. 2011, Whittaker, Woodhouse et al. 2015, Hunter and Bierma-Zeinstra 2019). For example, Risberg et al. (2016) showed us that following an ACL injury, the prevalence of TFJ OA was 42% after 20 years. However, in the non-injured knee, the prevalence was 13%. A significantly lower prevalence compared to an ACL injured knee.

Gender is also associated with a higher prevalence of knee OA, as females often are more affected (Boyan, Tosi et al. 2012). This difference in prevalence between sex is more evident in the older population, from 60 years and forward (Felson, Lawrence et al. 2000). Regarding the possible development of PTOA, women are at a 2-8 times higher risk of getting an ACL injury than men (Waldén, Hägglund et al. 2011, Bahr R.

2014). Young female athletes seem to have a 2-3-fold increased risk of ACL injury (Kaeding, Léger-St-Jean et al. 2017). It has been theorized that the anatomy could play a part as females often have wider hips and thus a more valgus alignment of the knee joint (Hewett, Myer et al. 2005). But newer research does not support this theory since the quadriceps angle seems only to affect the frontal plane and not the rotational plane in ACL injuries (Nguyen, Boling et al. 2009). Genetics is also a risk factor in developing knee OA with an estimated 40-80% genetic component (van Meurs 2017, Magnusson, Turkiewicz et al. 2020).

4.5.2 Modifiable risk factors

Strong evidence indicates that obesity is a risk factor for developing knee OA (Johnson and Hunter 2014, Whittaker, Woodhouse et al. 2015, Hunter and Bierma-Zeinstra 2019). As obesity has become a global pandemic, it will most likely result in more people affected by knee OA. Studies have shown that being overweight increases the risk of knee OA, and a 5-unit increase in body mass index (BMI) is associated with 35% increased risk (Jiang, Tian et al. 2012). Therefore, it can be speculated that the benefit of weight-reducing is linked to the reduced compressive forces resulting from the lesser weight (Messier, Gutekunst et al. 2005, Messier, Mihalko et al. 2013).

Quadriceps strength is another modifiable risk factor. Øiestad et al. (2010) found that a loss of quadriceps strength between 2 and 10-15 years after an ACL injury showed significantly higher odds for symptomatic radiographic knee OA. Øiestad et al. (2015) also conducted a systematic review that concluded a weakness of the quadriceps muscle was a risk factor in developing symptomatic knee OA. The quadriceps muscle´s job is to act as a shock absorber and reduce knee joint loading patterns and conserve the joint surface under loading and motion (Øiestad, Holm et al. 2010). So, if the quadriceps are weak, there is a possibility of increased mechanical stress on the AC and thereby contributes to the progression of knee OA (Øiestad, Juhl et al. 2015).

A lower hop test limb symmetry index (LSI) is associated with the development of PTOA as an LSI score lower than 75% showed 2,9 times higher odds of PTOA 10 years after ACLR (Losciale, Bullock et al. 2020). However, this association lacks strong evidence, and

Losciale et al. (2020) also suggest further research investigating the relationship between the knee PTOA and hop test results.

4.6 Pain

OA often starts with the slow depletion of the AC. The AC is anural and avascular, and thus the cartilage cannot directly produce nociceptive pain (Hunter, McDougall et al. 2009). If the AC is incapable of producing pain symptoms, why do they occur?

The subchondral bone, periarticular ligaments, synovium, and joint capsule are innervated and can generate nociceptive pain. Nociceptive pain is a neurophysiological term and is the results of the neural process of noxious stimuli by nociceptive neurons, but it is not always perceived as painful (Gwilym, Pollard et al. 2008, Loeser and Treede 2008).

The nociceptive pain can occur from loading on a damaged joint and from opening ion channels on nociceptive nerve endings (Fu, Robbins et al. 2018). The knee joint is innervated via peripheral nerve fibers, which act as nociception, vasoregulation, and proprioception. These nerve fibers, which consist of fast conducted thin myelinated and slow conduction unmyelinated, innervate the synovium, ligaments, menisci, and subchondral bone (Fu, Robbins et al. 2018).

One of the other main symptoms of pain in OA is the inflammatory component. When a joint is affected by arthritis, inflammatory mediators are released into the joint, making the threshold of the joint nociceptor lower. As a result, the joint nociceptors are more likely to respond to non-harmful and harmful stimuli. The more the disease advances, the more inflammatory mediators develop in the joint, and an automatic maintaining of the pain cycle is triggered (Hunter, McDougall et al. 2009). The pain signals make their way to the brain via ascending pathways to the higher central nervous system through the dorsal root into the dorsal horn of the spinal cord. Then the signals are carried via ascending pathways to the hypothalamus, thalamus, and cerebral cortex. Here the signals are translated as pain and giving affective traits (Fu, Robbins et al. 2018).

Contrary to nociceptive pain that occurs by physical tissue damage, neuropathic pain occurs with damage to the actual nervous system. Furthermore, this damage to the

nervous system or disease of the somatosensory system happens over a long period of time and can change the central nervous system to become more sensitive (Fingleton, Smart et al. 2015, Fu, Robbins et al. 2018).

As mentioned before, the inflammatory mediators released into the joint can sensitize the afferent nerves, which can cause ordinary painless joint movements to evoke a painful response. This is called hyperalgesia which can be present in the central sensitization of the central nervous system. Over an extended period of time this altered pain response can cause a change in the central nervous system (Hunter, McDougall et al. 2009). The neurons will fire together regularly, and they can become more efficient at firing, and the threshold for activation is lowered. An easy way to understand this is the term "neurons that fire together, wire together" (Keysers and Gazzola 2014). Hyperalgesia causes a heightened sensitivity to harmful stimuli along with a longer duration of pain. With this change in the central nervous system, a person with knee OA can experience a difference in pain perception and the degree of actually joint damage (Fu, Robbins et al. 2018). As is the case in allodynia which is a special case of hyperalgesia (Loeser and Treede 2008). Where allodynia is present, normal non-painful activity such as walking generates pain. Along with hyperalgesia and the increase in afferent nerve stimuli from the dorsal horn segment, plasticity change can happen in the central nervous system (Hansson 2014). This will cause a central sensitization in which the definition is described by the International Association for the Study of Pain (IASP) as: *"Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs."*(IASP 2017).

A large systematic and meta-analysis by Fingleton et al. (2015) found a connection of greater pressure pain sensitivity between people with knee OA and healthy controls -0.86 (CI 95% -1.09 to -0.62). This is an indication of the central sensitization that can occur in people with knee OA.

A different aspect of pain in people with knee OA is the social and psychological part. When you are viewing a person with knee OA, you need to look at the whole person and not just the biological elements. So, not only the joint or tissue damage, but also social and psychological factors can affect the perception of pain negatively (Cruz-Almeida, King et al. 2013, Fu, Robbins et al. 2018, Hunter and Bierma-Zeinstra 2019).

For example, the pain can be modified by the level of depression or anxiety (is the pain ever going to go away?). This can contribute to catastrophizing pain perception and keep the person with knee OA in a negative spiral (Gwilym, Pollard et al. 2008). Other factors like socioeconomic status, racial, and cultural background can also negatively affect the perception of pain (Hunter, McDougall et al. 2009). As Hunter et al. (2019) points out, up to 25% of patients who have had total knee replacement still complain of pain and disability one year after surgery. So even though the whole knee joint was replaced, some patients still had the perception of pain.

In summary, the concept of pain in knee OA is complex and not yet fully understood through research. There are different types of pain ranging from nociceptive pain from structural joint, and tissue damage, neuropathic pain with central sensitization from altered firing in the central nervous system, and psychological pain. The discordance between radiographically diagnosed OA and the perception of knee pain might be disturbed by the complex pain picture that people with knee OA experience.

4.7 Radiographic OA

Using radiographic imaging is considered the gold standard when diagnosing knee OA (Cai, Cicuttini et al. 2020). When examining the x-ray images, the focus is on possible joint space narrowing from cartilage loss and the presence of osteophytes. The cut-off for defining radiographic knee OA using the Kellgren & Lawrence grading is a score of grade ≥2, also defined as the mildest grade of OA (Kellgren and Lawrence 1957). However, there is some disagreement of the threshold when diagnosing radiographic OA as some studies have used a cut-off at Kellgren & Lawrence grade ≥1 (Kessler, Behrend et al. 2008, Harris, Driban et al. 2017). An expert panel has also suggested using Kellgren & Lawrence grade 0 and 1 when diagnosing early OA in combination with clinical signs and the presence of pain (Luyten, Bierma-Zeinstra et al. 2018).

Grade 2 of the Kellgren & Lawrence score involves both the presence of osteophytes and the possibility of joint space narrowing (Felson, Niu et al. 2011). As OA can affect the whole knee, pictures of both the TFJ and the PFJ should be observed (Schiphof, de

Klerk et al. 2008). Øiestad et al. (2011) investigated the association between radiographic knee OA and knee symptoms and function. This study showed that people with an ACL injury 10-15 years after ACLR, had more radiographic knee OA in the injured compared to the uninjured knee. Those who had radiographic knee OA had significantly more symptoms when compared with those without radiographic knee OA. The more severe the radiographic knee OA the participants had, the more pain, impaired function and reduced quality of life compared to those without radiographic knee OA (Oiestad, Holm et al. 2011). This is not always the case as some studies have found discordance between the presence of radiographic OA and the lack of pain symptoms; only in severe cases with Kellgren & Lawrence grade ≥3 is there a more evident relationship between radiographic OA and pain (Schiphof, Kerkhof et al. 2013).

A large systematic review investigated the prevalence of radiographic knee OA ten years after an ACLR (Chen, Wang et al. 2019). The results showed an increased rate of overall radiographic knee OA (both the TFJ and PFJ) in the ACLR knee by 3,73 times compared to the uninjured knee (Chen, Wang et al. 2019). These results correlate with earlier results by Ajuied et al. (2014). Thereby, there seems to be a clear relationship with an increased risk of developing radiographic knee OA following an ACL injury.

4.8 Symptomatic OA

There are different definitions in the literature when it comes to defining symptomatic knee OA. Some have defined it as a combination of radiographic Kellgren & Lawrence score ≥2 (or at least mild radiographic OA) and symptoms in the knee (Murphy, Schwartz et al. 2008). Øiestad et al. (2010) used a similar definition with pain in the injured knee in the past four weeks combined with a Kellgren & Lawrence grade ≥2.

Other studies have used self-reported symptoms such as pain, aching or stiffness around the knee joint in the past 30 days as a diagnose of symptomatic knee OA (Losina, Weinstein et al. 2013).

Wasserstein et al. (2015) proposed to use the KOOS questionnaire in different models to diagnose symptomatic knee OA. One of the models used only the pain subscale score

as it has shown to have the highest correlation with structural OA changes (Illingworth, El Bitar et al. 2014). The cut-off for symptomatic OA was a KOOS pain score of 72 out of 100 (Wasserstein, Huston et al. 2015). Ware et al. (2018) used the same cut-off, based on the Wasserstein definition, to determine the association of pre-ACLR KOOS score and the development of symptomatic knee OA.

Barenius et al. (2014) used a cut-off at 85-87,5 for any of the KOOS subscales for diagnosing symptomatic knee OA, based on the definition made by Lohmander et al. (2004). It seems that there is no consensus about the cut-off for pain using a KOOS questionnaire to diagnose symptomatic knee OA.

When diagnosing knee OA clinically, the most used tools are the ACR, EULAR, and NICE criteria. In 2010, 17 OA experts from 12 European countries were tasked to comply and write evidence-based recommendations for the diagnosis of Knee OA (Zhang, Doherty et al. 2010). They all agreed on three key symptoms (persistent knee pain, morning stiffness for less than 30 minutes, and reduced knee function) and three signs (crepitus, restricted movement, and bony enlargement). The morning stiffness time cut set at 30 minutes is to rule out autoimmune diseases like rheumatoid arthritis in which the morning stiffness often persists longer than 30 minutes. If a person has six of these symptoms and signs and is older than 45 years, the estimated probability of having radiographic OA is 99%.

Another often used recommendation for diagnosing clinical symptomatic OA were created by the ACR 1986 (Altman, Asch et al. 1986). The ACR criteria are mostly like the EULAR but differ in some ways. The clinical ACR criteria for diagnosing OA are: Age older than 50 years, morning stiffness for less than 30 minutes, crepitus, bony tenderness, bony enlargement, and no palpable warmth (Altman, Asch et al. 1986). According to these criteria, if a person has knee pain and at least three of these symptoms the sensitivity and specificity are 95% and 69%. This gives a high possibility of correctly diagnosing knee OA, but also of getting false-positive results.

The National Institute for Health and Care Excellence in the United Kingdom presented the NICE guidelines in 2014 for clinical diagnosing knee OA (National Clinical Guideline 2014). The NICE guidelines for diagnosing knee OA consist of only three criteria: The

person is 45 years or older, has activity-related joint knee pain and has no morning joint-related stiffness lasting longer than 30 minutes (National Clinical Guideline 2014). These guidelines base their sensitivity and specificity on two systematic reviews, which compare radiographic images with ACR classification and not the specific NICE guidelines (Schiphof, de Klerk et al. 2008, Kinds, Welsing et al. 2011). Kinds et al. (2011) present an agreement of both radiographic and clinical diagnosed OA in 4/39 studies, 7/39 studies had no agreement, and the last 28/39 studies was inconsistent.

Décary et al. (2017) examined the validity of clinical diagnosing knee OA using the ACR and EULAR criteria. They found them usable but suggested that more evidence to better define clinical or symptomatic OA is needed. Although there are similarities between the three of them and agreement on three symptoms, there are still ongoing discussions about which recommendations are the most optimal. A Danish study compared these three guidelines to see if they correlate in detecting knee OA clinically with participants who were more than 60 years old. The majority of the participants did not have PTOA (Skou, Koes et al. 2020). Of the 13.459 participants, 10.651(79.1%) had self-reported radiographic knee OA. There was some disagreement when comparing the symptoms between these three classification tools. Only 49,3% and 53,7% of the self-reported radiographic knee OA participants fulfilled the ACR and EULAR criteria. While 89,7% fulfilled the NICE criteria, the NICE guidelines were most successful at diagnosing knee OA clinically (Skou, Koes et al. 2020).

5.0 Methods

5.1 Design

The Delaware-Oslo ACL Cohort study is a prospective observational cohort study of sports active patients with an ACL injury. The study was started to investigate outcomes and prognostic factors between patients with an ACL injury who undergo ACLR with rehabilitation or rehabilitation alone. This master thesis is based on data from the 10-year follow-up of the Norwegian branch. It uses a cross-sectional study design to investigate the prevalence of radiographic and symptomatic OA in this cohort.

5.2 Data collection

The participants were initially contacted by mail containing information about the study and asked to participate in the 10-year follow-up (see written consent in appendix 1). The mail address was collected from the national registry. Afterwards, participants were contacted by telephone to schedule test appointments.

The 10-year follow-up was undertaken at Nimi, Ullevaal Stadion, Oslo, and the Department of Radiology, Oslo University Hospital. All data were stored in folders with individual ID numbers that were only identifiable by a master paper with all the participant´s names. All the data, together with identification codes, were stored in a safe at Nimi, Ullevaal Stadion, Oslo, where the data registration was done. The registration was performed in Microsoft Excel before it was exported to SPSS for further statistical analyses. All the data were double-checked to make sure that was no registration errors.

Before the day of testing, the participants filled out questionnaires that was sent to them. On test day, the participants first started at either Nimi or Oslo University Hospital. After completing the tests they then proceeded to the other facility. At Nimi, a physiotherapist instructed the participants to warm up on a stationary bike for 10 minutes (Technogym). After the warm-up, the participant performed the muscle strength test on the Biodex 6000 dynamometer (Biodex Medical Systems, Shirley, New

York, USA) before completing the hop test battery. At Oslo University Hospital the participants met the physiotherapist to perform x-rays and the laxity test using the KT1000 arthrometer. After completing the x-rays an experienced orthopedic surgeon analyzed and explained the radiographic findings to the participants. When data had been collected, it was stored manually in archives and locked with personal identification. All data were de-identified and handled without names or social security numbers.

5.3 Participants

One hundred and fifty non-professional athletes with ACL rupture were included in the Norwegian arm of the original cohort between 2006 and 2012. The deadline for this master thesis was set before all the participants were scheduled for their 10-year follow-up. Of the 123 eligible participants which was contacted and asked to participate before the deadline, 104 agreed to participate. Thus, the participant follow-up rate was 84.5 % (104/123). Dropout reasons were: Moved abroad, no response, withdrawal from the study and health issues. Of all the participants 13 were unable to perform all the tests or complete x-ray examination. The process is illustrated in figure 3.

Original inclusion criteria were age between 13 and 60 years, ACL injury during the last three months, and participation in pivoting sports (activity level 1 or 2) ≥two times/week before the injury. Sports such as basketball, soccer, tennis, skiing, and handball are defined as activity level 1 and 2 pivoting sports (Hefti, Müller et al. 1993). The participants were diagnosed via MRI and side-to-side difference of at least 3mm in anteroposterior laxity measured by manual maximal testing with a KT1000 arthrometer (MEDmetric, San Diego, California).

Original exclusion criteria were a current or previous injury to the ipsi- or contralateral knee, concomitant grade III ligament injury of the posterior cruciate ligament, lateral collateral ligament, or the medial collateral ligament, full-thickness AC damage, or fracture. In addition, participants with symptomatic meniscal injuries were also excluded if they had knee pain or swelling during or after plyometric activities.

5.4 Treatment algorithm

The following treatment algorithm was used in this cohort: The choice between ACLR and rehabilitation or rehabilitation alone was decided in unity between an orthopedic, physiotherapist, and the participant. The participant also had the opportunity to opt in for a delayed ACLR if the rehabilitation alone treatment was not sufficient. A ACLR performed six months after initial ACL injury was labeled as delayed ACLR. Before any decision on any treatment option, the participants went through a five-week protocol-based rehabilitation program based on Eitzen et al. (2010) article. This five-week rehabilitation program has been shown to improve knee function and muscle strength and is advised to be incorporated after ACL injury, but the participants should have no or minimal swelling of the knee joint and could jump on the injured leg (Eitzen, Moksnes et al. 2010). After the five-week rehabilitation program, the participants who choose the rehabilitation-alone received additional 2-3 months of rehabilitation.

The main reason for those who choose ACLR was a desire to return to pivoting sport, dynamic instability, and the participants preference (Grindem, Eitzen et al. 2014). The participants who underwent ACLR were operated using bone-patellar tendon-bone or a hamstrings autograft (Grindem, Snyder-Mackler et al. 2016). The participants who choose rehabilitation alone were significantly older, less prone to participate in level 1 sports preinjury, and lower likelihood of having a medial meniscus injuries compared to the ACLR group (Pedersen, Grindem et al. 2021).

Following ACLR, the participants went through a personalized postoperative rehabilitation program, divided into three phases, based on concomitant surgery, graft choice and function (Grindem, Snyder-Mackler et al. 2016). An acute phase focusing on reducing swelling, regaining normal range of motion, and minimizing muscle atrophy. Next phase was the rehabilitation phase, where regaining neuromuscular control and improving muscle strength was the primary target. The last phase was a return to sport with the aim of regaining ≥90% muscle strength and hop ability of the non-injured leg. In this last phase of the postoperative rehabilitation, the participants were advised to refrain from returning to pivoting sports until nine months post-operation, and LSI was

at ≥90%. The LSI expresses the performance of the involved limbs compared to the uninvolved in percent.

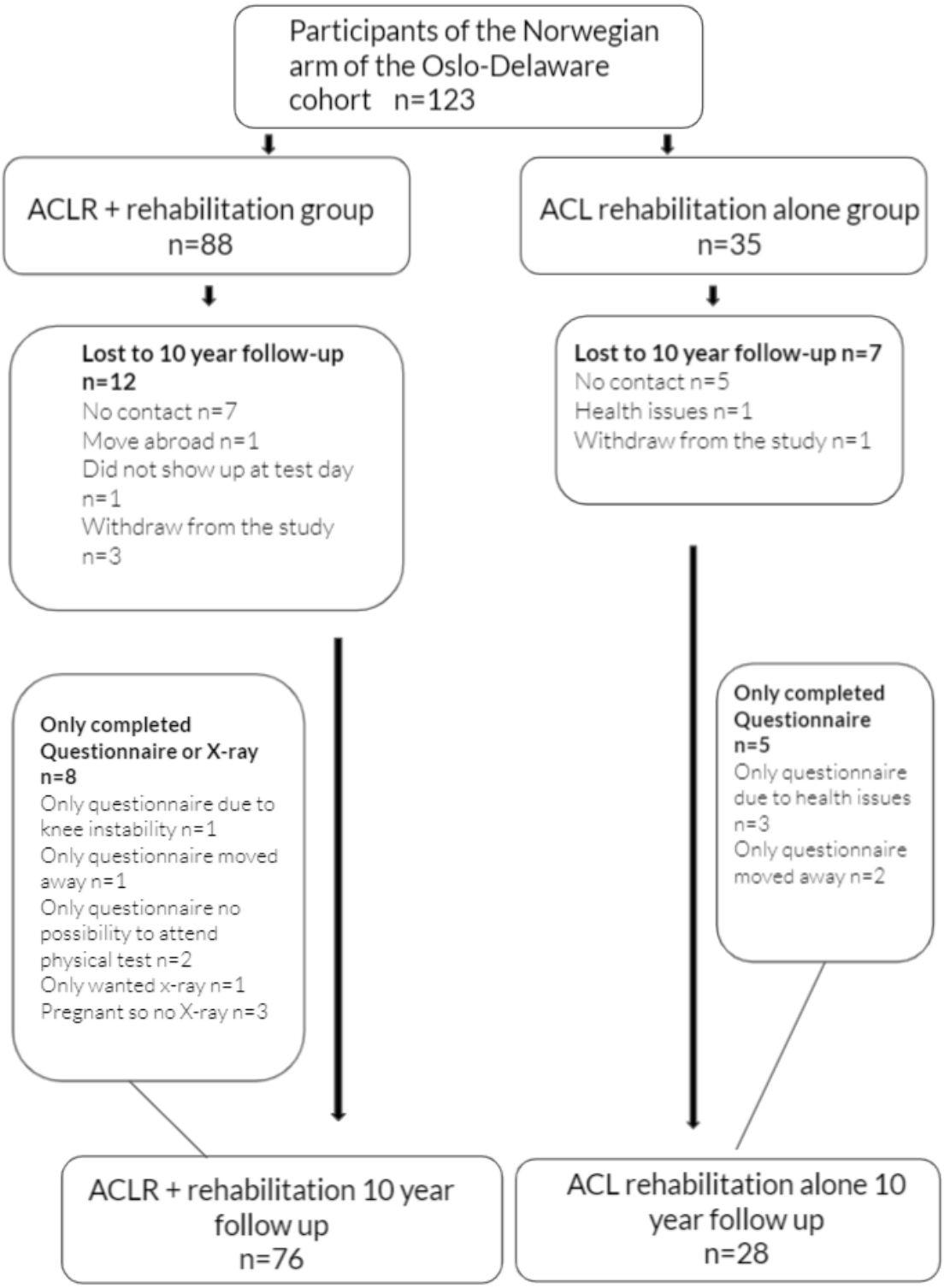

Figure 3: *Flowchart showing the distribution and reasons to drop out of the participating individuals in this master thesis*

5.5 Radiographic knee OA

Standardized, weight-bearing radiographs to assess radiographic knee OA were used in this study. The radiographic examination was conducted at Oslo University Hospital and viewed and scored by the same experienced radiograph. Assessing TFJ knee OA, posteroanterior radiographs were taken bilaterally using the SynaFlexer positioning frame (see figure 4). When using the Synaflexer frame, the knees are in approximately 20° of flexion, and the feet are in a position of 5° of external rotation. A skyline and lateral view of both knees were used to access knee OA of the PFJ. The use of this fixed flexion system has proven to ensure consistent and reproducible angulation and alignment of the knees during the x-ray and is validated at measuring joint space narrowing (Kothari, Guermazi et al. 2004).

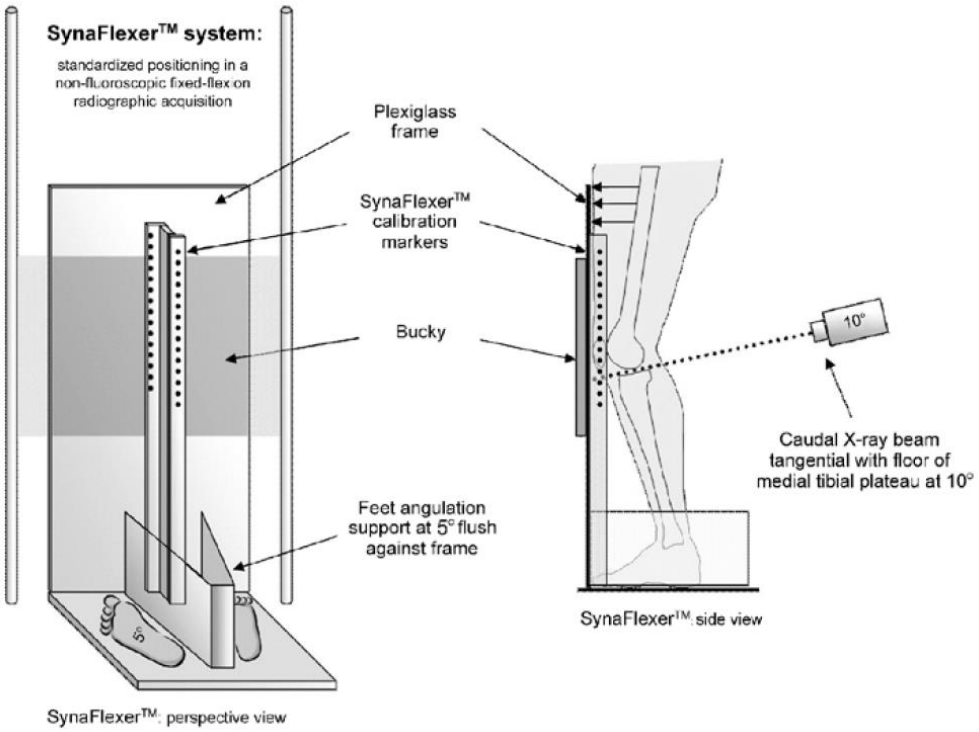

Figure 4: *A schematic illustration of the SynaFlexer system where the knees are placed in a fixed flexion position with a 10° caudal beam angulation to ensure alignment with the medial tibial plateau.*

Methods used when diagnosing knee OA radiographic vary in the literature. The most often used is the Kellgren & Lawrence (1957) classification criteria or Osteoarthritis

Research Society International (OARSI) (Altman, Hochberg et al. 1995). Knee OA can also be diagnosed via MRI imaging, where it is possible to detect osteoarthritic changes as cartilage defects, effusion synovitis, meniscal lesions, and MRI-detected osteophytes (Cai, Cicuttini et al. 2020).

The radiographs in this project were scored according to the Kellgren & Lawrence classification (Kellgren and Lawrence 1957). The classification system consists of five grades based on osteophyte formation and joint space narrowing as shown in table 1. The Kellgren & Lawrence classification is well recognized and often used throughout the literature for assessing knee osteoarthritis and is seen as a reliable classification of knee OA and OA progression (Ajuied, Wong et al. 2014, Bastick, Runhaar et al. 2015).

Description of radiographic knee OA grade 0-4	
Grade 0 (Normal)	No radiographic features of OA
Grade 1 (Doubtful significance)	Doubtful joint space narrowing, and possible osteophytic lipping.
Grade 2 (Minimal changes)	Definite osteophytes and possible joint space narrowing.
Grade 3 (Moderate changes)	Multiple osteophytes, definite joint space narrowing, sclerosis, possible bony deformity
Grade 4 (Severe changes)	Large osteophytes marked narrowing of joint space, severe sclerosis, and definite deformity of bone ends.

Table 1: *A detailed description of the different Kellgren & Lawrence grades.*

The presence of radiographic knee OA is operationally defined as Kellgren & Lawrence grade ≥2 in either tibiofemoral compartment (Kohn, Sassoon et al. 2016). When using this classification tool, it relies on the development of a new osteophyte to report new onset of knee OA. The development of osteophytes often begins with a small and borderline osteophyte. They are three-dimensional and can be visible from one angle of an x-ray and invisible from another. The Kellgren & Lawrence definition of grade 2 with

definite osteophytes, with emphasis on definite, raises questions about when an osteophyte turns into a definite one. The focus should also be on the loss of joint cartilage, a cardinal symptom of knee OA. A way to assess the loss of cartilage is to examine the joint narrow space, which is associated with loss of joint cartilage (Felson, Niu et al. 2011). In a longitudinal study, it is possible to survey the narrowing of joint space and thereby the loss of cartilage over a more prolonged period. Felson et al. (2011) have suggested that joint narrow space should be involved in the incident disease. An alternative Kellgren & Lawrence grade 2 with a new-onset disease with a grade 2/osteophytes score was recommended for future x-ray evaluations (Felson, Niu et al. 2011). The scoring used in this master thesis is the new alternative Kellgren & Lawrence grade 2a (development of definite osteophyte alone) and 2b (Definite osteophytes and possible joint space narrowing). The cut-off for diagnosing radiographic OA is ≥2b (Definite osteophytes and possible joint space narrowing) in this master thesis.

5.6 Symptomatic knee OA

To identify participants with symptomatic knee OA the KOOS questionnaire was used. Since there is no clear consensus on the definition of symptomatic knee OA, I will apply three different models as described in the literature. These three models for analyzing symptomatic knee OA are:

1. Model 1 Using only the pain subscale score with ≤72 points as symptomatic knee OA (Wasserstein, Huston et al. 2015, Ware, Owens et al. 2018)
2. Model 2 One or more KOOS score on any of the subscales below 86.1(pain), 85,7(symptoms), 86,8(ADL), 85(sport) and 87,5(QoL) and Radiographic OA Kellgren & Lawrence grade ≥2b (Definite osteophytes and possible joint space narrowing) (Barenius, Ponzer et al. 2014)
3. Model 3 Pain during the past four weeks in the injured knee using the KOOS P1 question and radiographic OA Kellgren & Lawrence grade ≥2a (development of definite osteophyte alone) (Oiestad, Holm et al. 2010, Risberg, Oiestad et al. 2016).

The KOOS questionnaire is a PRO-measurement, and it is self-administered (Roos, Roos et al. 1998). The KOOS questionnaire were constructed as an extension of the Western Ontario and McMaster Universities (WOMAC) OA index to have a specific purpose of evaluating both short- and long-term symptoms and function in people who have suffered a knee injury (Roos and Lohmander 2003). The KOOS questionnaire consists of 42 questions on how knee pain and function are perceived during the last seven days. The questions are divided into five subcategories, pain (9 questions), symptoms and stiffness (7 questions), function/daily living (17 questions), function/sports activities (5 questions), and in the end, quality of life (5 questions). The questions are scored by a 5-point Likert scale and scored by each subscale, with 0 being no problem and 4 extreme problems. A score between 0 and 100 is giving within every subscale, 0 is maximum joint problems, and 100 no joint problems. The equation of calculating a KOOS score for pain is illustrated in figure 5. A Norwegian translated version of the KOOS questionnaire were accessed and used in this master thesis (KOOS 2007).

$$100 - \frac{\text{Mean Score (P1}-\text{P9)}\times 100}{4} = KOOS\ Pain$$

Figure 5: *KOOS calculation equation for the pain subscale*

The KOOS questionnaire has proven reliable, has content validity, internal consistency, test-retest reliability, and construct validity (Roos and Lohmander 2003, Collins, Misra et al. 2011, Collins, Prinsen et al. 2016). The KOOS has also proven to be valid and reliable in measuring the functional status and pain after an ACL injury or reconstruction (Roos, Roos et al. 1998, Salavati, Akhbari et al. 2011). Previously published studies have used a cut-off score of ≤72 points for diagnosing symptomatic knee OA (Wasserstein, Huston et al. 2015, Ware, Owens et al. 2018). This number derives by setting the cut-off at two standard deviations below the mean.

Since the participants were asked to complete the KOOS questionnaire regarding the injured knee, the prevalence of symptomatic OA is only possible to investigate on the injured knee.

5.7 Physical activity

Participants were asked what their current physical activity level was based on their leisure time. This answer is then translated into the different physical activity levels 1-4 based on Hefti et al. (1993).

i. Pivoting, jumping, and hard cutting sports like football, basketball, handball, and soccer.
ii. Skiing (downhill) and tennis.
iii. Jogging, running, and cross-country skiing.
iv. Sedentary work and activities of daily living.

Table 2*: The four different physical activity levels from level 1: pivoting sports to level 4: sedentary work*

The participants also filled out a HUNT questionnaire to evaluate their physical activity level during leisure time (Moholdt, Wisløff et al. 2014). The participants were asked about how often they exercise on an average basis (never, less than once per week, once a week, two or three times per week, or four or more times per week). The questionnaire also contained questions about intensity (taking it slow and not getting sweaty or loss of breath, going so hard you get a sweat and shortness of breath or going almost all out) and duration (less than 15 minutes, 15-29 minutes, 30-60 minutes, or more than 60 minutes). The HUNT questionnaire can be seen in appendix 2. Based on their answers, the participants were divided into a physical activity index with four different grades (Moholdt, Wisløff et al. 2014). The index is based on the recommendations to promote and maintain healthy living (Haskell, Lee et al. 2007). They recommend a minimum of 30 minutes of moderate-intensity aerobic activity five days a week (150 minutes in total) or 20 minutes of vigorous-intensity activity three days a week (60 minutes in total). The four categories are as follows:

1. No activity
2. Low activity
3. Moderate activity
4. High activity

Table 3: *The four different physical activity levels using the HUNT questionnaire.*

The participants that answered “Never” on the first question regarding frequency were categorized as no activity. Participants who reported a physical activity below the recommendations were categorized as low activity. Those participants who reported an activity level fitting of the recommendations of either a weekly total of 150 minutes moderate-intensity or 60 minutes vigorous intensity was divided into moderate activity. Those who reported an activity level above the recommendations were categorized as high activity (Moholdt, Wisløff et al. 2014).

The HUNT 1 questionnaire has proven reliable and gives an appropriate measure physical activity of leisure time for men (Kurtze, Rangul et al. 2008). The questionnaire has high repeatability and also a moderate correlation with maximal oxygen uptake (Kurtze, Rangul et al. 2008).

5.8 Outcome variables describing the characteristics of the participants.

As mentioned earlier, under risk factors for knee OA, weak quadriceps strength and hop distance LSI ≤90% has been associated as a risk factor for the development of knee OA together with a high BMI. These outcomes are used to describe the characteristics of the participants in this cohort, 10 years after ACL injury.

5.8.1 Quadriceps muscle strength

After 10 minutes of ergometer bike (Technogym) warm-up the participants went straight ahead to test quadriceps strength using the Biodex 6000 dynamometer (Biodex Medical Systems, Shirley, New York, USA). The uninjured leg was tested first, and maximal muscle strength of the quadriceps was measured by isokinetic strength testing at 60˚/seconds and expressed by peak torque. The range of motion was set from 90˚ flexion to full extension and the participant was seated on the seat of the dynamometer. The seat was adjusted, so the axis of rotation was positioned at the lateral knee joint line. The arm lever was placed approximately 2 cm above the heel cap of the participants’ shoes. All straps were tightened and secured, and the participants

performed four practice repetitions with one-minute rest before five test repetitions were recorded. The participants were instructed to give their maximal effort in both the concentric and eccentric contractions. The tester gave information and encouragement under the trial and the test repetitions. The quadriceps muscle strength was expressed as LSI for peak torque as described by this formula: (peak torque of involved leg) / (peak torque of uninvolved leg) · 100.

The Biodex 6000 has proven to have a good to moderate validity and good reliability (ICC >90) (Logerstedt, Snyder-Mackler et al. 2010, Zawadzki, Bober et al. 2010).

Undheim et al. (2015) proposed this test protocol as a valid LSI assessment after systematically reviewing 39 studies that evaluated isokinetic strength protocols. Isokinetic muscle testing is previously reported to be correlating well to other functional tests in ACL patients (Järvelä, Kannus et al. 2002).

5.8.2 Hop tests

Four single-legged hop tests were: the single hop for distance, the triple hop for distance, the crossover hops for distance, and the 6-m timed hop. The tests were administered by a trained physiotherapist and were performed according to the protocol of Noyes et al. (1991).

The four hop-test is illustrated in figure 6. They were performed in the following order:

- Single hop
- Crossover hop
- Triple hop
- 6-m timed hop

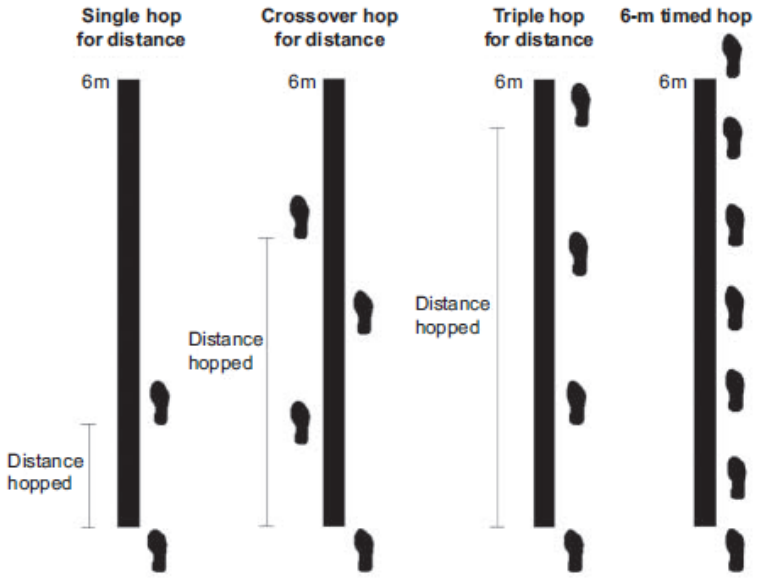

Figure 6: Illustration of the four-hop test with single hop, crossover hop, triple hop, and 6-m timed hop (Noyes, Barber et al. 1991).

The uninjured leg was tested first. Participants performed one practice trial for each leg before two trials were recorded. The test score was measured in centimeters on a measurement band that was fixed to the floor. Measurements were measured from the heel of the participants' shoes.

During the three first hop tests, trials were considered valid if the final landing was stable. The average score of the two trials per-hop test was used for analyses. The trial was ruled invalid and repeated if the participants contacted the floor or walls with their other foot or hands or performed an additional hop. There were no restrictions for arm movements. For the 6-m timed hop test, a stopwatch was used. The hop test results were expressed in LSI. If a participant scored below 90% LSI on one or more of the hop tests, the overall result of the hop tests was presented as LSI ≤90%.

This hop test battery has proven to have high intraclass correlation coefficients (ICC) for LSI index values (Reid, Birmingham et al. 2007). The hop test scores were statistically greater after 16 weeks, and three separate hop tests on the ACLR leg compared to the nonoperative. The conclusion made by Reid et al. (2007) was that the hop tests have proved to measure performance-based outcomes for people rehabilitating after ACLR, reliably and validly. The single-hop test has also been shown to predict self-reported

knee function after one year in ACL injured non-surgical patients (Grindem, Logerstedt et al. 2011).

5.8.3 BMI

Having a high BMI have been reported as risk factor for knee OA and therefore measuring height and weight for calculating BMI is important (Barenius, Ponzer et al. 2014, Bastick, Runhaar et al. 2015, Silverwood, Blagojevic-Bucknall et al. 2015). Height was measured to the nearest mm. Bodyweight was measured with an electronic weight registered to the nearest 0.1 kg. The participants wore light clothes, and the estimated weight of the clothes was subtracted (0.3 kg for light pants and t-shirt).

5.9 Statistical analysis

The statistical analysis was performed using the SPSS for Windows 14.0 software package (SPSS Inc., Chicago, Illinois, USA).

The participants characteristics was presented using descriptive data. Continuous data were presented with mean and standard deviation for the normally distributed data and with median and range for the skewed data.

Test of normality was performed for all the KOOS score results. The tests showed that the data was not normally distributed. This was done both by visually looking at the histogram and Q-Q plots and with the Kolmogorov-Smirnov test of normality. As a result of this, the means were analyzed with a non-parametric test Mann-Whitney for independent groups.

Age and BMI were deemed to be normally distributed and compared by means using an independent Student t-test.

Chi-square tests were used for group comparisons of two or more categorical variables when analyzing Kellgren & Lawrence grade of radiographic OA, and Fisher exact test

were performed to check for significant differences. Significant levels were set at $p<0.05$.

When comparing the results of the three different models of detecting symptomatic OA, Chi-square tests with Fisher exact test were performed to check for significant differences. Significant levels were set at $p<0.05$.

5.10 Ethics

This study was approved beforehand by the Regional Committee for Medical and Health Research Ethics, SouthEast, Norway, case number REK: 2018/433. REK approval can be found in the appendix 3. Together with project leader MAR a notice was sent to REK and informed of my inclusion in this study and the title and goals of this master thesis.

All participants signed a written informed consent informing the participants about the study´s potential risk, benefits, and purpose. All participants have been informed about their right to withdraw from the study at any point in time, and participation is entirely voluntary.

The written consent involves information about all the tests they have to perform together with the benefits and potential risks of performing these tests. In addition to this 10-year follow-up, the written consent also informed about the possibility of another long-term follow-up; and the possibility of contacting the participant if this becomes a reality. The 10 years follow-up written consent is attached in the appendix 1.

All data was handled without names or social security numbers and thereby de-identified. Approval of handling personal information were obtained through the privacy representative from Oslo University Hospital. Approval can be seen in the appendix 4.

6.0 Results

In the first part of the results chapter, a description of the participants anthropometrics will be presented: Gender, age, BMI. Followed by KOOS score, function, physical activity level and sports participating level. Afterwards the results of radiographic and symptomatic OA prevalence will be presented.

6.1 Participants characteristics

There were 104 (84.5% follow-up) participants who agreed to participate, and 91 of the 104 completed all the physical tests and x-rays. The remaining participants who were not able to participate and/or complete the physical test, still replied to the sent questionnaires. This is illustrated in figure 3.

The cohort was 52% female. The mean age for the ACLR group was 35 years. For the rehabilitation alone group it was 42 years. The mean BMI was 25,6 kg/m² for the ACLR group. For the rehabilitation alone group it was 24,6 kg/m². Of the 76 participants in the ACLR group, 13 participants had undergone delayed ACLR: Nine between 0 and 2- years, two between 2- and 5- years and two between the 5- and 10-years follow-up. These 13 participants did not differ from the rest of ACLR group regarding age, BMI, and prevalence of symptomatic and radiographic OA.

Table 4 shows demographics and characteristics of the 104 included participants at 10 years follow-up.

Participant's characteristics	ACLR n=76 (73.1%)	Rehab-Alone n=28 (26.9%)	Total n=104 (100%)
Male n (%)	36 (47.3)	14 (50)	50 (48)
Female n (%)	40 (52.7)	14 (50)	54 (52)
Mean age in years (±SD) *	35.6 (±6.9)	42.1 (±8.7)	37,4 (±7.9)
Mean BMI (±SD)	25.6 (±3.6)	24.6 (±2.3)	25,3 (±3.3)
KOOS Scores Median (min-max)			
• Pain	97.2 (36.1-100)	97.2 (72-100)	97.2 (36.1-100)
• Symptoms	96.4 (32.1-100)	96.4 (78.5-100)	96.4 (32.1-100)
• ADL	100 (76.5-100)	100 (96-100)	100 (76.5-100)
• Sport/rec	90 (10-100)	95 (50-100)	90 (10-100)
• QoL	81.1 (19-100)	81.1 (19-100)	81.2 (19-100)
Quadriceps strength			
• ≥90%LSI	47 (70.1)	17 (73.9)	64 (71.1)
• ≤90%LSI	20 (29.9)	6 (26.1)	26 (28.9)
Hop tests			
• ≥90%LSI	60 (82.2)	20 (80)	80 (81.6)
• ≤90%LSI	13 (17.8)	5 (20)	18 (18.4)
HUNT physical-activity n (%)			
• No activity	2 (2.6)	1 (3.7)	3 (2.9)
• Low	18 (23.7)	10 (37)	2 (27.2)
• Moderate	36 (47.4)	10 (37)	46 (44.7)
• High	20 (26.3)	6 (22.2)	26 (25.2)
10-year activity level n (%)			
• Level 1	8 (10.5)	1 (3.8)	9 (8.8)
• Level 2	25 (32.9)	8 (30.8)	33 (32.3)
• Level 3	40 (52.6)	15 (57.7)	55 (53.9)
• Level 4	3 (3.9)	2 (7.7)	5 (4.9)

Table 4: The participants characteristics and differences between ACLR and rehabilitation alone groups.

**Significant difference in age between the two groups (P=0.001) ACLR= Anterior Cruciate Ligament Reconstruction, KOOS= Knee injury and Osteoarthritis Outcome Score*

6.2 Radiographic OA

The prevalence of radiographic knee OA divided into the TFJ and PFJ is presented in diagrams 1 and 2.

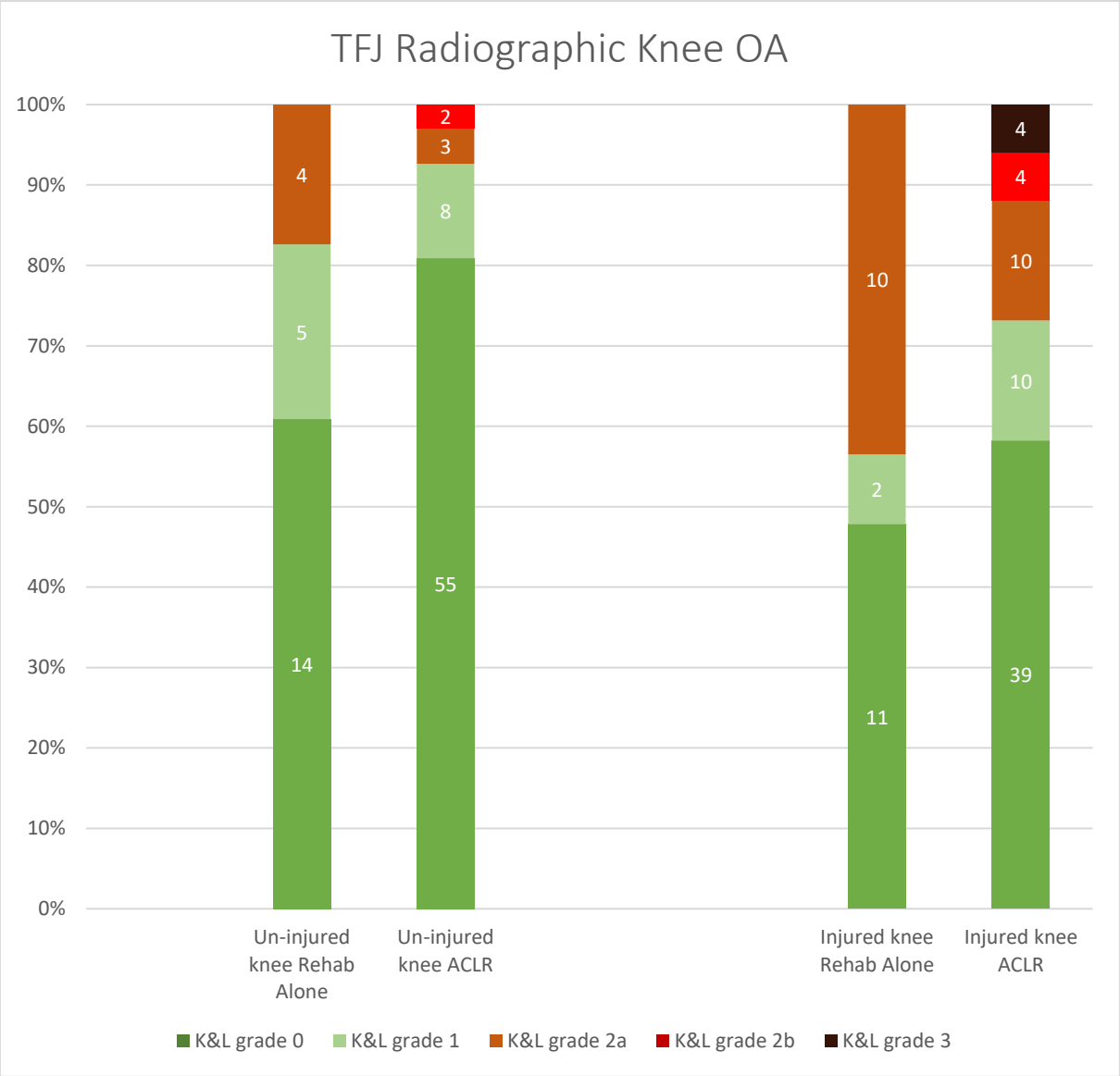

Diagram 1: *An illustration of the prevalence of TFJ radiographic OA. The green represents the participants with Kellgren & Lawrence grade 0 and 1, the orange represents those with grade 2a, and the red color represents those with radiographic TFJ OA with the cut-off at 2b and above. The numbers represent the occurrence of participants with the different grades of Kellgren & Lawrence. The percentage is shown on the y-axis.*

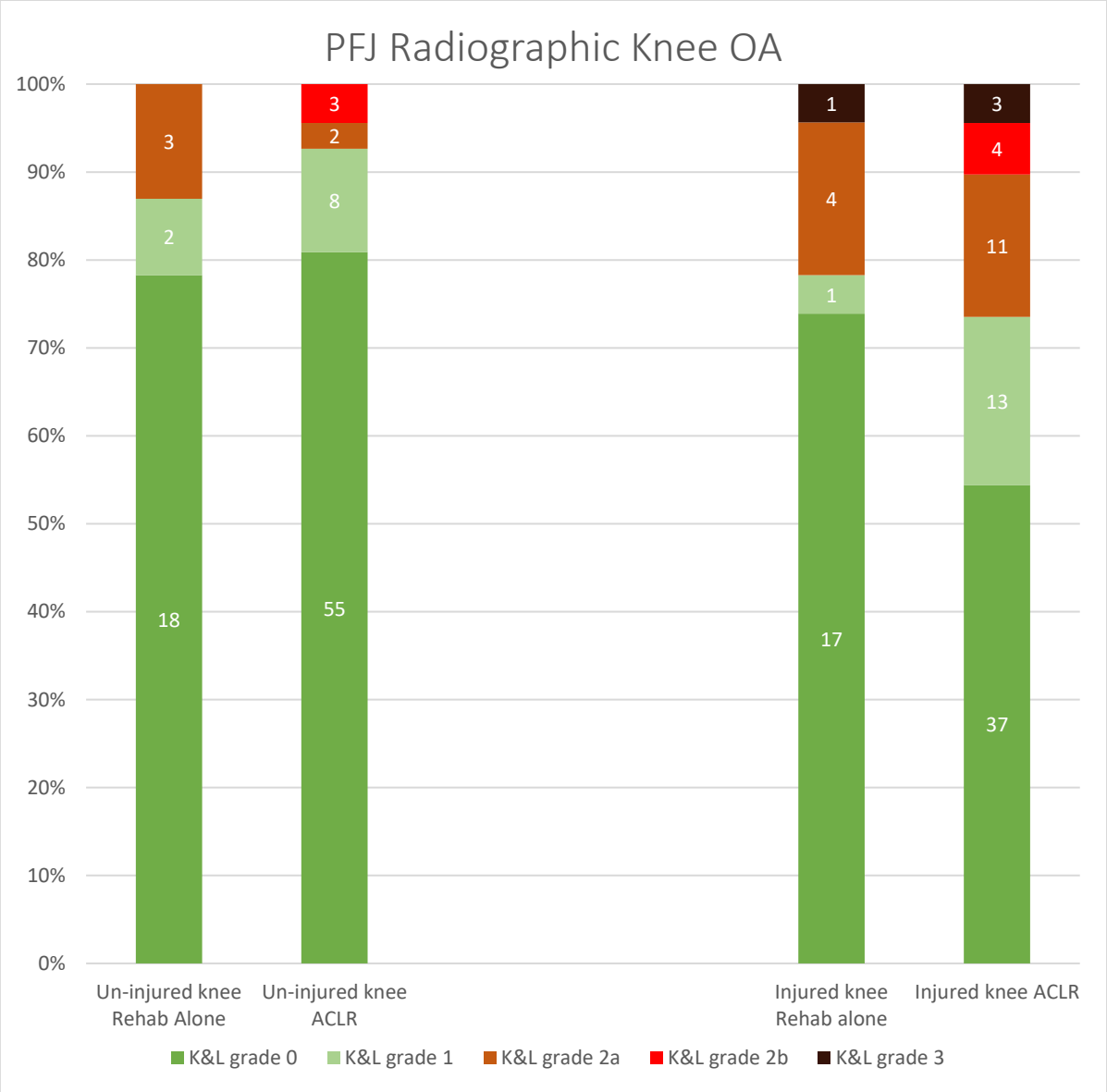

Diagram 2: *An illustration of prevalence of PFJ radiographic OA. The green represents the participants with Kellgren & Lawrence grade 0 and 1, the orange represents those with grade 2a, and the red color represents those with radiographic PFJ OA with the cut-off at 2b and above. The numbers represent the occurrence of participants with the different grades of Kellgren & Lawrence. The percentage is shown on the y-axis.*

In the ACLR group, eight participants (8/67[1] 11.9%) had TFJ radiographic knee OA in the injured knee. Two participants (2/68 2.9%) had TFJ radiographic knee OA in the uninjured knee.

In the rehabilitation alone group 0 participants had radiographic TFJ OA in either the injured or uninjured knee. There was no significant difference in the prevalence of radiographic TFJ OA between the ACLR and the rehabilitation alone group (P=0.064). However, a significant difference was observed with the prevalence of radiographic TFJ OA between the uninjured and injured knee (P=0.003).

In the ACLR group, seven participants (7/68 10.2%) had PFJ radiographic OA in the injured knee. Three participants (3/68 4.4%) had PFJ radiographic OA in the uninjured knee.

In the rehabilitation alone group, one participant (1/23 4.3%) had PFJ radiographic OA in the injured knee. 0 participants had radiographic PFJ OA in the uninjured knee. There was no significant difference in the prevalence of radiographic PFJ OA between the rehabilitation alone and ACLR group (P=0.326). A significant difference was observed between the uninjured and injured knee (P=0.04).

As seen in diagram 1 and 2, the prevalence of TFJ and PFJ radiographic OA was 15 combined. However as three participants had both TFJ and PFJ OA, this makes a total of 12 participants (12/135, 8.8%) with overall radiographic OA (both TFJ and PFJ). In the rehabilitation alone group one participant (1/46 2.1%) had overall radiographic OA.

[1] One participant had a hemi prosthetic

6.3 Symptomatic OA

The prevalence of symptomatic OA is presented in table 5 and diagrams 3 and 4.

Table 5: Prevalence of symptomatic OA.

	Rehab alone	ACLR	P Value
Model 1	**n=28**	**n=76**	
No symptomatic knee OA n (%)	28 (100)	73 (96)	0.301
Symptomatic knee OA n (%)	0 (0)	3 (4)	
Model 2	**n=23**	**n=68**	
No Symptomatic TFJ knee OA n (%)	23 (100)	61 (89.7)	0.106
Symptomatic TFJ knee OA n (%)	0 (0)	7 (10.3)	
No Symptomatic PFJ knee OA n (%)	22 (95.7)	61 (89.7)	0.477
Symptomatic PFJ knee OA n (%)	1 (4.3)	7 (10.3)	
Model 3	**n=23**	**n=68**	
No symptomatic TFJ knee OA n (%)	17 (74)	59 (86.8)	0.194
Symptomatic TFJ knee OA n (%)	6 (26)	9 (13.2)	
No Symptomatic PFJ knee OA n (%)	19 (82.6)	58 (85.3)	0.746
Symptomatic PFJ knee OA n (%)	4 (17.4)	10 (14.7)	

Table 5: *Models 1-3 with the prevalence of symptomatic OA when using the different models.*

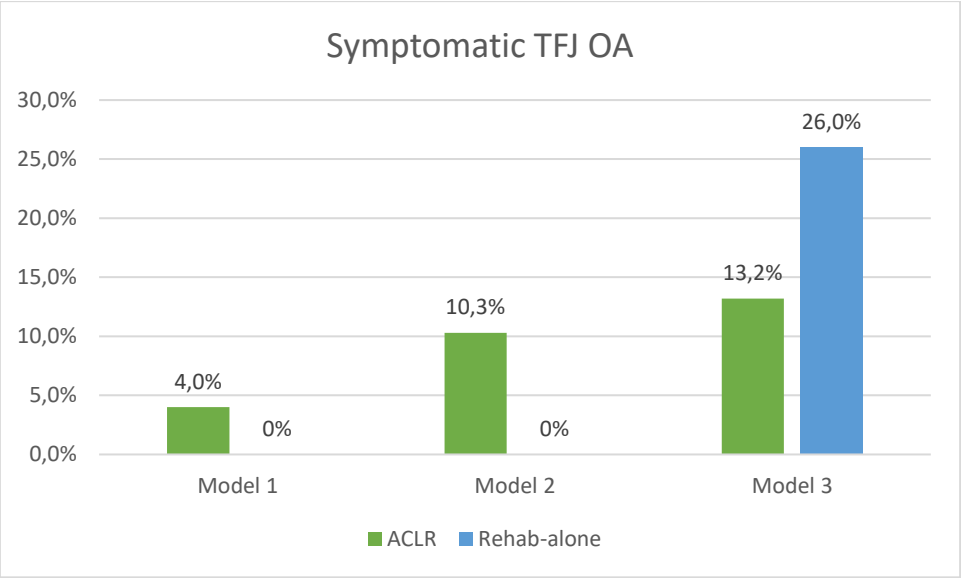

Diagram 3: *An illustration of prevalence of TFJ symptomatic OA according to the three models. According to model 1, three (4%) participants had symptomatic OA in the ACLR group, in the rehabilitation alone group there was 0. According to model 2 In the ACLR group 7 (10.3%) participants had symptomatic OA, in the rehabilitation alone group there was 0 participants. In the ACLR group 9 (13.2%) participants had symptomatic OA when applying model 3. In the rehab-alone group there was 6 (26%) participants who had symptomatic TFJ OA according to model 3.*

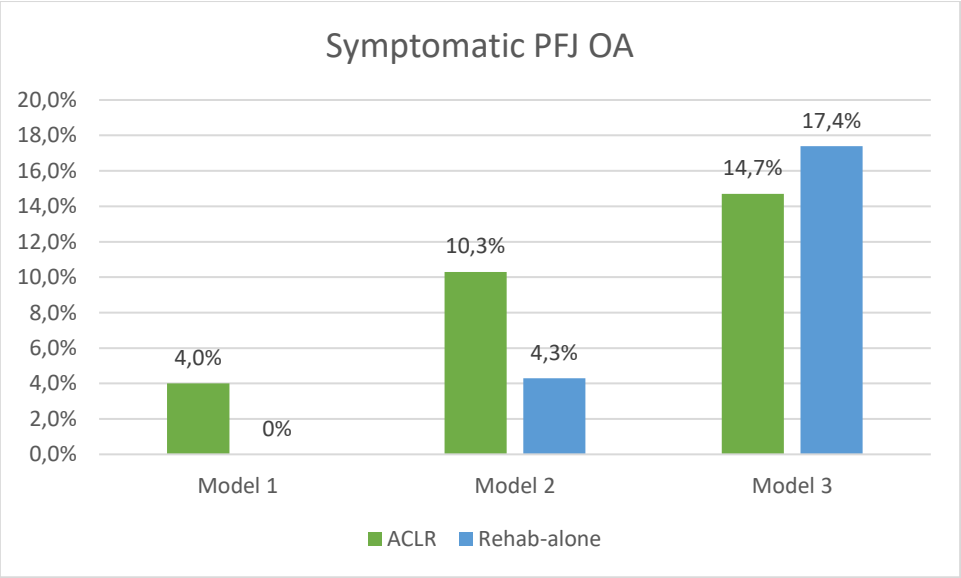

Diagram 4: *An illustration of prevalence of PFJ symptomatic OA according to the three models. According to model 1, three (4%) participants had symptomatic OA in the ACLR group, in the rehab-alone group there was 0. According to model 2 In the ACLR group 7 (10.3%) participants had symptomatic PFJ OA, in the rehabilitation alone group there was one (4.3%) participant. In the ACLR group 10 (14.7%) participants had symptomatic PFJ OA when applying model 3. In the rehabilitation alone group there was four (17.4%) participants who had symptomatic PFJ OA according to model 3.*

When applying model 1 (KOOS pain only) to identify the prevalence of symptomatic OA the results showed three participants (4%) in the ACLR group with symptomatic OA, and 0 participants in the rehabilitation alone group. There was no significant difference between the two groups (P=0.567).

When applying model 2 (using a score below 85-87.5 on any KOOS subscale combined with radiographic ≥2b) to identify the prevalence of symptomatic OA the results showed seven participants (10.3%) in the ACLR group with symptomatic TFJ OA, and 0 participants with symptomatic TFJ OA in the rehabilitation alone group. There was no significant difference between the groups (P=0.185). In the ACLR group seven participants (10.3%) had symptomatic PFJ OA, and one participant (4.3%) in the rehabilitation alone group had symptomatic PFJ OA. There was no significant difference between the two groups (P=0.674).

When applying model 3 (knee pain during the last four weeks combined with radiographic OA ≥2a) to identify the prevalence of symptomatic OA the results showed nine participants (13.2%) in the ACLR group with symptomatic TFJ OA and six participants (26%) with symptomatic TFJ OA in the rehabilitation alone group. There was no significant difference between the two groups (P=0.194). In the ACLR group 10 participants had symptomatic PFJ OA (14.7%), and 4 participants (17.4%) in the rehabilitation alone group had symptomatic PFJ OA. There was no significant difference between the two groups (P=0.746).

7.0 Discussion

In the discussion, the overall findings of this master thesis will be presented and discussed, followed by discussing the methodological considerations. The main objective of this master thesis was to investigate the prevalence of symptomatic and radiographic knee OA between those treated with ACLR and in those treated with rehabilitation alone, 10 years after an ACL injury. The results will be discussed and compared with previous studies with the same objectives.

7.1 Discussion of results

7.1.1 Radiographic OA

The main findings in this master thesis were the low prevalence of radiographic knee OA 10 years after an ACL injury and that there were no significant differences between the ALCR group and the rehabilitation alone group. In the ACLR group, eight participants (11.9%) had TFJ radiographic knee OA in the injured knee. Two participants (2.9%) had TFJ radiographic knee OA in the uninjured knee. In the rehabilitation alone group 0 participants had radiographic TFJ OA in either the injured or uninjured knee. In the ACLR group, seven participants (10.2%) had PFJ radiographic OA in the injured knee. Three participants (4.4%) had PFJ radiographic OA in the uninjured knee. In the rehabilitation alone group, one participant (4.3%) had PFJ radiographic OA in the injured knee. 0 participants had radiographic PFJ OA in the uninjured knee. The were no significant differences in the prevalence of TFJ or PFJ radiographic OA between the ALCR group and the rehabilitation alone group. However, there was a significant difference between the injured and uninjured knee and the prevalence of TFJ and PFJ radiographic OA. The significant difference in radiographic OA between the injured and uninjured knee is in line with previous findings (Ajuied, Wong et al. 2014, Barenius, Ponzer et al. 2014, Chen, Wang et al. 2019).

A previous systematic review by Harris et al. (2017) showed similar results regarding no differences in the prevalence of radiographic knee OA between the ACLR group, and the rehabilitation alone group. Nevertheless, it showed a higher prevalence of radiographic

knee OA, ranging from 24.5% to 51.2% for the TFJ. The prevalence of radiographic OA between the ALCR group and rehabilitation alone group varied from 41.4% (CI=35%-48.1%) and 30.9% (CI=24,4%-38.3%) overall. This systematic review by Harris et al. (2017) consisted of four retrospective studies, with a mean follow-up of at least 10 years, all using Kellgren & Lawrence grading to diagnose radiographic OA, but with two different gradings. Two of the four studies used a cut-off of a Kellgren & Lawrence score grade ≥1 to define the presence of knee OA (Lohmander, Ostenberg et al. 2004, von Porat, Roos et al. 2004). The other two studies used a standard cut-off at grade ≥2 (Kessler, Behrend et al. 2008, Meuffels, Favejee et al. 2009). This could explain the higher prevalence of radiographic OA in this systematic review. There was little information about what kind of treatment the rehabilitation alone groups received. Two of the studies had no explanation of the nonoperative treatment (Lohmander, Ostenberg et al. 2004, von Porat, Roos et al. 2004). In the other two studies, the rehabilitation alone group followed a standardized rehabilitation program (Kessler, Behrend et al. 2008, Meuffels, Favejee et al. 2009). Compared to the Delaware-Oslo ACL cohort, there was a clear explanation of what kind of treatment and follow up both groups received. Both groups in the Delaware-Oslo ACL cohort completed the same five-week rehabilitation program with a comprehensive follow-up during the rehabilitation period. This was followed by a typical 2-3 month of rehabilitation for the rehabilitation alone group, and the ACLR group underwent surgery before their more extended rehabilitation period (Grindem, Eitzen et al. 2014). This rehabilitation program has been shown to give better PROs than usual ACLR care (Grindem, Granan et al. 2015).

A five-year follow-up randomized controlled trial called the KANON study compared ACL injured participants who underwent either ACLR or rehabilitation alone (Frobell, Roos et al. 2013). This study showed no significant differences between the two groups regarding the prevalence of radiographic knee OA. The prevalence after five years post-surgery was 11% and 23% for the TFJ and PFJ. The results for the rehabilitation alone group were 12% and 8%. It is difficult to directly compare the KANON study and the results presented in this master thesis because of the differences in follow-up, mean age, and grading method of the x-rays. The participants in Delaware-Oslo ACL cohort

had their own choice of ACLR or rehabilitation alone with the option of delayed ACLR if needed. The participants in the KANON study were randomly assigned to early ACLR or rehabilitation alone and with option of delayed ACLR (Frobell, Roos et al. 2010). The difference between having the option to choose your own treatment and the randomized allocation have their own pros and cons and makes a direct comparison between the two cohorts challenging.

The KANON study used the osteoarthritis research international atlas when defining radiographic OA, and the cut-off used was approximate to grade 2 on the Kellgren & Lawrence scale. The participants in the KANON study had a mean age of 25.8 to 26.4 years compared to 35.6 to 42.1 in the Delaware-Oslo ACL cohort. The inclusion criteria were also different. The KANON study included meniscus tear either left untreated or treated with partial resection but had no focus on symptoms or function. A participant with a meniscus tear was only excluded if the postoperative treatment interfered with the rehabilitation protocol. This is unlike the Delaware-Oslo ACL cohort, where a participant with a meniscus injury was excluded if there was a major swelling or they were unable to jump on the injured knee. The participants in the Delaware-Oslo ACL cohort were not tested immediately after injury but on average eight weeks after the injury. In the KANON study, 63% in the ACLR group and 51% in the rehabilitation alone group had a meniscus injury in either the medial or lateral compartment at inclusion. The same number in the Delaware-Oslo ACL cohort was respectively 47% and 37% at inclusion. Recent research has shown that associated meniscus and cartilage injures resulted in worse long-term PRO-measures 2-10 years after ACLR (Pedersen, Johnson et al. 2020).

The participants in the KANON study seemingly had more pain and knee symptoms when comparing the KOOS results with the participants in this master thesis at a 10-year follow-up. For example, when comparing KOOS scores on four subscales (pain, symptoms, sport & recreation, and knee-related quality of life) the participants in the KANON study scored 80 for the ACLR group and 82 rehabilitation alone group compared to respectively 91.7 and 93 in this master thesis (Frobell, Roos et al. 2013).

The differences in outcome between these two cohorts have previously been discussed (Grindem, Risberg et al. 2015). A suggested explanation was the differences in the

rehabilitation programs and a more hands-on approach with supervised and motivational support from the clinicians (Grindem, Risberg et al. 2015).

A large systematic review and meta-analysis investigated radiographic knee OA minimal 10 years after ACLR with 19 included studies (Chen, Wang et al. 2019). In addition, the prevalence of TFJ and PFJ radiographic OA was evaluated of the injured and uninjured knee. The results from this systematic review showed an overall (both TFJ and PFJ) knee OA rate that ranged from 8.3-79.2% with a mean of 51.6% on the injured knee and 3.6-35.7% with a mean of 15.5% on the uninjured knee (Chen, Wang et al. 2019). This is a higher rate of radiographic knee OA compared to the results presented in this master thesis, where the prevalence of overall radiographic OA for the injured knee was 8.8% and 2.1% for the uninjured knee.

The follow-up period for the studies included in the systematic review by Chen et al. (2019) ranged from 10 to 23 years with a mean follow-up of 15.4 years. The development of OA increases over time, and with a more elongated follow-up period, like in this case five more years, arguably the prevalence of OA will be higher. This could be one of the explanations for the higher prevalence of radiographic knee OA in this systematic review (Chen, Wang et al. 2019). There is also no mention of what kind of rehabilitation the included participants went through.

Chen et al. (2019) included 18 studies, with two of them using a Kellgren & Lawrence cut-off at grade ≥2. The last two studies used a different cut-off by comparing the injured to the uninjured knee and defining the presence of OA if the injured knee had a higher rate of OA than the uninjured knee. The cut-off for defining radiographic knee OA in this master thesis was ≥2b, but if the cut-off were lowered to ≥2a, the prevalence of radiographic OA would be higher. Using a cut-off at ≥2a the prevalence of radiographic TFJ OA, when combining both the ACLR group and the rehabilitation alone group, is 31.1% in the ipsilateral and 9.8% in the contralateral knee. When combining both rehabilitation alone and ACLR groups, the prevalence of radiographic PFJ is 25.2% in the ipsilateral and 8.8% in the contralateral knee. The overall prevalence of radiographic OA using the ≥2a cut-off is 27.7% and 9.2% for the ipsilateral and contralateral knee, respectively. Nevertheless, using this lower cut-off at ≥2a is rarely seen in other studies and systematic reviews.

7.1.2 Symptomatic OA

Three different models were proposed to identify the prevalence of symptomatic OA based on previous studies; this is, by my knowledge, the first time these three models have been applied in the same study.

Based on Wasserstein et al. (2015) and Ware et al. (2018), the first model using only the KOOS pain subscale score ≥72 points, showed a low prevalence of symptomatic OA. The cut-off number of 72 points derived from two standard deviations below the mean KOOS pain score of one study (Wright, Spindler et al. 2011). It would be of interest to compare the mean KOOS pain score of more than one study to investigate if the scores would differ between different cohorts with longer follow-up.

Prevalence of symptomatic OA using model 1 in this master thesis consisted of 4.3% in the ACLR group and 0% in the rehabilitation alone group, with no significant difference between the two groups. Similar findings were demonstrated in the MOON study by Wasserstein et al. (2015), with a prevalence of 9% symptomatic OA out of 1506 ACLR participants. The MOON study is a prospective longitudinal cohort study with a six-year follow-up with a median age of 23 years for the included participants (Wasserstein, Huston et al. 2015). Ware et al. (2018) also investigated symptomatic OA with the same model of KOOS pain subscale seven years after ACLR. Similar results were found with a 9.7% prevalence of symptomatic OA (Ware, Owens et al. 2018). Both studies by Wasserstein et al. (2015) and Ware et al. (2018) had a shorter follow-up period than this master-thesis but a slightly higher prevalence of symptomatic OA based solely on patient-reported knee pain. Both two studies only included ACLR participants and did not have a rehabilitation alone group (Wasserstein, Huston et al. 2015, Ware, Owens et al. 2018).

The KOOS pain subscale is a direct indication of knee pain but has a weak correlation with structural OA changes (Illingworth, El Bitar et al. 2014). Illingworth et al. (2014) suggest that no single variable can be the primary sinner, but a combination of different variables. Many experts still propose using pain as a clinical sign of knee OA and suggest that the KOOS score is the most appropriate tool (Luyten, Bierma-Zeinstra et al. 2018). However, you could argue that using self-reported knee pain as a sole indicator for

symptomatic OA is not enough and needs to be supplemented by other clinical signs and/or radiographic images. This challenge is also highlighted by the seemingly discordance between the severity of knee OA and pain symptoms (Schiphof, Kerkhof et al. 2013). Schiphof et al. (2013) showed that only 39.6% of the people with Kellgren & Lawrence grade 2 reported the presence of pain. These results should be interpreted with caution regarding the age of the people in this study (mean age 71.5) and how pain was defined by answering yes or no to the question "have you had pain in the knee in the last month or/and in the last five years" (Schiphof, Kerkhof et al. 2013). It seems though that there is a clear indication of more pain with moderate and severe (Kellgren & Lawrence grade 3 and 4) radiographic OA (Oiestad, Holm et al. 2011, Schiphof, Kerkhof et al. 2013). All these different findings illustrate some of the challenges when using pain as a sole indicator for symptomatic knee OA.

The second model that was used in this master-thesis defined symptomatic knee OA as a KOOS score on any of the subscales below 86.1(pain), 85,7(symptoms), 86,8(ADL), 85(sport), and 87,5(QoL), and radiographic OA Kellgren & Lawrence grade ≥2b (Definite osteophytes and possible joint space narrowing) as first described by Barenius et al. (2014). The cut-off scores for the KOOS subscale was first described by Lohmander et al. (2004). These cut-off scores originate from the following statement: If 50% of the questions within the subscale had an answer at least 1 step decrease from the best response on the 5 point Likert scale, and then converted to 0-100 KOOS scores (Lohmander, Ostenberg et al. 2004).

The Barenius et al. (2014) study only had an ACLR group and showed that 59% of the participants had overall (both TFJ and PFJ) symptomatic OA. The result from this study differs from the result I have presented in this master thesis using the same model. The prevalence of symptomatic TFJ and PFJ OA combined in the ACLR group was 10.3% and 2.1% in the rehabilitation alone group. The follow-up was 14 years compared to 10 years in this master-thesis (Barenius, Ponzer et al. 2014). There were some differences regarding the number of meniscus resections between the two cohorts that could explain this difference in prevalence of symptomatic OA. The number of meniscus resection of the medial and lateral meniscus was 31.1% and 32% in the Barenius et al. (2014) study compared to 5% and 15% in the Delaware-Oslo ACL cohort (Grindem,

Eitzen et al. 2014). As previously stated, the risk of getting knee OA is increased following an ACL injury, and combined with a meniscus injury the risk is even higher (Muthuri, McWilliams et al. 2011, Risberg, Oiestad et al. 2016, Poulsen, Goncalves et al. 2019). The lesser number of participants in the Delaware-Oslo ACL cohort with a meniscus injury and surgery is because of the exclusion of participants with symptomatic meniscus injuries that was not resolved within three months of initial ACL injury.

The third model used to investigate symptomatic TFJ OA showed a prevalence of 13.2% in the ACLR group, and 26% in the rehabilitation alone group. The prevalence of symptomatic PFJ OA was 14.7% in the ACLR group, and 17.4% in the rehabilitation alone group. When considering the difference in follow-up time, the results presented in this master thesis are similar to the results presented by Risberg et al. (2016) with 168 participants 20 years after an ACLR. The prevalence of TFJ symptomatic OA was 25%, and 14% PFJ symptomatic OA (Risberg, Oiestad et al. 2016).

The definition of symptomatic knee OA was defined as pain during the last four weeks, and radiographic OA Kellgren & Lawrence grade ≥2b (Risberg, Oiestad et al. 2016). Øiestad et al. (2010) also investigated the prevalence of symptomatic OA 10-15 years after ACLR and found that 41% of the subjects had symptomatic knee OA. This study used the identical definition and method to identify the prevalence of symptomatic OA as Risberg et al. (2016). The results from these two studies differ even though the same method is used, and the challenge of using self-reported pain as an outcome is highlighted. As the author also points out, only 41% of those with radiographic OA reported they had knee pain, so a discordance between what the x-rays tell us and what the patient is feeling is a factor (Risberg, Oiestad et al. 2016).

To sum up, to investigate the prevalence of symptomatic OA, three different models based on PROs and x-rays was used. The results showed a low prevalence of symptomatic OA using all three models. Model 3 with the use of Kellgren & Lawrence grade ≥2a and KOOS subscale scores showed the highest prevalence of symptomatic knee OA.

7.2 Methodological considerations

7.2.1 Design

Prospective observational studies are best suited at following the development of exposure over time to investigate associations along with causality (Thomas 2015). The cohort used in this master thesis is ACL injured participants, which have been followed since 2007. By using a cross-sectional study design, it is possible to examine the prevalence of an outcome. Using a cross-sectional study design also enables the researcher to get an instant snapshot of a given problem, and thereby find the prevalence of a given outcome or disease. The outcome in this master thesis was prevalence of radiographic and symptomatic knee OA. The limitation when using a cross-sectional study design is that the outcome and exposure are measured simultaneously, and to establish causality is impossible because of the lack of temporal sequence timing (Thomas 2015). If the baseline radiographic images and KOOS scores had been compared with those collected 10 years later, it might have been possible to draw certain conclusions.

Since this is a follow-up study there is a possibility of familiarity to the different tests. For example, the participants had performed the hop test three times before the 10-year follow-up. This could have affected how the participants performed the tests (Thomas 2015). However, it was five years since the last follow-up, and there is the possibility of forgetfulness. Another detriment when doing a follow-up of a cohort study is the difficulty of keeping track of a large number of people over a lengthy period. This can result in a high drop-out rate, and poses a threat in the form of biased estimates of the exposure-disease relationship (Thomas 2015).

7.2.2 Participants

Loss to follow-up can cause a great threat to the internal validity (Thomas 2015). If the participants who withdrew from the study could have affected the study´s overall results, bias can occur. To avoid this, having a low dropout rate is preferable. Of the 123 participants eligible for a 10-year follow-up, 104 participants agreed to participate. This makes the overall follow-up after 10 years 84.5%. It has been suggested that a dropout <5% poses little to no bias, and >20% poses a serious threat to validity (Dettori 2011). Even though the number lost to follow-up does not exceed 20%, those who dropped out could have affected the outcome measures. With this said, an 84.5% follow-up after 10 years is still a respectable result. There were no significant differences between the two groups regarding BMI, KOOS scores, quadriceps strength, hop test or physical activity level. The only significant difference between the two groups was age, with the rehabilitation alone group being an average of 6.5 years older. In the ACLR group 13 participants had delayed ACLR (more than 6 months after injury), and there were no apparent differences between those who had delayed ACLR or early ACLR. These results are in line with a recent study (Pedersen, Grindem et al. 2021).

The population in this master thesis had similar age and BMI as other studies within this specific population (von Porat, Roos et al. 2004, Kessler, Behrend et al. 2008, Meuffels, Favejee et al. 2009, Frobell, Roos et al. 2013). These studies used the Tegner activity score to categorize the level of participating in sports activities. The Tegner activity score is a questionnaire with a single question on what kind of sports or work the subject is participating in and was initially intended as a supplement to the Lysholm scale and not a stand-alone measure (Collins, Misra et al. 2011). The physical activity assessment in this master thesis was obtained via the HUNT questionnaire (Moholdt, Wisløff et al. 2014). It is challenging to compare physical activity based on Tegner activity score with HUNT questionnaire as Tegner activity score is just a classification of sport or physical activities. In the KAN2 study, only 27-31% of participants in the age group 20-49 fulfilled the Norwegian recommendations of weekly physical activity (Bjørge H Hansen, Steene-Johannessen et al. 2015). When comparing these numbers with the participant´s results in this master thesis, there is an indication that our cohort

is significantly more physically active. In the ACLR and rehabilitation alone groups, 73.7% and 59% of the participants fulfilled the weekly recommendations of physical activity. When looking at physical activity level, the participants in this cohort are highly physical active compared to the standard Norwegian population. The gender distribution was even as 52% was female.

Quadriceps strength and hop LSI was identical between the two groups as approximately 70% and 80% had LSI ≥90% in the biodex testing and hop tests. Quadriceps weakness has been described as a risk factor in developing knee OA, but other studies have shown no relationship between quadriceps weakness and knee OA (Øiestad, Holm et al. 2010). Øiestad et al. (2010) showed that participants who lost quadriceps strength between 2 and 10-15 years after ACLR had greater odds of symptomatic radiographic knee OA. A limitation of the cross-sectional study design used in this master thesis is the lack of baseline quadriceps strength to compare these results to 10 years later. This would be of interest regarding the possible correlation between loss of quadriceps strength over time and the development of knee OA.

At inclusion in the Delaware-Oslo ACL cohort, a number of participants also had meniscus injuries in addition to ACL injury. However, one of the exclusion criteria were that participants with symptomatic meniscus injuries that were not resolved within three months from the injury were to be excluded (Grindem, Granan et al. 2015). So, by having these exclusion criteria, the likelihood of weeding out the participants with more pain and less function is more prominent. This could lead to a cohort that has better preconditions than some of the other studies with the same ACL deficient population (Kessler, Behrend et al. 2008, Meuffels, Favejee et al. 2009, Frobell, Roos et al. 2013). This could in turn reduce the external validity of this study.

To sum up, the participants in this master thesis were representative of the ACL injured population according to age and BMI. Due to the exclusion criteria of meniscus injuries, and the mean time of testing was 8 weeks after injury. The participants in the Delaware-Oslo ACL cohort might have had less additional injuries at the inclusion compared to other studies with ACL injured participants.

7.2.3 X-Ray

All x-rays were taken at the same place using the same machinery and the same experienced radiograph evaluated all x-rays. Using x-rays to diagnose knee OA has long been the gold standard and most often used method (Cai, Cicuttini et al. 2020). A recent study suggests that an x-ray might not be the best method to diagnose knee OA (Cai, Cicuttini et al. 2020). MRI has some clear advantages over radiographic imaging. With MRI, it is possible to visualize the whole joint with joint tissues like cartilage, bone marrow lesions, meniscal lesions, and synovitis (Guermazi, Roemer et al. 2011). One of the main OA findings on an x-ray is the signs of joint narrow spacing. But when the first signs of joint narrow spacing are visible on x-rays, 10% of the cartilage is already gone (Jones, Ding et al. 2004). Even though MRI is more sensitive to mapping structural changes than x-rays, the difference when comparing the prevalence of radiographic knee OA between MRI and x-ray is minimal (Cai, Cicuttini et al. 2020). MRI is also a more expensive and time-consuming outcome measure than an ordinary x-ray.

Luyten et al. (2012) suggested diagnosing early knee OA using the similar criteria as used in model 3 to detect symptomatic knee OA. They are knee pain (two episodes > 10 days in the last year), Kellgren & Lawrence grade 0, 1 and 2a and at least one of two structural criteria findings of arthroscopic or MRI. Later in 2018 these criteria were altered. MRI and arthroscopic examination were removed, and clinical examinations were added (Luyten, Bierma-Zeinstra et al. 2018). These new criteria were joint line tenderness or crepitus along with 2 out of the 4 KOOS subscales scores ≤85% (Pain, symptoms, function and QoL). Another way to diagnose the earlier signs of knee OA is using the Kellgren & Lawrence grade 2a definition as presented by Felson et al. (2011).

Different definitions for grading radiographic OA have been used throughout the literature, and there is still no consensus on the correct one. Schiphof et al. (2008) searched through the studies from 1966 to 2006 that had used the original Kellgren & Lawrence scale and found five different descriptions. This is a challenge when comparing results between studies as the grading is done differently. There is also a challenge of how the knee is fixed, straight or semi-flexed, when the x-rays are taken. Since the Kellgren & Lawrence scale is not tuned on the knee position this can also give

different Kellgren & Lawrence grading (Schiphof, Boers et al. 2008). The 2a cut-off has shown to have good reproducibility, high sensitivity, and specificity and has been recommended to be used when determining definite/mild OA from none or possible OA (Schiphof, de Klerk et al. 2011). One thing that seems consistent throughout the newer research on defining earlier knee OA is the clinical aspect combined with self-reported knee pain and the presence of lower grades of Kellgren & Lawrence radiographic OA.

7.2.4 KOOS

The KOOS questionnaire originates from the WOMAC questionnaire, which was created to assess pain, stiffness, and function in patients with OA in the hip or knee (Roos and Lohmander 2003).

The KOOS questionnaire is a further extension of WOMAC, focusing on measuring the outcome after a knee injury. This specific focus is one of the advantages of using the KOOS questionnaire when inquiring about the perceived perception of pain in this cohort. In addition, the KOOS questionnaire has been tested abundantly and found to be a reliable and valid measure for patients with knee OA of different ages as well (Collins, Prinsen et al. 2016).

When dealing with PROs, it is crucial that participants provide the correct information, and recall bias threatens internal validity (Thomas 2015). The KOOS focus on the last seven days, so this short time lowers the risk of recall bias. A possible effort to further lower the risk of recall bias is completing the KOOS more than once during a seven-day period.

People with OA often experience fluctuating pain varying from day to day or week to week (Allen, Coffman et al. 2009). So, by only focusing on the last seven days, there is a chance this could affect the overall score with an understating or overstating based on the resent form (Zhang, Nevitt et al. 2011, Thomas 2015).

Throughout the literature there is no definite definition for symptomatic OA when using PROs (Wasserstein, Huston et al. 2015). However, the KOOS questionnaire was used to investigate the prevalence of symptomatic OA in this master thesis. The different

definitions and criteria's for diagnosing symptomatic OA makes it challenging to compare results in the literature. The KOOS is still used extensively in the literature and has proven to be reliable and valid when investigating pain and symptoms for people with a knee injury (Roos and Lohmander 2003, Collins, Misra et al. 2011, Collins, Prinsen et al. 2016).

7.2.5 Quadriceps muscle strength

The test of quadriceps muscle strength was performed using the Biodex 6000 dynamometer by different testers given specific training (Biodex Medical Systems, Shirley, New York, USA). The Biodex has good reliability and good intra-tester reliability (Logerstedt, Snyder-Mackler et al. 2010, Zawadzki, Bober et al. 2010). However, you can argue that having different test personnel could cause measurement errors as previous studies have shown a low inter-rater reliability (Wongcharoenwatana J 2019). The biodex have however shown to have high interrater reliability, but with a different population (Eitzen, Hakestad et al. 2012). A way to try and avoid measurement errors, is using a standardized protocol with the same order of sequence that each tester must follow. The advantage of isokinetic testing is that it gives an objective measure of muscle strength and function, reinforcing the study´s internal validity and quality.

7.2.6 Hop tests

The Hop tests have previously shown high interrater reliability, with ICCs between 0.82 to 0.97, for the LSI index and measure of performance-based outcomes after an ACL injury (Ross, Langford et al. 2002, Reid, Birmingham et al. 2007). The hop tests were performed under the supervision of trained physiotherapists. There is a risk of systemic measurement errors when more than one person conducts the test. To minimize the chance of this, all testers had to follow a strict protocol. There is a possibility of familiarity with the tests since the participants have done them before, and therefore, a chance of better performance (Thomas 2015). The participants also performed the hop tests last after the muscle strength test, and a chance of fatigue could occur.

8.0 Clinical implications

The main findings in this master thesis were that there is no significant difference between ACL injured people treated with ACLR plus rehabilitation or rehabilitation alone, regarding the prevalence of radiographic and symptomatic OA. There was no indication that one treatment was far superior to the other. The prevalence of radiographic and symptomatic OA was lower than other studies on the same population with the same long-term follow-up. The treatment algorithm in the Delaware-Oslo ACL cohort included a progressive rehabilitation program. The participants could choose method of treatment, including an option of delayed ACLR. A good rehabilitation program pre- and post-operation, together with a hands-on approach from the physiotherapist is key. The inclusion and exclusion criteria in the cohort could also be a reason for the low prevalence of radiographic and symptomatic OA, for example regarding the exclusion of participants with severe meniscus injuries.

The results from this master thesis indicate that the prevalence of PTOA 10-years post ACL injury is not necessarily as high as previous studies have shown. Going forward, this information is important to present to people with a new ACL injury considering treatment options. You can still have a functional and pain free knee without an ACLR. The more data we have on prognostics factors long term after an ACL injury, the more informed advice we can give a person with a resent ACL injury.

The three guidelines that are used most often to clinically diagnose symptomatic OA is the ACR, EULAR and NICE. A Danish study by Skou et al. (2020) compared these sets of clinical classification with the purpose to see how well they correlate. This study concluded that the EULAR and ACR criteria only identified around half of the participants with self-reported radiographic knee OA, meanwhile the NICE criteria identified 90%. The NICE criteria, that are based on age ≥45years, knee related pain and no morning joint-related stiffness lasting longer than 30 minutes, should be implemented when clinically diagnosing knee OA. The age criteria should be taken with a grain of salt when a patient exhibits knee symptoms resembling these signs and has a former knee injury, as it has been pointed out that patients with PTOA often are of younger age (PM Holm 2018). Even though the prevalence of radiographic and

symptomatic OA findings in this master thesis were low, it was not 0 and the mean age in both groups was 35 and 42 years of age.

Further research on these two groups, ALCR or rehabilitation alone, is warranted and is highlighted by the Cochrane review by Monk et al. (2016). In this systematic review of RCTs comparing surgery with conservative treatment, they could only find one study to include, and that being the study by Frobell et al. (2010). For future research, a clear definition and consensus for radiographic knee OA should be defined and implemented. It would be interesting to see more research on the validity and reliability of using Kellgren and Lawrence grade 2a when diagnosing radiographic knee OA. Further research on the prevalence of symptomatic OA should be conducted with at least one clinical sign in addition to PRO-measures. This will give the clinician better tools to diagnose knee OA in the earlier stages and administer the proper treatment sooner. Then the treatment will be active and not reactive (Luyten, Bierma-Zeinstra et al. 2018).

9.0 Conclusion

The results from this cross-sectional study, on the prevalence of radiographic and symptomatic OA 10 years after an ACL injury, show no significant difference between those who underwent ACLR or rehabilitation alone. There was a low prevalence of radiographic OA in both groups. The prevalence in the ACLR group was 11.9% TFJ OA and 10.2% PFJ OA in the injured knee. The prevalence in the rehabilitation alone group was 0% TFJ OA and 4.3% PFJ OA in the injured knee. There was no significant difference between the two groups regarding the prevalence of radiographic TFJ and PFJ OA. Using three different models to investigate symptomatic OA, all showed a low prevalence of symptomatic OA. Model 3 detected the highest prevalence of symptomatic OA. Model 1 showed a prevalence of 4% symptomatic OA in the ACLR group, and 0% in the rehabilitation alone group. Model 2 showed a prevalence of 10.3% symptomatic TFJ OA and 10.3% PFJ symptomatic OA in the ACLR group. Model 2 showed a prevalence of 0% symptomatic TFJ OA and 4.3% PFJ symptomatic OA in the rehabilitation alone group.

Model 3 showed a prevalence of 13.2% symptomatic TFJ OA and 14.7% PFJ symptomatic OA in the ACLR group. Model 3 showed a prevalence of 26% symptomatic TFJ OA and 17.4% PFJ symptomatic OA in the rehabilitation alone group.

A clear definition of early radiographic and symptomatic OA should be of interest in further research.

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Acronyms

ACL	Anterior Cruciate Ligament
ACLR	Anterior Cruciate Ligament Reconstruction
OA	Osteoarthritis
PTOA	Post-traumatic osteoarthritis
TFJ	Tibial-femoral joint
PFJ	Patella-femoral joint
LSI	Limb symmetry index
ICC	Intraclass correlation coefficients
CI	Confidence Interval
KOOS	Knee injury and Osteoarthritis Outcome Score

Appendix

Appendix 1: Written consent

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET

DYNAMISK STABILITET I ET KORSBÅNDSKADET KNE

Dette er en henvendelse til deg som tidligere har deltatt i prosjektet "Dynamisk stabilitet i et korsbåndskadet kne" (The Delaware-Oslo ACL Cohort Study). Dette er en langtidsoppfølgingsstudie og et samarbeidsprosjekt mellom Ortopedisk divisjon, Oslo universitetssykehus, Norges idrettshøgskole, Nimi og Universitetet i Delaware, USA. Data har blitt samlet inn fra 150 korsbåndspasienter i Norge og 150 korsbåndpasienter i USA. Det er omtrent 5 år siden du sist ble innkalt til testing. Vi inviterer deg nå til å delta i en ny testrunde i prosjektet, det vil si ca 10-12 år etter skade/kirurgi.

Målet er å kartlegge langtidsfølger og belastningsskader ved fremre korsbåndskader og faktorer som er viktige for å få et godt resultat av behandling. Denne kunnskapen vil kunne bidra til å utvikle bedre behandling for personer med fremre korsbåndskade og ikke minst gi deg ytterligere informasjon om testresultat også knyttet til utvikling av belastningsskader i kneet. På testdagen vil du få informasjon om resultater av prosjektet opp til 2 års kontrollen og dersom det er ønskelig få tilsendt de aktuelle publikasjonene som har utgått fra prosjektet.

HVA INNEBÆRER PROSJEKTET?

Du vil gjennomføre de samme testene som du tidligere har gjennomført: Måling av instabiliteten i kneet, muskelstyrketest, fire ulike hinketester, utfylling av spørreskjemaer om symptomer, funksjon og tilfredshet, i tillegg til vanlige røntgenbilder. Dersom godkjenning blir gitt fra personvernombud vil vi ved denne oppfølgingen sende ut flere av spørreskjemaene elektronisk. Dersom du skulle ønske å fremdeles fylle ut alt på papir vil det selvsagt la seg gjøre.

Tidligere har vi ikke undersøkt fysisk aktivitet, det ønsker vi nå å måle ved hjelp av både akselerometer og spørreskjemaer. Akselerometeret måler objektivt kroppens bevegelse og akselerasjon, noe mange i dag også benytter via sine smarttelefoner (ulike type Apper). Det akselerometeret vi benytter til forskningen er en liten måler på størrelse med en liten fyrstikkeske som festes i et belte på hoften på dagtid. Akselerometeret skal brukes i 7 dager for å måle ditt aktivitetsnivå. I tillegg vil vi måle vekt, høyde, midjeomkrets og hofteomkrets.

Totalt vil undersøkelsene ta ca 1-1,5 timer, og i tillegg kommer røntgenundersøkelsen som du får en separat time til. Røntgenundersøkelsen av begge knær tar høyst 15 minutter.

Eventuelle tilleggsskader eller behandling du har fått i oppfølgingsperioden er sentralt for å vurdere langtidskonsekvensene av korsbåndskaden din. Derfor vil vi innhente opplysninger om deg fra medisinske journaler der du oppgir hvilket sykehus eller medisinske senter du har vært til behandling hos. Dette begrenser seg kun til opplysninger om kneskaden og behandling av kneskaden din. Dersom du har gjennomført korsbåndoperasjon eller proteseoperasjon vil vi innhente disse opplysningen fra Nasjonalt register for leddproteser (som også inkluderer Korsbåndregisteret).

MULIGE FORDELER OG ULEMPER

Testing av kneets funksjon kan være nyttig og interessant for de aller fleste med tanke på innsikt i sin egen funksjon og å se endringer over tid. Vi vil kunne gi deg tilbakemeldinger basert på tidligere testresultater.

Du har vært igjennom alle disse testene og undersøkelsene tidligere, bortsett fra bruken av akselerometeret for måling av fysisk aktivitet. Det kan være at du opplever noe ubehag i kneet ved gjennomføring av hinketestene, men det er svært liten risiko for at dette skal føre til forverring av din skade. Dette er tester som vi har lang erfaring med og som blir benyttet også internasjonalt til testing av pasienter med fremre korsbåndskade. Ved røntgen av kneet utsettes du for en liten dose røntgenstråler. Imidlertid er dosen stråling sammenlignbar med den naturlige bakgrunnsstrålingen mennesker utsettes for over noen få dager. Risikoen ved å ta røntgen av kneet er derfor minimal. Gravide kvinner skal ikke gjennomføre røntgenundersøkelsen. Akselerometeret er ikke til hinder for din normale fysiske aktivitet.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål angående prosjektet, kan du kontakte fysioterapeut og doktorgradsstipendiat Marie Pedersen (marie.pedersen@nih.no), eller professor og prosjektleder May Arna Risberg (m.a.risberg@nih.no).

HVA SKJER MED INFORMASJONEN OM DEG?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert. Dataene som innhentes vil lagres i manuelle arkiv med personidentifikasjon som låses inn. Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger ved statistiske analyser. En kode knytter deg til dine opplysninger gjennom en navneliste som oppbevares innelåst. Ved sammenslåing av data fra Norge og USA for analyser er alle data anonymisert og da ikke personidentifiserbar.

Prosjektleder har hovedansvaret for forskningsprosjektet og at opplysninger om deg blir behandlet på en sikker måte. Informasjon om deg vil bli anonymisert eller slettet senest fem år etter prosjektslutt i tråd med gjeldene forskrifter og lover for oppbevaring av data.

FORSIKRING

Du vil være dekket av pasientskadeloven under testing i prosjektet.

UTLEVERING AV OPPLYSNINGER TIL SAMARBEIDSPARTNERE

Dette prosjektet har fra starten av vært et samarbeidsprosjekt med Universitet i Delaware, USA, med inklusjon av pasienter fra begge land. For å kunne analysere data vil data derfor slås sammen. Ved sammenslåing av data vil data være anonymisert. Ved å delta i prosjektet, samtykker du til at anonyme opplysninger om deg kan utleveres til vår samarbeidspartner ved Universitetet i Delaware, USA. Disse opplysningene vil ikke inkludere navn, fødselsdato, kode eller annet som kan kobles til din identitet.

OPPFØLGINGSPROSJEKT

Vi ber om å få kontakte deg på nytt dersom bruk av data til andre formål eller flere langtidsoppfølginger blir aktuelt. Vi ber også om at få koble data fra denne 10 års oppfølgingen mot Leddproteseregisteret 20 år etter inklusjon for å evaluere prognostiske faktorer for en eventuell kneprotese etter 20 år.

ØKONOMI

Du vil få dekket eventuelle reiseutgifter til testingen etter gjeldene statlige satser og lovverk.

GODKJENNING

Prosjektet er godkjent av Regional Komite for Medisinsk og Helsefaglig Forskningsetikk Sør-Øst og av personvernombud ved Oslo Universitetssykehus (saksnummer hos REK: 2018/433).

SAMTYKKE TIL DELTAKELSE I PROSJEKTET

JEG ER VILLIG TIL Å DELTA I PROSJEKTET

Sted og dato Deltakers signatur

Deltakers navn med trykte bokstaver

Jeg bekrefter å ha gitt informasjon om prosjektet

Sted og dato Signatur

Rolle i prosjektet

Appendix 2: HUNT questionnaire

MOSJON/FYSISK AKTIVITET Med mosjon mener vi at du f.eks går tur, går på ski, svømmer eller driver trening/idrett.		
Hvor ofte driver du mosjon? (Ta et gjennomsnitt)	□ Aldri □ Sjeldnere enn en gang i uka □ En gang i uka □ 2-3 ganger i uka □ Omtrent hver dag	
Dersom du driver slik mosjon, så ofte som en eller flere ganger i uka; hvor hardt mosjonerer du? (Ta et gjennomsnitt)	□ Tar det rolig uten å bli andpusten eller svett □ Tar det så hardt at jeg blir andpusten og svett □ Tar meg nesten helt ut	
Hvor lenge holder du på hver gang? (Ta et gjennomsnitt)	□ Mindre enn 15 minutter □ 15-29 minutter	□ 30 minutter – 1 time □ Mer enn 1 time

Appendix 3: REK approval

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Claus Henning Thorsen	22845515	17.04.2018	2018/433/REK sør-øst c

Deres dato: 13.02.2018

Deres referanse:

Vår referanse må oppgis ved alle henvendelser

May Arna Risberg

Norges Idrettshøgskole Arbeidsadresse:

Seksjon for Idrettsmedisinske fag

0806 Oslo

2018/433 Dynamisk stabilitet i et korsbåndsskadet kne

Forskningsansvarlig: Oslo universitetssykehus HF **Prosjektleder:** May Arna Risberg

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst) i møtet 22.03.2018. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10.

Prosjektomtale

Vi har siden 2007 fulgt prospektivt både opererte og ikke-opererte pasienter med fremre korsbåndskade i samarbeid med Delaware, USA. Testbatteriet består av både klinisk testing, røntgenundersøkelse og pasient rapporterte spørreskjema. Pasientene er fulgt fra etter skade, 6 uker, 6 mndr,1, 2 og 5 år. Nå søkes det om en 10-12 års oppfølging der formålet er å: -Undersøke langtidsresultater og prognostiske faktorer for fremre korsbåndskade ift kneartrose, reskader, knefunksjon, muskelstyrke, og fysisk aktivitetsnivå hos både opererte og ikke-opererte pasienter. - -Sammenlikne 10-års utfall i vår kohort med pasienter i fra det Nasjonale Korsbåndregisteret. - Koble våre data opp mot Nasjonalt Leddprotese register for å evelauere prognostiske faktorer for kneprotese -Identifisere cut-offs på selvrapporterte utfallsmål som representrer pasientenes opplevelse av vellykket/mislykket resultat av behandling.

Vurdering

I dette samtykkebaserte prosjektet vil man undersøke hvordan det går med pasienter med korsbåndskade 10 år etter skade, og relatere dette til hvilken behandling de har fått. Målet er å kartlegge langtidsfølger og belastningsskader ved fremre korsbåndskader og faktorer som er viktige for å få et godt resultat av behandling. Man vil sammenlikne med tilsvarende utvalg pasienter fra Leddproteseregisteret (som inneholder Korsbåndregisteret).

Studien er et 10-årig samarbeidsprosjekt med Universitetet i Delaweare med forskningsmidler fra National Institutes of Health. Ved samtykke som ble underskrevet ved 5 års oppfølgingen, har deltakerne samtykket til å bli kontaktet på ny. Den norske delen omfatter 150 pasienter med fremre korsbåndskade.

Deltakerne skal gjennomgå de samme testene som de tidligere har gjennomført. I tillegg vil man måle fysisk aktivitet ved hjelp av akselerometer, samt ved besvarelse av spørreskjema. Måling av høyde, vekt, midjeomkrets og hofteomkrets vil også bli gjort.

Besøksadresse: Gullhaugveien 1-3, 0484 Oslo
Telefon: 22845511
E-post: post@helseforskning.etikkom.no
Web: http://helseforskning.etikkom.no/

Komiteen mener dette er et nyttig og godt beskrevet prosjekt.

Komiteen har ingen merknader til at man i samarbeidet med Universitetet i Delaweare baserer seg på en såkalt «signed sub award agreement».

Pasientinformasjonen er god, men det bør i samtykkedelen fremgå hvem som har informert om studien. Komiteen forutsetter at dette innarbeides, det er ikke nødvendig å sende inn skjemaet på nytt.

Vedtak

Prosjektet godkjennes, jf. helseforskningslovens §§ 9 og 33.

Tillatelsen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden og protokollen, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Tillatelsen gjelder til 15.12.2040. Av dokumentasjons-og oppfølgingshensyn skal opplysningene likevel bevares inntil 15.12.2045. Opplysningene skal lagres avidentifisert, dvs. atskilt i en nøkkel-og en opplysningsfil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato.

Komiteens avgjørelse var enstemmig.

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jfr.

helseforskningsloven § 10, tredje ledd og forvaltningsloven § 28. En eventuell klage sendes til REK sør-øst C. Klagefristen er tre uker fra mottak av dette brevet, jfr. forvaltningsloven § 29.

Sluttmelding og søknad om prosjektendring

Prosjektleder skal sende sluttmelding til REK sør-øst på eget skjema senest 15.06.2041, jf. hfl. §

12. Prosjektleder skal sende søknad om prosjektendring til REK sør-øst dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Med vennlig hilsen

Britt Ingjerd Nesheim professor dr. med. leder REK sør-øst C

Claus Henning Thorsen

Rådgiver

Kopi til:lars.nordsletten@medisin.uio.no

Beskrivelse av database og prosedyrer for datalagring for Delaware-Oslo ACL Cohort (n=300)

Inklusjon av pasienter i Delaware-Oslo ACL Cohorten ble startet 2007 etter at studien ble godkjent av REK og personvern i desember 2006. Studien har hatt midler fra National Institutes of Health (NIH) fra oppstarten og første hovedmål var å evaluere outcome etter 2 år. Deretter ble det søkt om å fortsette Cohorten med en 5 års oppfølging, noe som ble godkjent av REK og personvern i 2011. I februar 2018 ble det søkt REK for 10 års oppfølging og personvern vil bli søkt for 10 års oppfølgingen før inklusjonstart.

Forskningsansvarlig institusjon i USA er Universitetet i Delawrae og forskningsleder for hele studien er professor Lynn Snyder-Mackler (Primary Investigator, PI). Forskningsansvarlig institusjon i Norge er Oslo Universitetssykehus, og forskningsleder i Norge er professor May Arna Risberg (co-PI for hele studien).

Norge:

Data for pasienter rekruttert i Norge (n=150) lagres på forskningsserver på Oslo Universitetssykehus. Det er etablert databehandleravtale med Nimi da alle norske pasienter testes der (se egen databehandleravtale for lagring av data på Nimi på sikker server). Data lagres på papir innlåst i skap etter gjeldende retningslinjer og i tråd med informasjon gitt til personvern. Alle opplysninger om pasientene som lagres elektronisk vil lagres avidentifisert. Krysslister ligger innelåst i safe. Elektronisk ligger da data kun med ID-koder, alt i henhold til beskrivelse av prosedyrer sendt personvern.

University of Delaware database og prosedyrer for alle data (n=300)

Data som er samlet inn i Norge (n=150) overføres anonymisert i felles database for den norske og amerikanske armen av prosjektet (totalt n=300). For å ivareta anonymisering er det utarbeidet en databasefil som ikke inkluderer navn, adresse, postnummer, telefonnummer, epostadresse, etnisitet, fødselsdato, personnummer eller ID-nummer som kan kobles mot kryssliste i safe. Når data som er samlet inn i Norge lastes opp i felles database, overføres denne anonymiserte databasefilen alltid med alle variabler og caser. Ved oppdatering av felles database vil tidligere data fra Norge slettes, og data fra anonymisert database erstatter disse

dataene, dvs alle data lastes opp på nytt. Variabelnavn og rekkefølge på variabler i anonymisert databasefil skal ikke endres med mindre dette skjer samtidig med endring av strukturen i felles database.

Delaware database for all data (n=300)

Database: Microsoft SQL Server 2014 is the Database storage software

Server: The server is hosted on central IT's VM cluster, within a secured data center with a physical address of 192 South Chapel Street, Newark DE 19716.

The Hardware and data center are managed by the universities Infrastructure Group.

Access types:

All access is cleared by Primary Investigator (PI) of the study, professor Lynn Snyder-Mackler and then access is granted via data manager. Direct database access is limited to the Database administrator.

Portal access is available to Research Team Members - their access is via user login and password

The database is stored on secure segments of the universities server banks. They are managed offsite by the university cyber security team. All access to the Delaware-Oslo ACL Cohort data is cleared by PI, professor Lynn Snyder-Mackler, University of Delaware. Data are not encrypted, but passwords are.

Appendix 4: Privacy representative from Oslo University Hospital

From: May Arna Godaker Risberg
To: Marie Pedersen; Hege Grindem (hege.grindem@nimi.no)
Cc: "Kristin Bølstad (Kristin.bolstad@nimi.no)"
Subject: VS: Skjema personvern for prosjekt 2018/433 Dynamisk stabilitet i et korsbåndsskadet kne
Date: 31 May 2018 14:12:32
Attachments: image001.png

Hei
Her er svaret fra PVO.
Så da er vi klare for planlegging av 10 års oppfølgingen (men må altså huske at vi nevner i samtykket/informasjonen dette med USA og data, se under)
MA

Fra: May Arna Risberg [mailto:MARISB@ous-hf.no]
Sendt: 29. mai 2018 15:54

Til: May Arna Godaker Risberg <m.a.risberg@nih.no>
Emne: VS: Skjema personvern for prosjekt 2018/433 Dynamisk stabilitet i et korsbåndsskadet kne

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Fra: OUSHF PB Personvern
Sendt: 29. mai 2018 14:49
Til: May Arna Risberg
Emne: SV: Skjema personvern for prosjekt 2018/433 Dynamisk stabilitet i et korsbåndsskadet kne Hei!
Takk for god tilbakemelding.
Dere er selv ansvarlige for å vurdere hvorvidt opplysningene som utleveres til Delaware er tilstrekkelig anonymiserte eller ikke. For mer informasjon om anonymisering av helse- og personopplysninger, se eHåndboka her: http://ehandboken.ous-hf.no/document/112192?preview=true
Dersom opplysningene som utleveres er anonymiserte, må dere også oppdatere samtykket, slik at det nå står at det ikke vil være mulig å trekke sine opplysninger fra materialet som brukes. (Dersom de utleverte dataene er anonymiserte, skal de jo heller ikke kunne gjenfinnes). Det er i orden at dere bruker samme område på K:\Sensitivt, så fremt det er de samme prosjektmedarbeiderne som skal delta i 10 -årsoppfølgingen, og det ikke skal inkluderes nye pasienter.
mvh
Annika Mortensen
Personvernrådgiver
Avdeling for informasjonssikkerhet og personvern | Stab pasientsikkerhet og kvalitet
Oslo universitetssykehus HF
Telefonnummer: 22 11 80 80 Besøk:
Kirkeveien 166 (Ullevål sykehus)
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Fra: May Arna Godaker Risberg [mailto:m.a.risberg@nih.no]
Sendt: 21. mai 2018 10:19
Til: OUSHF PB Personvern
Kopi: May Arna Risberg; lars.nordsletten@medisin.uio.no
Emne: SV: Skjema personvern for prosjekt 2018/433 Dynamisk stabilitet i et korsbåndsskadet kne Hei
Beklager litt sen respons på dette.
Kort bakgrunn:
Denne studien, Delaware-Oslo ACL Cohort (Dynamisk stabilitet i et korsbåndskadet kne), startet i 2006 (etter vedtak REK, samtykke, og personvern). Det er riktig som dere sier at i det første samtykke fra 2006 står det:
" Prosjektet planlegges avsluttet i 2017, og alle sensitive persondata vil bli slettet innen 2 år etter at studien er ferdig. Dersom nye studier basert på innsamlede opplysninger blir aktuelle, ber vi om tillatelse til å henvende oss til deg for nytt samtykke for slik bruk."

Denne studien har vært et samarbeid mellom Universitet i Delaware og Oslo

Universitetssykehus med forskningsmidler fra National Institutes of Health (NIH) i USA siden 2006 (Oslo som Subaward, se Subaward agreement for siste 5 års periode (20172022) vedlegg). Dette har vært tydelige i alle søknadene våre. REK svarte spesifikt at denne avtalen var tilstrekkelig ift dette med samarbeidsavtaler (Subaward agreement).

Vi henvendte oss i tråd med dette til pasientgruppen igjen for 5 års oppfølging etter at endringsmelding og vedtak fra REK forelå (se vedlegg) i 2011. Vi vurderte det i 2011 at vi ikke da trengte å henvende oss til PVO på nytt da det var en endringsmelding til REK. Det er mulig vi skulle også ha sendt søknad til dere (PVO) for 5 års oppfølgingen basert på endringsmeldingen til REK, men det ble altså ikke gjort. I samtykket for 5 års oppfølgingen heter det: "Prosjektet planlegges avsluttet i 2020, og alle sensitive persondata vil bli slettet innen 2 år etter at studien er ferdig. Dersom nye studier basert på innsamlede opplysninger blir aktuelle, ber vi om tillatelse til å henvende oss til deg for nytt samtykke for slik bruk."

Når jeg nå henvendte meg til REK for 10 års oppfølgingen så spurte jeg spesifikt om vi skulle sende inn en ny endringsmelding, slik som ble gjort for 5 års oppfølgingen, eller om vi skulle skrive ny søknad. REK mente at siden det var så langt tilbake i tid som i 2006 og 2011, ønsket de en ny søknad, men med tydelige presiseringer om hva som var endringene. Det ble sendt ny søknad og vedtaket foreligger (se vedlegg).

I løpet av 5 års oppfølgingen i denne studien ble det utviklet en elektronisk database for å "merge data" i den norske armen av studien med den fra USA. Det har etter min forståelse, også etter veiledning fra Forskningsstøtte, OUS, at denne type "merging av data" kan gjennomføres når dataene er fullstendig anonymiserte. Vi har utviklet prosedyrer der vi nettopp beskriver hvordan dette gjøres for å opprettholde fullstendig anonymisering av data (se vedlegg). Vi tar selvsagt tilbakemeldinger på om dette er godt nok beskrevne prosedyrer.

Konkrete svar på spørsmålene fra dere:

1. AD sletting av data: Dataene for denne internasjonale studien ble ikke slettet i 2017 basert på endringer til REK i 2011 som inkluderte nytte samtykke som pasientene signerte for 5 års oppfølingen der det står at data vil bli slettet 2020. I 5 års samtykket ba vi også om at vi fikk kontakte de igjen for nytt samtykke dersom videre oppfølging skulle gjennomføres. Det planlegges da nå med 10 års oppfølgingen, etter vedtaket fra REK. I det nye vedtaket fra REK heter det: " Tillatelsen gjelder til 15.12.2040. Av dokumentasjons-og oppfølgingshensyn skal opplysningene likevel bevares inntil 15.12.2045. Opplysningene skal lagres avidentifisert, dvs. atskilt i en nøkkel-og en opplysningsfil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato."
2. Ad oppbevaring av kodelister: Dette er beskrevet i alle søknaden i denne studien. Kodelister er oppbevart i tråd med gjeldende retningslinjer fra 2006 til i dag, angitt i tidligere søknader: innelåst i brannsikker safe.
3. Ad kobling med leddproteseregisterdata: Vi har på langt nær kommet så langt at dette er aktuelt å gjennomføre i 2018. Planleggingen av denne delen av prosjektet vil gjennomføres etter 2018, og vi vil i tråd med nedenfor nevnte krav sende en bekreftelse fra registerets fagråd, når den foreligger, om at utlevering er i orden og i tråd med opprinnelig formål og samtykke.
4. AD forskingsserver OUS (K:\Sensitivt\...): Siden denne 10 års oppfølgingen er en langtidsoppfølging av den studien som inkluderer data på mappen K:\Sensitivt for prosjektet 2011/20631 "Dynamisk stabilitet i et korsbåndsskadet kne", ønsker vi

at vi skal kunne fortsette å benytte denne mappen. Dersom det er umulig så er det fint om dere oppretter en ny mappe for oss for denne oppfølgingsstudien.

Ser frem til tilbakemelding på dette svaret og evt behov for ytterligere informasjon. Kopiert inn min leder på Forskningsavdelingen, Ortopedisk klinikk, Professor Lars Nordsletten.

Vennlig hilsen

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Fra: OUSHF PB Personvern
Sendt: 7. mai 2018 13:03
Til: May Arna Risberg
Emne: SV: Skjema personvern for prosjekt 2018/433 Dynamisk stabilitet i et korsbåndsskadet kne Hei!

Viser til prosjektdokumentasjon for prosjektet «Dynamisk stabilitet i et korsbåndsskadet kne». Ser av REK- vedtaket at dere skal koble data med Nasjonalt leddproteseregister. Dersom dere skal koble med andre registre, behøver vi å få tilsendt en bekreftelse fra registerets fagråd om at utlevering er i orden og i tråd med opprinnelig formål og samtykke.

Jeg har også noen spørsmål. Er det slik at data skal utleveres til samarbeidspartnere i Delaware? Hvordan skal i så fall utleveringen gjøres? Jeg lurer også på hvordan kodelisten for prosjektet er oppbevart?

Du skriver også at du ønsker å benytte mappen på K:\Sensitivt for prosjektet 2011/20631 "Dynamisk stabilitet i et korsbåndsskadet kne". Det er i midlertid slik at prosjektdokumentasjon i nye prosjekt skal lagres på eget område, selv om det kan være tidligere prosjekter med relevans for og tilknytning til det nye prosjektet. I vår oversikt over forskningsprosjekter ved OUS er det også oppnevnt at data i dette prosjektet skulle vært slettet/anonymisert innen 31.12.2017. Er kodelisten og prosjektdokumentasjon blitt slettet/anonymisert? mvh

Annika Mortensen
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Fra: Elsa Roland **På vegne av** OUSHF PB Sentral Godkjenning
Sendt: 7. mai 2018 11:17
Til: May Arna Risberg
Kopi: OUSHF PB Personvern

Emne: SV: Skjema personvern for prosjekt 2018/433 Dynamisk stabilitet i et korsbåndsskadet kne Hei

Takk for mottatt prosjektdokumentasjon. Studien er registrert i ForPro og arkivert med nr. 18/09371 i nytt arkivsystem. P360 erstatter tidligere ePhorte nr. 2011/20631. Merk at dokumentasjon som er arkivert i ePhorte er tilgjengelig fremdeles, men all ny prosjektdokumentasjon vil bli lagret i nytt arkivnummer.

Hvis du ønsker tilgang for å søke i prosjektdokumentasjonen i Public 360 kan dette søkes via Min Sykehuspartner (OUS intranett).

Vennlig hilsen Forskningsstøtte

Avdeling for forskningsadministrasjon og biobank

Regional forskningsstøtte

Biobank

Forskningsstøtte på OUS-research

Fra: May Arna Risberg
Sendt: 7. mai 2018 11:13
Til: OUSHF DL godkjenning
Emne: Skjema personvern for prosjekt 2018/433 Dynamisk stabilitet i et korsbåndsskadet kne

Viser til vedlagt vedtak fra REK og utfylt skjema til prosjektet som har fått godkjenning av REK: «2018/433 Dynamisk stabilitet i et korsbåndsskadet kne»

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IKKE SENSITIVT INNHOLD