# Long-term risk of arthroplasty and patient-reported outcomes following focal cartilage lesions in the knee

Thomas Birkenes

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2024

UNIVERSITY OF BERGEN

# Long-term risk of arthroplasty and patient-reported outcomes following focal cartilage lesions in the knee

Thomas Birkenes


Thesis for the degree of Philosophiae Doctor (PhD)
at the University of Bergen

Date of defense: 22.11.2024

Year: 2024

Title: Long-term risk of arthroplasty and patient-reported outcomes following focal cartilage lesions in the knee

Name: Thomas Birkenes

Print: Skipnes Kommunikasjon / University of Bergen

# Contents

# 1. Scientific environment

This thesis was part of the Norwegian Cartilage Project (NCP) led by Professor Asbjørn Årøen at Akershus University Hospital. The studies included in this thesis were conducted in close collaboration with the Norwegian Arthroplasty Registry (NAR) at The Department of Orthopaedic Surgery, Haukeland University Hospital in Bergen. This work was funded by the Norwegian Research Council via NCP (Grant No. 2015107) and by NAR.

This thesis was conducted at the NAR and in the Sports Traumatology and Arthroscopy Research Group (STAR) affiliated with the Department of Clinical Medicine (K1) of the University of Bergen. However, the thesis has been conducted despite the resistance of a bureaucratic Faculty of Medicine at the University of Bergen.

# 2. Acknowledgements

During the work of this thesis, I worked as a consultant knee surgeon in the Department of Orthopaedic Surgery at Haukeland University Hospital. I would like to take the opportunity to thank all my colleagues in the department for their support and inspiration during these years. I am also very grateful to all the patients who meticulously filled out and returned all the questionnaires. Without you, this research would not have been possible. Furthermore, I would like to thank Asbjørn Årøen and the NCP group for providing me with the opportunity to write this thesis and for funding it. You seem to have kept your faith in me, even when progress was slow. A special thanks to:

My supervisors Håvard Visnes, Ove Furnes, Eirik Solheim and Stein Håkon Låstad Lygre. For sharing extensive experience in research and always taking time from your busy schedule to answer even the simplest questions from a research novice. Thank you for your patience when the clinical work took all my time, and the research progress was slow. Furthermore, for supporting me when the reviewers did not agree with my "brilliant" work and for pushing me towards the finalisation of the thesis.

The staff at NAR facilitating my research by providing me with an office and helping with questionnaire logistics. Special thanks to the statisticians for patently helping the statistical novice.

All my coauthors, for helping me identify the patients eligible for our studies and sharing your research results with me. Thank you for your encouragement and insightful comments on the manuscript drafts. Special thanks to Jon Olav Drogset for inviting me to watch proper football during my visit to Trondheim.

My fellow knee surgeons on Haukeland, Eivind, Asle, and Heid Elin, and physiotherapist Renate and Ørjan for your support during the PhD period and for compensating for my absence in the clinical work. I am truly grateful for having you as my colleagues and friends.

Heidi Andreassen and Ingrid Trøan, research coordinators at Akershus University Hospital and Oslo University Hospital for your kind assistance in identifying eligible

patients and providing all necessary information regarding the included patient's surgical report.

The STAR group, for all the support and inspiration during my research and for pushing me towards the finish line.

Knut Fjeldsgaard and Asle Kjellsen for introducing me to advanced knee surgery and patiently teaching me all I know about the topic.

My parents Ragnar and Randi Mina who have always been considerate and supportive. Finally, I would like to thank my lovely wife, Maria, who is the cornerstone of my life and always there to support me and compensate for all my weaknesses. And to our three children Sara, Filip, and Lea for constantly reminding me of what’s important in life.

# 3. List of abbreviations

| | |
|---|---|
| ACI | Autologous Chondrocyte Implantation |
| ACL | Anterior Cruciate Ligament |
| AMIC | Autologous Matrix-Induced Chondrogenesis |
| CI | Confidence Interval (95%) |
| ECM | Extracellular matrix |
| FCL | Focal Cartilage Lesion |
| GAG | Glycosaminoglycan |
| HR | Hazard Ratio |
| ICRS | International Cartilage Regeneration & Joint Preservation Society |
| KA | Knee Arthroplasty |
| KL | Kellgren Lawrence |
| KOOS | Knee injury and Osteoarthritis Outcome Score |
| MACI | Matrix-induced Autologous Chondrocyte Implantation |
| MSC | Mesenchymal stem cell |
| NICE | National Institute for Health and Care Excellence - UK |
| NSAID | Non-steroid anti-inflammatory drug |
| OAT | Osteochondral Autologous Transplantation (Mosaicplasty) |
| OR | Odds Ratio |
| PRP | Platelet rich plasma |
| QoL | Quality of Life |
| VAS | Visual Analogue Scale |
| WOMAC | Western Ontario and McMaster Universities Osteoarthritis Index |

# 4. Abstract in English

**Background**
Focal cartilage lesions are common in knees. No treatment strategy for such lesions has been shown to be superior. Few studies have reported the long-term prognosis, and the risk of subsequent knee arthroplasty is unknown.

**Aims**
The aim of the studies was to evaluate the long-term patient-reported outcomes and the risk of subsequent knee arthroplasty in patients with focal cartilage lesions in the knee. Furthermore, to evaluate the patient-reported outcomes (PROM) after knee arthroplasty in patients with a history of focal cartilage lesions.

**Methods**
Patients with arthroscopically verified focal cartilage lesions in the knee and at least one patient-reported outcome, between 1999-2012 from six Norwegian hospitals were identified. The patients received a questionnaire regarding their current knee function, characteristics, any additional knee surgery, and Knee injury and Osteoarthritis Outcome score (KOOS). The patient cohort was linked to the Norwegian Arthroplasty Register (NAR) and any ipsilateral knee arthroplasty was registered. A matched cohort from NAR received the same questionnaires.

**Results**
Of the 516 eligible, 322 patients (328 knees) consented to participate in the cartilage cohort. The mean age at the time of arthroscopically verified cartilage lesion was 36.8 years. The mean follow-up period for the cartilage cohort was 19.8 years. The 20-year cumulative risk of knee arthroplasty was 19.1%, which was significantly higher than that in the age-matched Norwegian general population. Surgical treatment of the lesion did not reduce the risk of later knee arthroplasty compared to non-surgical.

Subsequent cartilage surgery had been performed in 17.7 % of the patients. Patients treated with autologous chondrocyte implantation had significantly higher KOOS QoL subscores (+18.2) and a lower risk (odds ratio 0.3) of treatment failure. A body mass index >25 was associated with a lower KOOS QoL subscore and a higher risk of knee arthroplasty.

Patients with knee arthroplasty with a history of focal cartilage lesions reported significantly lower KOOS subscores (Symptoms -8.4, Pain -11.8, and QoL -10.6) and had significantly lower odds of reaching the Patient Acceptable Symptoms State (PASS) for the KOOS subscores (odds ratio: Symptoms 0.4, Pain 0.3 and QoL 0.4) than the matched cohort.

**Conclusion**

At a mean 20-year follow-up, patients with previous focal cartilage lesions in the knee had a significantly increased risk of knee arthroplasty compared with the general population. Patients treated with ACI had significantly better PROM and lower odds of treatment failure than those without surgical cartilage treatment. At mid-term follow-up, patients who underwent knee arthroplasty after a previous cartilage lesion had lower PROM scores and lower odds of reaching the PASS threshold than a matched cohort compared to the control group.

**Implications**

Focal cartilage lesions may significantly impair the quality of life. Improvement in knee function can be anticipated regardless of the treatment strategy; however, normal knee function following a symptomatic lesion is rarely achieved. Current treatment options do not seem to reduce the risk of knee arthroplasty and randomised control trials including an arm of sham surgery should be performed. Lowering body mass index appears to be the only modifiable risk factor for reducing the risk of poor treatment outcomes. Previous cartilage lesions predict poor outcomes, even after knee replacement surgery. These are important factors to consider in shared decision making regarding the choice of optimal treatment in patients with cartilage lesions.

# 5. Sammendrag

**Bakgrunn**

Fokale brusklesjoner er vanlige i kneet. Ingen av behandlingsmodaliteten for slike lesjoner er vist å være bedre enn andre. Få studier har rapportert den langsiktige prognosen, og risikoen for påfølgende kneprotesekirurgi er ukjent.

**Formål**

Kartlegge de langsiktige pasientrapporterte resultatene og risikoen for påfølgende kneprotesekirurgi hos pasienter med fokale brusklesjoner i kneet. Kartlegge pasientrapporterte resultater (PROM) etter kneprotesekirurgi hos pasienter med tidligere fokale brusklesjoner.

**Metode**

Pasienter med artroskopisk verifiserte fokale brusklesjoner i kneet, og minst ett pasientrapportert utkomme, operert mellom 1999-2012 ved seks norske sykehus, ble identifisert. Pasientene mottok et spørreskjema angående deres nåværende knefunksjon, karakteristika, eventuelle tilleggsoperasjoner i kneet og Knee injury and Osteoarthritis Outcome score (KOOS). Pasientkohorten ble koblet til Nasjonalt Register for Leddproteser (NRL) og eventuelle kneproteser på samme side ble registrert. En matchet kohort fra NRL mottok de samme spørreskjemaene.

**Resultater**

Av de 516 pasientene som ble identifisert, samtykket 322 pasienter (328 knær) til å delta i bruskohorten. Gjennomsnittsalderen ved tidspunktet for artroskopisk verifisert brusklesjon var 36,8 år. Gjennomsnittlig oppfølgingstid i bruskohorten var 19,8 år. Den 20-årige kumulative risikoen for kneprotese var 19,1 %, som var betydelig høyere enn i den aldersmatchede norske normalbefolkningen. Kirurgisk behandling av lesjonen reduserte ikke risikoen for senere kneprotesekirurgi sammenlignet med ikke-kirurgisk behandling.

Ytterligere bruskirurgi hadde blitt utført hos 17,7 % av pasientene. Pasienter behandlet med autolog kondrocyttimplantasjon (ACI) hadde signifikant høyere KOOS QoL delskår (+18,2) og lavere odds (odds ratio 0,3) for behandlingssvikt.

Kroppsmasseindeks (KMI) >25 var assosiert med lavere KOOS QoL delskår og høyere risiko for kneprotesekirurgi.

Pasienter med kneprotesekirurgi med en historie med fokal brusklesjon rapporterte signifikant lavere KOOS delskår (Symptomer -8,4, Smerte -11,8, og QoL -10,6) og hadde signifikant lavere odds for å oppnå Pasient Akseptabelt Symptom Nivå (PASS) for KOOS delskårene (Odds ratio: Symptomer 0,4, Smerte 0,3 og QoL 0,4) enn den matchede kohorten.

**Konklusjon**

Etter gjennomsnittlig 20-års oppfølging hadde pasienter med tidligere fokale brusklesjoner i kneet signifikant økt risiko for kneprotesekirurgi sammenlignet med normalbefolkningen. Pasienter behandlet med ACI hadde signifikant bedre PROM og lavere odds for behandlingssvikt enn pasienter uten kirurgisk bruskbehandling. Ved oppfølgingen hadde pasienter med kneprotesekirurgi etter en tidligere brusklesjon lavere PROM-skårer og lavere odds for å nå terskelverdien for PASS.

**Konsekvenser**

Fokale brusklesjoner kan redusere livskvaliteten betydelig. Forbedring i knefunksjon kan forventes uavhengig av behandlingsstrategi, men normal knefunksjon oppnås sjelden. Nåværende behandlingsalternativer ser ikke ut til å redusere risikoen for senere kneprotesekirurgi. Å redusere KMI synes å være den eneste modifiserbare risikofaktoren for å redusere risikoen for dårligere behandlingsresultater. Tidligere brusklesjoner er assosiert med dårligere behandlingsresultater selv etter kneprotesekirurgi. Dette er viktige faktorer som gir felles beslutningsgrunnlag for pasient og behandler ved valg av optimal behandling for pasienter med brusklesjoner.

# 6. List of Publications

Paper I:

Birkenes T, Furnes O, Laastad Lygre SH, Solheim E, Aaroen A, Knutsen G, Drogset JO, Heir S, Engebretsen L, Løken S, and Visnes H. The Long-Term Risk of Knee Arthroplasty in Patients with Arthroscopically Verified Focal Cartilage Lesions: A Linkage Study with the Norwegian Arthroplasty Register, 1999 to 2020. The Journal of bone and joint surgery American volume. 2023;105(12):951-61.

Paper II:

Birkenes T, Furnes O, Laastad Lygre SH, Solheim E, Aaroen A, Knutsen G, Drogset JO, Heir S, Engebretsen L, Løken S, and Visnes H. (2024) Long term results after arthroscopically verified focal cartilage lesion in the knee. A 20-year multicentre follow-up with patient reported outcome. (Accepted for publication in The Journal of bone and joint surgery American volume.) DOI: 10.2106/jbjs.23.00568

Paper III:

Birkenes T, Furnes O, Laastad Lygre SH, Solheim E, Aaroen A, Knutsen G, Drogset JO, Heir S, Engebretsen L, Løken S, and Visnes H. (2024) Previous cartilage surgery is associated with inferior patient-reported outcomes after knee arthroplasty. *Knee Surgery, Sports Traumatology, Arthroscopy*, 32, 361-370. DOI: 10.1002/ksa.12050

# 7. Introduction

## 7.1 Cartilage

### *7.1.1 Types of cartilage in the human body*

There are three types of cartilage in the adult human body[1], with different biomechanical and structural features[2]. Elastic cartilage can be found in the trachea, earlobe, and epiglottis for instance[1]. The random orientation of elastin fibres provides tissue flexibility and shape[2]. Fibrocartilage can be found in intervertebral discs, tendons, menisci, and the symphysis[1]. This is the hardest cartilage and consists of more collagen type I and, to a lesser extent, collagen type II[1, 3]. It is avascular and aneural tissue. The most abundant type of cartilage in the human body[1] and the focus of this thesis is hyaline cartilage. It is found in synovial joints and is often referred to as articular cartilage but can also be found in the nasal septum and costal cartilage. Hyalin cartilage is also the base of bone formation in embryo[1]. It is an aneural and avascular tissue consisting of less than 5% chondrocytes and more than 95% extracellular matrix (ECM)[2]. Collagen type II is the most abundant type of collagen in hyaline cartilage[1].

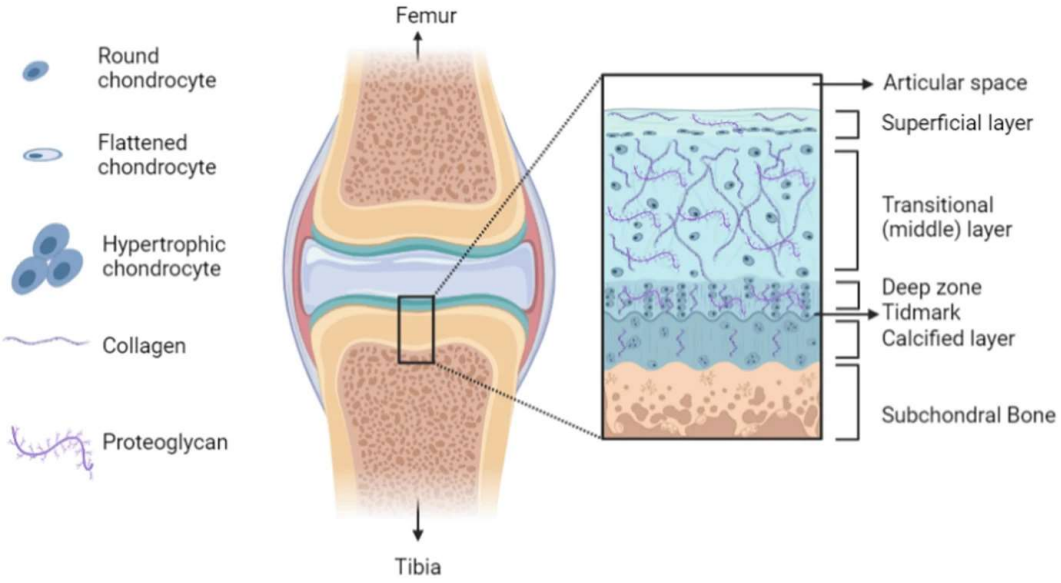



*Fig 1. Schematic drawing of the different structural layers of full-thickness articular cartilage showing different compositions and component organisation. Reprinted from Cartilage: From Biology to Biofabrication, Springer Verlag with permission.*

### *7.1.2 Physiology of normal articular cartilage*

Articular cartilage is the highly specialized connective tissue of synovial joints. To provide a smooth, lubricated surface for articulation and to facilitate the transmission of loads with a low frictional coefficient is the key function[4]. It is divided into the superficial-, the middle-, the deep-, and the calcified zones at the border to the subchondral bone. The superficial layer is in contact with the synovial fluid and plays an important role in withstanding the sheer, tensile and compression forces imposed on the joint surface[4]. The middle zone embodies approximately 50% of cartilage volume and bridges the superficial and deep layers. The deep zone resists most of the compressive forces and is separated from the calcified layer by the tide mark. The calcified layer plays an important role in securing cartilage to the subchondral bone[4]. Owing to the avascular nature of cartilage, it is dependent upon motion and mechanical loading to facilitate fluid containing nutrients and molecules to move into the cartilage from the synovial fluid[5].

The ECM in articular cartilage is a complex protein network that provides a structural scaffold and cartilage with unique properties[6]. Collagen fibrils are a major part of the ECM, accounting for approximately 2/3 of the dry weight of the adult articular cartilage. Collagen fibrils display different molecular organisations and orientations depending on their location in the cartilage. At the joint surface, they run parallel to the surface, whereas at deeper zones, the fibrils are thicker and perpendicular to the surface[7]. Articular cartilage contains several types of collagen, dominated by type II. Type XI, and IX are other important collagens almost exclusively found in cartilage[8]. The thickness of collagen fibrils increases through the layers of cartilage, with the deep layer having the thickest fibrils[4]. The different types of collagen form a complex architectural network that is difficult to recreate after osteochondral trauma[7].

Another key component of the ECM is proteoglycans which consist of a core protein surrounded by glycosaminoglycan (GAG) chains[6] and is via glycoproteins[9] kept in place by the collagen network[8]. GAGs are also found in other tissues of the human body. One of the most studied proteoglycans is aggrecan which together with link protein and hyaluronan forms the aggrecan-hyaluronan network. This network immobilises negatively charged ions, resulting in an osmotic process that absorbs water into cartilage tissue[6, 10]. This is a crucial part of cartilage's ability to absorb and distribute mechanical loads.

The most important cell type in cartilage is the chondrocyte which is highly metabolically active and plays a key role in the development, maintenance, and repair of ECM[4]. The cellular organisation of cartilage is consistent between different types of joints, with only minor variations due to mechanical loading[11]. In the superficial layer of articular cartilage, chondrocytes are relatively abundant and oriented parallel to the surface as flattened and elongated cells that produce hyaluronic acid to lubricate the joint. Chondrocytes in the middle zone are rounder and produce ECM components, such as aggrecan and type II collagen. In the deeper layer, chondrocytes are more scarce and larger, with a hypertrophic appearance at the tide mark[11]. Chondrocytes are surrounded by a pericellular matrix consisting of proteoglycans and glycoproteins which are contained by collagen fibrils that also involve type IV collagen[4, 7]. The

pericellular matrix does not allow chondrocyte migration to adjacent areas and cell-to-cell contact is rare. Chondrocytes respond to stimuli, such as growth factors, mechanical loading and hydrostatic pressure[4]. As collagen is long-lasting, with a half-life of 100 years, chondrocytes are mostly involved in the homeostasis of GAGs[5].

Approximately 80% of the weight of cartilage consists of water, and most resides in the interfibrillar ECM. The relative water concentration decreases from approximately 80% in the superficial zone to 65% in the deep zone, and its main function is the transport of nutrients and inorganic ions to the cells, as well as lubrication[4]. The ability of cartilage to withstand extensive loads is dependent on the high frictional resistance and pressurisation of water in ECM[4].

### *7.1.3 Epidemiology of focal cartilage lesions of the knee*

Focal cartilage lesions (FCLs) are one or more well-delineated lesions surrounded by the normal cartilage. There might be several causes of a FCL, such as trauma, degeneration, and osteochondritis dissecans. Degenerative lesions usually have poorly defined borders and are part of generalised degenerative progression (osteoarthritis) of the joint. FCLs is a common finding in knee arthroscopies of any cause. In a large cohort of more than 25 000 patients undergoing knee arthroscopy, Widuchowski et al.[12] found a cartilage lesion in 60% of knees, 67% of which were classified as focal lesions. Twelve percent of the lesions were full-thickness lesions. The findings of Widuchowski et al.[12] concur with those of Curl et al.[13] in a large database study from the US. In Norway, both Hjelle et al[14] and Aroen et al.[15] reported cartilage lesions in 1000 consecutive knee arthroscopies. Cartilage lesions of any kind were found in 61% and 66% of arthroscopies, respectively, and full-thickness lesions were found in 10% and 11%, respectively.

Ding et al. found cartilage lesions in 44% of MRIs scans obtained from a cohort of 372 healthy individuals from Australia[16]. The participants were 26-61 years old, and the lesions varied from partial to full thickness[16]. These findings concur with another study of asymptomatic women, 30-49 years old, with cartilage lesions found in 53.5% of the knees[17]. Furthermore, Zanetti et al.[18] found cartilage lesions in 25% of asymptomatic knees, with more than 50% of the lesions being full-thickness. Even in younger

patients, asymptomatic lesions can be found. In a study of 76 patients (age 15-27) with a history of contralateral knee injury, Whittaker et al[19]. found cartilage injuries in 4.2% of the asymptomatic knees. Cartilage lesions appear to be even more frequent in young athletes. Pappas[20] found cartilage abnormalities in 75% of the knees on pre-seasonal MRI in a cohort of 24 college basketball players.

In 2015, Engen et al.[21] reported the incidence of cartilage surgeries in Norway between 2008 and 2011. A National incidence of 56/100 000 inhabitants was found, and nearly 400 cartilage restorative/reparative cartilage surgeries were performed annually.

### *7.1.3 Clinical presentation of focal cartilage lesions*

Although some focal cartilage lesions may remain asymptomatic, as described in the previous paragraph, others can be detrimental to knee function. Symptoms can arise in patients with or without a history of trauma. The most common symptoms are pain, intermittent swelling, crepitus, and mechanical symptoms such as popping, clicking, catching, and locking. The latter symptoms suggest instability of the lesion or the presence of loose bodies.

In 2010 Heir et al[22] presented as study comparing KOOS in patients scheduled for cartilage surgery to preoperative KOOS in ACL and knee arthroplasty patients. They found that the KOOS QoL subscore in cartilage patients was similar to the subscore in knee arthroplasty patients and worse than the subscore in ACL patients. However, the other KOOS sub-scores were better in cartilage patients. The KOOS QoL subscore of 27 reported by Heir et al. was similar to that reported by other authors, such as Wondrasch et al[23], and Saris et al[24].

## 7.2 Osteoarthritis

### *7.2.1 Pathophysiology of osteoarthritis*

Osteoarthritis is characterised by the progression of cartilage loss, calcification of the cartilage, subchondral bone changes, synovia inflammation, and osteophyte formation[5]. It may cause significant disability and is the most common joint disorder in the adult population. Currently, there is no available treatment that can reverse

osteoarthritic changes. Mechanical overload mediated by increased load on the joint surface or loss of protective mechanisms, such as muscle atrophy or joint instability, is the leading cause of osteoarthritis[25]. Genetic factors are also important contributors in osteoarthritis, but mostly in hip osteoarthritis and less in the knee[26]. The osteoarthritic process is believed to begin with the loss of negatively charged GAGs with increased water content as a result. This leads to swelling of the matrix and cartilage surface fibrillation which progresses to deeper fissures and exposes the deeper layer of the joint cartilage. Furthermore, chondrocytes undergo phenotypic changes, including a catabolic state and gene expression of proteinases that degrade collagen type II and aggrecan[5]. Even a small amount of collagenolysis can cause irreversible cartilage injury[27]. The resulting damage-associated molecular patterns (DAMP) also induce inflammation and release of proinflammatory cytokines in the adjacent synovium. Synovitis negatively influences chondrocyte function and appears to be an important factor in the development of osteoarthritis[5].

Several changes in bone morphology have been observed in osteoarthritis. Typically, increased cortical plate thickness, osteophyte formation, flattening of the joint contour, and loss of the subchondral trabecular bone can be found[28]. An increased cortical plate thickness reduces the shock-absorbing capability of the subchondral bone. This increases the load forces on the cartilage, adding to the overload and aggravating the osteoarthritis process[5]. Microcracks appear in the osteochondral junction, allowing blood vessels to invade the calcified layer of the cartilage, and bioactive factors to be exchanged between the cartilage and subchondral bone[28]. This process leads to hypertrophic differentiation of chondrocytes, resulting in the thickening of the calcified layer and further thinning of the cartilage[5, 28].

### *7.2.2 Risk factors for knee arthroplasty in the general population*

Knee arthroplasty is the most common treatment for symptomatic end-stage osteoarthritis. Several risk factors for requiring knee replacement have been identified. Inflammatory joint diseases such as rheumatoid arthritis and psoriatic arthropathy are known to increase the risk of knee replacement. Apold et al[29] reported the risk of knee arthroplasty due to primary osteoarthritis in the general Norwegian population.

Elevated BMI was identified as the most important risk factor, with a more than 6 times and 11 times elevated risk of knee replacement for men and women, respectively, with a BMI >27.3 compared to patients with normal weight. Furthermore, heavy manual labour increased the risk compared with sedentary work. High body height was also found to be a risk factor independent of BMI. The findings of Apold et al[29] are consistent with those of a review and meta-analysis by Blagojevic et al[30] looking at risk factors for knee osteoarthritis, although the effect of BMI was substantially lower in their study. Blagojevic also identified previous knee trauma, older age, female sex, and poor mental health as risk factors for symptomatic osteoarthritis. Both meniscal and ACL injuries are associated with an increased risk of symptomatic osteoarthritis and subsequent knee replacement[31, 32].

## 7.3 Patient reported outcomes

### *7.3.1 Introduction*

Traditionally, outcomes of surgical procedures have been reported empirically with variables such as complications and the risk of needing further surgery. Since the early 1980s, the importance of patient-reported outcome measures (PROM) has been recognised[33]. PROMs offer insights into the patients' view of their health, well-being, and satisfaction pre- and post-surgery, providing a more comprehensive evaluation of surgical outcomes beyond clinical measures alone. Several knee-specific PROMs have also been developed. In this section, the most widely used knee PROMs are discussed.

### *7.3.2 Lysholm/Tegner*

The Lysholm score was first introduced in 1982[33] and revised into its current version in 1985[34]. It consists of eight questions: limp, support, locking, instability, pain, swelling, stair climbing, and squatting. The maximal score is 100, indicating high knee function. It is commonly used in combination with the Tegner Activity Score. The Lysholm score has been validated for a variety of knee conditions, including focal cartilage lesions[35], but has not been validated in patients with osteoarthritis, despite its frequent use. The questionnaire is usually completed in a short time owing to a few questions, and the patient burden is thus considered low[36]. No floor or ceiling effect

has been reported, but the test-retest reliability is less than adequate in patients with mixed pathologies of the knee[36].

### *7.3.3 Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)*

WOMAC was introduced in 1982 as a PROM for patients with knee- or hip-osteoarthritis[36]. It has been revised several times, and the current version is version 3.1. It consists of 3 subscales (pain, stiffness, and physical function) with a total of 24 questions. Higher scores indicated worse pain, stiffness, and function. The current version is available on a 5-point Likert, a 100 mm visual analogue scale, and an 11-box numerical rating scale version. Despite being available only at pay per use directly from the developer, Prof. Bellamy, the questionnaire has been widely used. It has been validated for use in knee and hip osteoarthritis, but has also been used in other knee conditions such as ligamentous injuries and cartilage injuries[36]. Both floor and ceiling effects have also been reported[36].

### *7.3.4 Oxford Knee Score (OKS)*

The Oxford knee score was introduced in 1998 as a questionnaire for knee replacement patients[37]. It was later modified to the current version with a score ranging from 0 to 48, with the latter being the best score[38]. The questionnaire is patient administrated with 12 questions, each of which was assigned a score between 0 and 4. It has been validated for use in knee osteoarthritis and arthroplasty, with adequate test-retest reliability[37]. Although OKS has not been validated for other knee conditions, it has been used for conditions as ligamentous injuries, fractures, and chondral lesions[38, 39]. No floor or ceiling effect were found[40].

### *7.3.5 Cincinnati knee rating system*

The modified Cincinnati knee rating scale was originally introduced in 1990 as a modification of the Noyes knee rating scale[41]. It consists of eight sections (Pain, Swelling, Giving way, overall activity level, Walking, Stairs, Running, Jumping, or twisting) and has a maximum score of 100, constituting excellent knee function. It has been validated in patients with ACL, with no floor effect and a moderate ceiling effect[42]. Marx et al. also validated it in a population with various knee conditions[43].

Other authors have further modified the Cincinnati score; however, to the best of our knowledge, they have not validated the modified versions[44].

### *7.3.6 Knee Injury and Osteoarthritis Outcome Score (KOOS)*

The KOOS was developed in 1995 to meet the need for a PROM covering several types of knee injuries and including osteoarthritis[45]. KOOS contains WOMAC 3.0 questions and the WOMAC score can thus be extracted from the KOOS score. The questionnaire is comprehensive, patient-administered, and contains five subscores with a total of 42 questions. The score ranges from 0 (worst) to 100 (excellent knee function). The scores of each sub-score (Symptoms, Pain, Activities of daily living (ADL), Sports/Recreations and Quality of Life (QoL)) are reported separately. A total KOOS score has never been validated. However, the use of the KOOS questionnaire with subscores has been validated in several knee conditions, such as cartilage injuries[46, 47], ligamental injuries[45], osteoarthritis[45], and knee replacement[48]. Thus, it can be used to evaluate not only the impact of injury on patient-reported knee function but also the long-term effects of osteoarthritis and knee arthroplasty. Age- and sex-stratified normative values in the general population have been reported[49, 50]. The KOOS questionnaire exhibit good or adequate validity and responsiveness without floor- or ceiling effects[36]

Several additional versions of the KOOS have been developed. The KOOS-Physical Function Short Form was published in 2008[51] and has been validated in patients with knee osteoarthritis[52]. The questionnaire consists of seven items derived from the KOOS ADL and Sport/rec sub-scores. The KOOS was found to not be well understood by children, and as a response, the KOOS-Child Questionnaire was developed in 2012[53]. The questionnaire contains the same five domains as the original KOOS, but only contains 39 questions, of which several have been highly modified. It has been validated in children and adolescents with knee disorders[54].

With 42 questions, the burden on KOOS respondents was substantial, and consequently, the KOOS 12-item short form was developed in 2019. It consists of four questions from the QoL subscore and eight questions from the Pain, ADL, and sport/rec subscores. It provides pain, function, and QoL subscores, and, contrary to the

original KOOS, a summary knee impact score can be estimated[55]. The 12-items short form has only been validated in patients with osteoarthritis and knee arthroplasty[55].

### *7.3.7 International Cartilage Regeneration & Joint Preservation Society (ICRS) score*

The International Cartilage Regeneration Score was introduced in a spring letter in 1998. This has never been validated and has gained little recognition. Few studies have used the questionnaire in patient follow-up and usually only the Pain score is reported as a VAS 0-100[15, 56].

### *7.3.8 International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form*

The patient administered IKDC Subjective Knee Evaluation Form that was first published in 2001 as a revision of the IKDC standard evaluation form developed in 1993[36, 57]. It contains 18 items in three domains: symptoms (7), daily function and sports participation (10), and current knee function (1). The score from each item is summarised as a total score ranging from to 0-100, where 100 represents the best score with no knee-related symptoms or limitations of activity. The IKDC form has been validated for several knee conditions, such as ligamentous, cartilage, and meniscal injuries as well as osteoarthritis[57, 58]. The IKDC subjective score has been found to have good or adequate validity, responsiveness, and test-retest reliability without floor or ceiling effects[59]. As with KOOS, the IKDC subjective form has not been well understood among children, and a Pedi-IKDC subjective form was thus introduced and validated in 2011[60].

## 7.4 Treatment of focal cartilage lesions

When a patient presents with a symptomatic focal cartilage lesion in the knee, numerous operative and non-operative treatments are available. The treatment strategy depends on the symptoms, patient preferences, and extent of cartilage damage. In order to be able to compare different treatment strategies classification systems are

needed. Cartilage lesions can be classified based on either MRI or peroperative findings.

### *7.4.1 Classification of cartilage lesions*

Several systems have been proposed for classifying focal cartilage lesions during surgery. The two most frequently used cartilage classification systems are described in this section. Outerbridge published a classification of peroperative findings in chondromalacia patella in 1961[61]. This classification was later adopted for use in any cartilage lesion of the knee[62]. Outerbridge consists of four groups: Grade 0 represents normal cartilage, grade I is characterized by softening and swelling of the cartilage, grade II is characterized by fragmentation and fissuring of an area less than 0.5 inches in diameter, grade III is the same as grade II but larger than 0.5 inches and grade IV is lesions extending down to bone[61].

The International Cartilage Repair Society (ICRS) was founded in 1997, and the cartilage classification was developed by a working group published in 1998[63]. The ICRS classification consists of five grades. Grade 0 indicates a normal cartilage. Grade 1-nearly normal, refers to softening of the cartilage (A) or superficial fissures (B). Grade 2-Abnormal, is lesions extending down to <50% of the cartilage thickness. Grade 3-Severely abnormal, lesions extending down > 50% of the cartilage thickness (A), down to the calcified layer (B), and down to the subchondral bone (C) or cartilage blisters (D). Grade 4-Severely abnormal consists of lesions extending down in the subchondral bone[63]. Although the ICRS classification is comprehensive and some studies have questioned interobserver reliability, several studies have demonstrated good intra- and interobserver reliability[64].

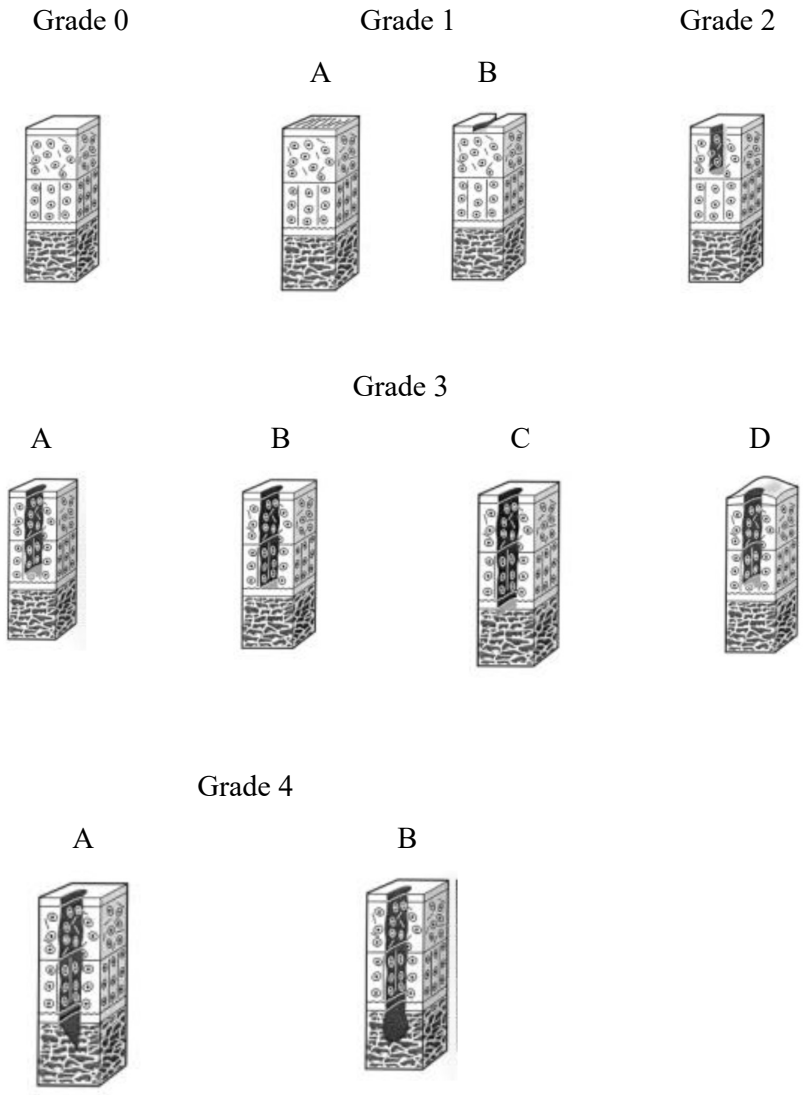



*Fig 2. ICRS Classification of the severity of cartilage lesions. Reprinted with permission from the ICRS.*

The FCL size is usually measured using a standard 4 mm arthroscopic probe or ruler[65, 66]. There seems to be a slight but acceptable tendency to overestimate FCL size in arthroscopic surgery compared with open arthrotomy[65]. Moderate to good intraobserver and interobserver reliabilities have been demonstrated for size measurement using either an arthroscopic probe or a ruler[66].

### *7.4.2 Non-operative treatment*

Non-operative treatment of focal cartilage lesions includes painkillers such as NSAIDs for symptom relief, physiotherapy, intra-articular injections of drugs, blood-derived products such as PRP, or stem cells.

Conservative treatment of osteoarthritis with exercise treatment is well documented. Several studies have demonstrated meaningful effects on improving symptoms and function, as documented in a Cochrane review in 2015[67]. However, there is limited evidence of exercise treatment for focal cartilage lesions. As early as 1996, Messner et al[68] claimed to demonstrate good/excellent results at 14 years follow-up in 28 athletes with non-surgically treated FCL. However, 19 of the patients had received treatment such as Pridie drilling, shaving, or removal of loose bodies. Widuchowski et al[69] presented a study with 15 years of follow-up of 37 patients with arthroscopically verified Outerbridge 3-4 lesions of 2-4 $cm^2$. Most of the patient had symptom debut after a knee trauma. Good to excellent patient-reported outcomes were observed, with Lysholm and WOMAC scores comparable to those reported after cartilage surgery. These findings may indicate that not all cartilage injuries require surgery. Currently, only one published study has evaluated the effectiveness of a physiotherapy-guided physical training program for treating patients with focal cartilage injuries. Wondrasch et al[23] conducted a feasibility study of a 3-month active rehabilitation program in 48 patients scheduled for cartilage surgery for a symptomatic full-thickness focal cartilage lesion. The participants had significant and clinically relevant improvements in the KOOS QoL subscore and IKDC score after concluding the rehabilitation program, and 65% of the patients cancelled their scheduled cartilage surgeries. However, there is currently no consensus on the ideal rehabilitation program for patients with focal cartilage lesions.

PRP injections have been mostly used and studied in the setting of osteoarthritis and, to a lesser extent, in focal cartilage lesions. PRP is not one single product, and three different production methods are available: blood filtration and plateletpheresis, single-spinning centrifugation, and double-spinning centrifugation[70]. This provides four different PRP categories: Pure PRP (P-PRP) with a low number of leukocytes;

Leukocyte-rich PRP (L-PRP) which contains more leukocytes as well as more platelets as P-PRP, Pure platelet-rich fibrin (P-PRF) obtained by double-spinning and is stiffer than P-PRP; and non-injectable leukocyte- and platelet-rich fibrin (L-PRF)[70]. Additionally, several different methods of PRP activation exist, and substantial variations in platelet concentration can be anticipated, even when using the same method[70]. Combining these factors makes it difficult to compare the results of previous studies on the effectiveness of PRP.

Several in vitro studies have shown promising results with PRP treatment. PRP seems to stimulate chondrocytes to synthesise proteoglycans and collagen, possibly through growth factors such as platelet-derived growth factors (PDGF) and transforming growth factor beta (TGF-β)[71]. Furthermore, PRP stimulates stem cell proliferation and differentiation towards chondtrocytes[71]. However, clinical studies on PRP are of low quality and include relatively small cohorts of patients. Although some studies have demonstrated significantly better results with PRP in osteoarthritis or as an adjunct in FCL surgery, a review by Shahid et al[70] and the NICE-guidelines[72] from the NHS-England concluded that there is no hard evidence of the clinically meaningful effects of PRP in cartilage patients.

Intra-articular injections of hyaluronic acid (Hyaluran) have been available since the 1990s and are mostly used in the setting of osteoarthritis. A large meta-analysis by a Canadian consensus group[73] concluded that hyaluronic acid was safe and provided significantly better pain and functional outcomes than placebo. However, an increased risk of adverse effects has been observed. Furthermore, only two of the included reviews demonstrated clinically meaningful improvements compared with placebo. When including only higher-quality studies on hyaluronic acid, there seems to be no clinically relevant effect[74, 75].

### *7.4.3 Surgical treatment of focal cartilage lesions*

#### 7.4.3.1 Cartilage repair

The most inexpensive surgical treatment for FCL is chondroplasty or debridement. While the two terms are frequently inconsistent and interchangeably used,

chondroplasty most often only consist of smoothening of the surface with removal of loose cartilage flaps or fragments. On the other hand, debridement most often refers to removal of loose cartilage down to the subchondral bone to achieve stable edges of the lesion, thus converting the lesion to an ICRS 3 lesion. It can be used as a single procedure but is most often used as the first step in cartilage repair or inductive procedures. Chondroplasty and debridement can be performed using either a curette, shaver, or radiofrequency probe. Both procedures have been found to significantly improve IKDC and KOOS above the minimal clinical important difference[76-78].

Subchondral drilling was first popularised by Pridie in 1959[79]. He proposed to drill holes "not too far apart" in the subchondral bone to promote the formation of fibro-cartilage. This technique was modified and further popularised as microfracture (Mfx) by Steadman et al. in the 90s[80]. The first step of the microfracture technique is to debride the FCL down to the subchondral bone, removing the calcified layer and any loose cartilage. The edges of the lesion should be perpendicular to the surrounding healthy cartilage[80, 81]. Multiple holes or microfractures about 4 mm deep and 3-4 mm apart are then made in the exposed bone using an arthroscopic awl to allow bone marrow containing mesenchymal stem cells (Msc) to form a clot in the lesion[80]. This clot is thought to facilitate cartilage formation in defects. The Mfx procedure is one of the most commonly used procedures in cartilage surgery worldwide, and is considered the gold standard[82]. Mfx mostly produces fibrocartilage, although some hyaline-like cartilage is also found[82]. Steadman et al[83] demonstrated excellent results after microfracture; however, concerns regarding the long-term results have been presented by several authors[82, 84]. Microfracture is mostly used for smaller lesions without subchondral bone defects[85]. In a review by Devitt et al[84], microfracture were found to be comparable to or inferior to other cartilage treatments, such as mosaicplasty or ACI, but never superior.

In 2005 Behrens et al[86] presented a modification of Mfx using a matrix/membrane scaffold to contain the MCS-containing clot in the defect. This method is known as autologous matrix-induced chondrogenesis (AMIC). The authors recommend it for ICRS 4 lesions with a size of <1,5 $cm^2$ in patients with a single FCL without any

rheumatoid arthritis, malalignment, or ligamentous deficiencies. However, this method has also been used for larger, full-thickness lesions. Debridement of the lesion and microfracture or drilling is performed before the defect is covered by a collagen membrane using fibrin glue. Originally, the AMIC procedure was performed as an open surgery; however, arthroscopic techniques were later developed[87]. Significant clinical improvements have been demonstrated after the AMIC procedure[88] but seems not to be superior to microfracture[89] or ACI[90].

#### 7.4.3.2 Transplantation of osteochondral grafts

The transplantation of osteochondral grafts can be used to fill chondral or osteochondral lesions. Both allograft as well as autograft can be utilised.

Osteochondral Autologous Transplantation (OAT), commonly referred to as mosaicplasty, was described by Bobic[91] in 1996 and further popularised by Hangody et al. in 1997[92]. Mosaicplasty can be performed as open or arthroscopic surgery. After debridement of the lesion, 15 mm deep osteochondral cylinders are harvested from the less weight-bearing edges of the trochlea. The chondral lesions is then prepared with a drill of the same diameter as the harvested grafts, and the osteochondral grafts firmly embedded in the lesion. This usually results in–60-70% filling of the defect with hyaline cartilage and 30-40% fibrocartilage (between the grafts)[92]. Donor-site chondral defects usually heal with fibrocartilage. Owing to the limited availability of donor sites, mosaicplasty is not recommended for lesions measuring > 4 $cm^2$ [93]. Good clinical results can be achieved in the short term; however, there are concerns regarding the long-term results[94].

Osteochondral allograft (OCA) was first reported by McDermott in 1985[95]. Its advantage over autografts is that there is no donor site morbidity, and graft availability for larger defects is thus not a problem. Technically, the procedure is performed as mosaicplasty, but the graft size can be substantially larger. Chondrocyte viability was demonstrated for forty-five days, but decreased substantially after twenty-eight days when stored in a culture medium at 4°C[96]. The disadvantages of OCA include the risk of transmitting diseases and high financial burden[97]. Currently, OCA is not available in Norway. In a review by Familiari et al.[97], the OCA graft survival rate was 87% at five

years, declining to 73% at 15-years. Furthermore, a reoperation rate of 30% was found, but overall significant improvements in PROM could be expected.

#### 7.4.3.3 Chondroinductive techniques

Autologous Chondrocyte Implantation (ACI) was first reported by Lars Peterson, and Mats Brittberg et al. in 1994[98]. ACI consist of two surgeries. In the first (arthroscopic) surgery, the chondral lesion is evaluated, and chondral biopsies are taken in a less weight-bearing area of healthy cartilage. The chondral biopsies are then minced and treated with collagenase to isolate chondrocytes. The chondrocytes are cultivated in the lab for 2-3 weeks before the second (open) surgery. A debridement of the lesion is then performed before covering the lesion with a periosteum-flap sutured to the surrounding cartilage. The cultivated chondrocytes are then injected in the defect. ACI with periosteum-flap are commonly referred to as 1st generation ACI. The ACI treatment has since been modified. In 1st generation ACI, there was a problem with periosteal hypertrophy; thus a 2nd generation ACI where the periosteum flap was replaced with a collagen membrane was developed. The membrane/matrix used in the later generation of ACI was the same as that used in the previously described AMIC procedure. The initial results of 2nd generation were comparable to the 1st generation, but without the hypertrophy problem[99]. Later a 3rd generation ACI, referred to as Matrix-Induced Autologous Chondrocyte Implantation (MACI), was developed. In MACI, chondrocytes are injected into a collagen matrix, which facilitates a more even distribution of chondrocytes in the defect[99]. However, no randomised trials have demonstrated the superiority of MACI over 1st or 2nd generation ACI. Regardless of the generation used, several studies have suggested that good short-term and long-term clinical outcomes can be expected after ACI surgery[84, 99].

# 8. Background for the thesis

Focal cartilage lesions (FCL) in the knee are found in approximately 60% of arthroscopies of any reason[12-14]. Knee-related quality of life may be impaired at the same level in patients with FCL as in those with end-stage osteoarthritis[22]. However, FCLs can also be found on MRI scans of asymptomatic knees[16, 18, 20]. Hyalin cartilage, which covers the knee joint line, has little or no potential for self-healing[100]. Acute

FCL defects usually heal with fibrocartilage, which does not have the same biomechanical quality as that of hyaline cartilage. Several treatment options for symptomatic FCLs, both non-operative and operative, are available, as outlined in the previous chapter. No treatment has been proven to be consistently superior, and the optimal treatment is still controversial[84], especially in the longer-term. No treatment has been able to reliably restore the normal hyaline cartilage[100]. Furthermore, the ability to reduce the risk of later osteoarthritis has not yet been demonstrated in any available treatment of FCLs.

Patients with a history of knee surgery have been reported to be significantly younger at the time of knee arthroplasty than those in the general population[101]. The risk of KA after ACL surgery has been reported to be as high as 40% within 35 years[102]. Several long-term cartilage surgery studies have reported that some of the included patients later received KA[103-105]; however, the incidence of KA and its risk factors remain unknown.

Patient-Reported Outcome Measures (PROM) after knee arthroplasty in patients with ACL deficiency appear to be comparable to those in patients with primary osteoarthritis[102]. Few studies[106, 107] have reported patient-reported outcomes after knee arthroplasty in individuals with a previous FCL. However, these studies have several limitations, such as a small number of participants and only including patients treated with microfracture or the inclusion of patients with concomitant meniscal allografts. This limits their external validity and overall quality. The results of knee arthroplasty in patients with a previous FCL are thus largely unknown.

# 9. Objectives of the thesis

The overall aim of this thesis was to evaluate the long-term results in Norway after an arthroscopically verified FCL in the knee and to estimate the risk of subsequent knee arthroplasty surgery. Furthermore, to evaluate the results of knee arthroplasty in patients with a previous FCL.

The specific aims of each study were as follows:

### Paper 1:

1. To evaluate the long-term cumulative risk of knee arthroplasty in patients with arthroscopically verified focal cartilage lesions of the knee.
2. To investigate the risk factors for knee arthroplasty in patients with previous cartilage lesions.
3. Estimate the relative risk of knee arthroplasty in patients with arthroscopically verified focal cartilage lesions compared to the risk in the general population.

### Paper 2:

1. To evaluate the long-term patient-reported outcomes of arthroscopically verified FCL in the knee with Knee injury and Osteoarthritis Outcome Score (KOOS) Quality of Life (QoL) subscore.
2. To examine the need for subsequent cartilage surgery.
3. Identification of risk factors for treatment failure after an FCL.
4. Compare long-term patient reported outcomes and risk of treatment failure after different treatment options, including non-operative treatment of FCL.

### Paper 3:

1. To examine patient-reported results of knee arthroplasty following a focal cartilage lesion.
2. To compare these results with those of a matched national cohort of patients with knee arthroplasty.

## 10. Materials and methods

The large language model of paperpal.com has been used to grammatically proofread the thesis and improve the wording, but not to generate any text. The entire thesis is the work of the author.

### Patient cohort

Patients with arthroscopically verified focal cartilage lesions in the knee, treated surgically at one of six Norwegian hospitals between 1999-2012 were invited to participate in these studies. The six hospitals were: Haraldsplass Deaconess Hospital, St Olavs Hospital, University Hospital of North Norway, Martina Hansens Hospital, Oslo University Hospital and Akershus University Hospital. These hospitals were chosen because they had conducted or participated in several prospective cartilage studies during the study period. The inclusion and exclusion criteria for the cartilage cohort were as follows.

Inclusion:

- Minimum 18 years of age at the time of cartilage surgery
- Arthroscopically verified and classified focal cartilage lesion of the knee
- At least one PROM was documented at the time of the surgery.

Exclusion:

- Any cartilage lesion classified by the surgeon as osteoarthritis at the time of surgery.
- “Kissing-lesion” (FCL on both proximal and distal part of the same joint compartment)

Eligible patients were identified from previous research protocols as well as from the surgical administrative system at each hospital. As PROMs are not routinely registered in cartilage surgery at most hospitals, we anticipated that most eligible patients would have been included in at least one clinical cartilage study. From the surgical report or previous trial data, the following information was registered: any prior cartilage surgery; the location, size, and ICRS classification of the FCL; the type of cartilage procedure; any additional procedures; and the preoperative PROM. Patients registered as emigrated or deceased in the Norwegian Population Register were excluded from the study. Written consent was obtained from each patient prior to inclusion in the present studies. Each patient received by post a questionnaire regarding their present knee function, level of activity, any additional ipsilateral knee surgery weight, height,

and education level. The PROMs used at the index cartilage surgery were the pain VAS from the ICRS, Lysholm, and KOOS scores. The participants received the same PROM as that registered at the time of the index surgery. Additionally, all the included patients were asked to report their present KOOS scores. Final follow-up was performed between 6th of March and 31st of December 2020. Differences in baseline data between the included patients and those who did not consent to participate in the present study were examined using Student T-test and $\chi^2$-test as appropriate.

The studies included in this thesis were approved by the regional ethics committee (2017/1387) before the inclusion of patients. The data were stored in a Microsoft Access database at the Helse Bergen Research Server. SPSS and Stata were used for statistical analysis.

Power analysis:

Power analysis was performed prior to inclusion. To achieve an 80% chance of detecting a 4-times higher risk of knee arthroplasty in the focal cartilage lesion cohort than in the general population, we needed to include at least 181 participants.

A (before-after) difference of 10 units in the KOOS subscale was considered clinically significant. To have an 80% chance of detecting a significant (at the 2-sided 5% level), difference of 10 units in mean KOOS subscale values between the patient groups studied, with an assumed standard deviation of 20, 64 individuals in each group were required.

Paper 1:

All patients included in the cartilage cohort were included in Paper 1. The Norwegian Arthroplasty Register (NAR) has registered knee arthroplasty surgery in Norway from 1994 and has documented a >95% completeness of reporting[108]. After any knee arthroplasty procedure, the surgeon files a report to the NAR. The report contains information on the identity and general health of the patient, any previous knee condition or procedure, the presumed reason for osteoarthritis, the type and brand of the knee replacement impant, and the type of fixation of the arthroplasty[109].

Furthermore, any subsequent knee surgeries are also reported to NAR. In the present study, a patient was registered as having knee arthroplasty when their ipsilateral knee was registered in the NAR and/or the patient reported an ipsilateral knee arthroplasty in the questionnaire. Patients and their knees were identified based on their Norwegian 11-digit identification numbers and laterality in both the cartilage cohort and the NAR. Population data were recorded using the Norwegian Population Register.

Statistics:

The risk of knee arthroplasty was assessed using the Kaplan-Meier method[110], and Cox regression models were used to analyse the risk factors. A graphical causal model (www.dagitty.net/dags.html) was employed to determine the variables that required adjustment as recommended by Westreich and Greenland[111].

Preoperative Lysholm and ICRS VAS pain scores were documented for 185 and 114 patients, respectively, and none of the patients had recorded >1 preoperative PROM. The Cox model's linear assumption was validated using the Box-Tidwell procedure for the preoperative VAS pain score. Survival times were calculated as the duration between cartilage surgery and knee arthroplasty or the conclusion of the study on 31 December 2020. The proportional hazards assumption was met for all variables analysed, with the exception of the BMI group and ACL surgery (yes or no). Using a visual examination of the Kaplan-Meier plot, the two variables were individually assessed based on the duration of follow-up ($< 12$ or $\geq 12$ years). Additionally, a subset of patients who did not undergo any concurrent procedures at the time of the index procedure was examined using the same Cox model as described previously. The relative risk of undergoing knee arthroplasty after cartilage injury compared to the risk in the age-matched general population was assessed. The absolute risk of knee arthroplasty in the cartilage injury cohort was calculated by dividing the number of knee arthroplasties by the total number of knees with cartilage injury in each age-matched group. For the general population, the numerator was the number of all other patients undergoing knee arthroplasty without inflammatory arthritis or previous cartilage surgery, as reported to the NAR between 1 January 1999 and 31 December 2020. The denominator was the average number of Norwegian citizens in the same

period, retrieved from the Norwegian Population Register. The results were stratified into 10-year groups based on the age at the time of knee arthroplasty. To aid the clinical interpretation of the relative risk of knee arthroplasty in the cartilage injury cohort as compared to the general population, we also stratified each 10-year age group at the time of knee arthroplasty according to at what age the patient underwent the index cartilage procedure. For the general population, the absolute risk was estimated as described in the previous paragraph. In the cartilage injury cohort, the numerator was the number of knee arthroplasties in each 10-year age group (at the time of cartilage surgery) and the denominator was the total number of patients with cartilage injury in the same age group.

Paper 2:

The same cohort as in paper 1 was included in this study. The primary outcome was KOOS-QoL subscore at the final follow-up. Failure was defined as a subsequent KA, osteotomy, or KOOS-QoL score <50 at the final follow-up. KOOS QoL <50 is generally considered to be the Patients Acceptable Symptom State (PASS) after cartilage surgery[112].

Patients who had undergone a KA or an osteotomy of the knee were excluded from the PROM analysis, but were included in the analysis of treatment failure.

Multiple logistic regression models were used to identify risk factors for failure at the final follow-up, whereas multiple linear regression models were used to assess the factors influencing the KOOS-QoL score at the final follow-up. A Graphical Causal Model (www.dagitty.net/dags.html) was utilised to identify the variables that necessitated adjustment in the regression models, as proposed by Westreich [111]. A subset of patients, excluding those with patellofemoral lesions, was analysed using the same model. The time since cartilage surgery was calculated as the time between the index cartilage surgery and the questionnaire follow-up in the KOOS analysis and the end of the study on 31 December 2020 for the failure analysis. A paired sample t-test was used to assess the difference in PROM-score preoperatively and at the final follow-up.

Paper 3:

The 59 patients ( with 59 knees) from the cartilage cohort, who underwent subsequent knee arthroplasty, were eligible for this study. One patient was excluded because sufficient details regarding the arthroplasty surgery were not available. Thus, 58 patients who underwent subsequent knee arthroplasty after previous FCL were included.

A matched control group (1:3) was recruited from the NAR operated between 1994 and 2020, constituting 174 eligible participants. Patients in the NAR registered as deceased, having rheumatoid arthritis, having had a previous FCL, having undergone any type of cartilage surgery, or having a previous multi-ligament injury were excluded prior to matching. The FCL group and the control group were then matched on the following variables: year of birth (+/−10 years), sex, primary or revision arthroplasty (and cause of revision), type of arthroplasty (total, unicondylar, or patellofemoral), year of arthroplasty surgery, and the type and producer of the knee replacement implant. Patients eligible for the control group received the same questionnaire as the cartilage cohort in addition to the KOOS.

The demographic differences between the previous cartilage patients and the control group were evaluated using the Student T test and the $\chi^2$ test. Multiple linear regression models were employed to analyse the differences in KOOS sub-scores between the previous cartilage patients and the patients from the control group. The models were adjusted for the following variables: sex, age at the time of arthroplasty surgery, level of education, primary or revision arthroplasty, type of arthroplasty, body mass index (BMI) group, and any additional knee surgery before arthroplasty surgery, except cartilage surgery or purely diagnostic arthroscopy. The continuous variables in the model were evaluated and linear correlations were identified. Logistic regression models were utilized to estimate the odds ratio of not reaching the patient acceptable symptom state (PASS) for each KOOS subscore. These models were adjusted using the same variables as those in the multiple regression models. The PASS score for

KOOS subscores at 3 years follow-up after knee arthroplasty reported by Connelly et al.[113], with a threshold of a KOOS Symptoms score of 84.0, KOOS Pain 87.5, KOOS activities of daily living (ADL) 87.5, and KOOS QoL 66.0 was used.

# 11. Results

Of the 553 patients (563 knees) who were identified, 46 patients were registered as deceased or emigrated or did not have a valid postal address and were thus excluded. Five hundred and seven patients (516 knees) were eligible for the cartilage cohort in the present study, of which 322 patients (328 knees) consented to participate (referred to as responders). One hundred and sixty-four of those patients (169 knees) had participated in studies with previously published intermediate to long-term results[94, 114, 115]. At the time of index cartilage surgery, the responders were 3.0 years older (p=0,002) compared to the non-responders. There were no statistically significant differences in FCL size, ICRS classification, preoperative PROM, or sex between the responders and the non-responders.

The mean age at index cartilage surgery was 36,8 years and the mean duration of follow-up was 19.8 (CI 19.4-20.2) years. Most of the lesions were ICRS 3/4 (84.1%) and the mean size was 2.0 (CI 1.8-2.2) $cm^2$. At the final follow-up, 59 patients (18%) had undergone KA surgery at mean 12,7 years after the index cartilage surgery. Four patients (1.2%) had undergone later femoral- or tibial-osteotomy. There were no patients with more than one category of preoperative PROM registered; 8.8% had KOOS-scores, 56.4% Lysholm-score and 34.8% ICRS Pain-VAS registered preoperatively. Most patients had a pre-enrolment weight-bearing radiograph which did not show any joint-space narrowing. The radiographs were, however, not available for the study group.

Fig 3. Flowchart illustrating the inclusion of the patients in the cartilage cohort of studies 1 and 2.

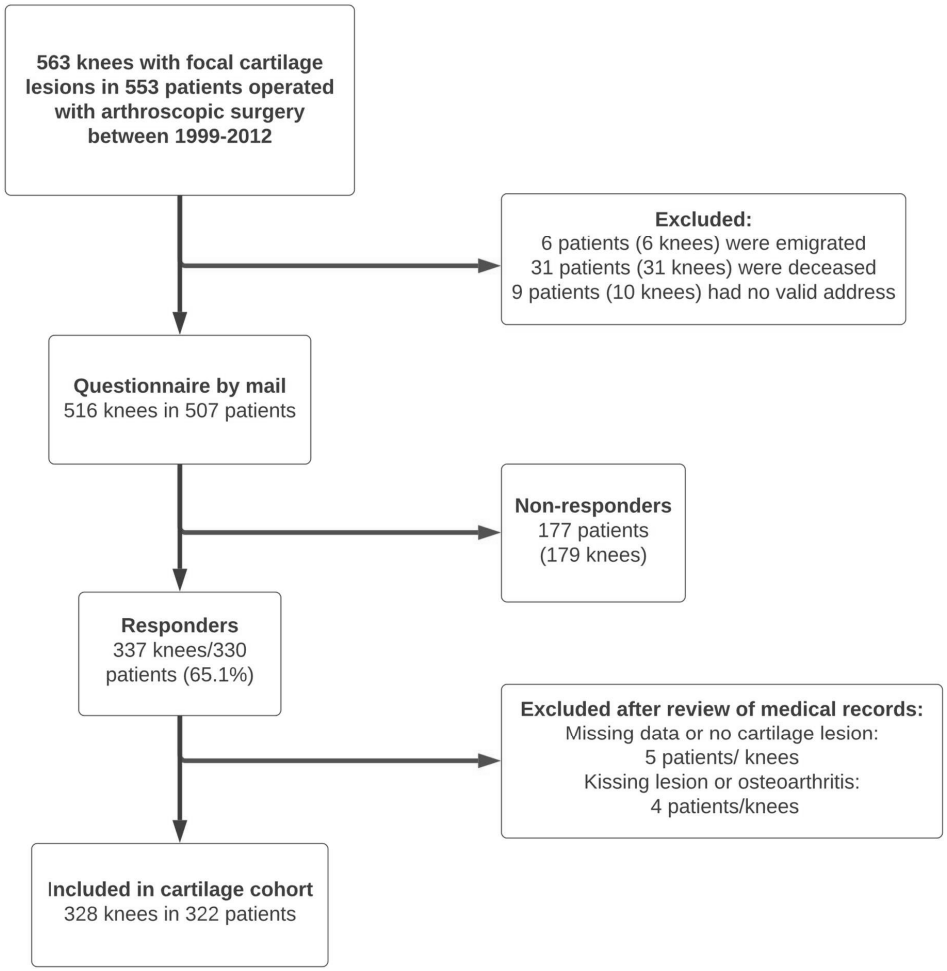


Table 1 Demographics and descriptive statistics of the 328 knees in 322 patients included in the cartilage cohort as presented in paper 1[116]

| | **Frequency or mean*** |
|---|---|
| Knees | 328 |
| Male/Female | 188(57%)/140(43%) |
| Right/left knee | 173(53%)/154(47%) |
| Age at the time of surgery | 36.8 years (35.6, 38.0) |
| Time from index surgery to end of study | 19.8 years (19.4, 20.2) |
| Cartilage lesion ICRS 1-2/ 3-4 | 52(16%)/276(84%) |
| Size of cartilage lesion ($mm^2$) | 201.3 $mm^2$(178.9, 223.7) |
| Location of cartilage lesion | |
| – Patellofemoral | 73 (22.3%) |
| – Medial | 204 (62.2%) |
| – Lateral | 51 (15.5%) |
| Type of treatment: | |
| – No cartilage treatment | 93 (28.4%) |
| – Microfracture | 124 (37.8%) |
| – Debridement | 10 (3.0%) |
| – ACI | 30 (9.1%) |
| – Mosaicplasty | 53 (16.2%) |
| – Other | 18 (5.5%) |
| Level of education: | |
| – High school | 155 (47.3%) |
| – Bachelor/Master degree | 164 (50.0%) |
| Body mass index (BMI) at end of study | 27.4 (26.9, 27.9) |
| – <25 | 100 (30.5%) |
| – 25-29 | 137 (41.8%) |
| – ≥30 | 75 (22.9%) |
| ACL reconstruction in ipsilateral knee | 50 (15.2%) |
| – At index surgery | 15 (4.6%) |
| – Before or after index surgery | 35 (10.7%) |
| – No | 278 (84.8%) |
| Meniscal resection in ipsilateral knee | 100 (30.5%) |
| – At index surgery | 46 (14.0%) |
| – Before or after index surgery | 54 (16.5%) |
| – No | 228 (69.5%) |
| Osteotomy | 4 (1.2%) |
| Knee arthroplasty | 59 (18.0%) |
| – Male | 39 (16.0%) |
| – Female | 29 (20.7%) |
| Knee arthroplasty (KA) | 59 (18.0%) |
| – Total KA | 48 (81.4%) |
| – Unicompartmental KA | 8 (13,6%) |
| – Patellofemoral KA | 3 (5.1%) |
| Age at the time of KA surgery | |
| – Male | 56.4 (53.1-59.7) years |
| – Female | 51.9 (47.6-56.1) years |
| Time(mean) from index cartilage surgery to KA | |
| – Male | 13.9 (11.9-16.0) years |
| – Female | 11.4 (9.0-13.8) years |

Paper 1:

Patients with arthroscopically verified FCL in the knee had a 19.1% (CI 14.6-23.6) 20-year cumulative risk of undergoing a KA procedure and a significantly increased risk of KA compared with the general population. The relative risk was particularly elevated in the younger population. The most important risk factors for knee arthroplasty were as follows: age >40 years at cartilage surgery (HR 3.7, CI 1.8, 7.7), overweight (HR 3.9, CI 1.7, 9.0) or obesity (HR 5.9, CI 2.4, 14.3), ICRS grade 3-4 lesion (HR 3.1 CI 1.1, 8.7), ACI treatment of the FCL (HR 3.4, CI 1.0, 11.4) compared to no surgical treatment), and higher VAS of pain at index cartilage surgery (HR 1.1 CI 1.0, 1.1). The size or location of the FCL did not significantly influence the risk of a subsequent knee arthroplasty. Neither did the patients' sex or educational level, nor any concomitant ACL reconstruction or meniscal surgery.

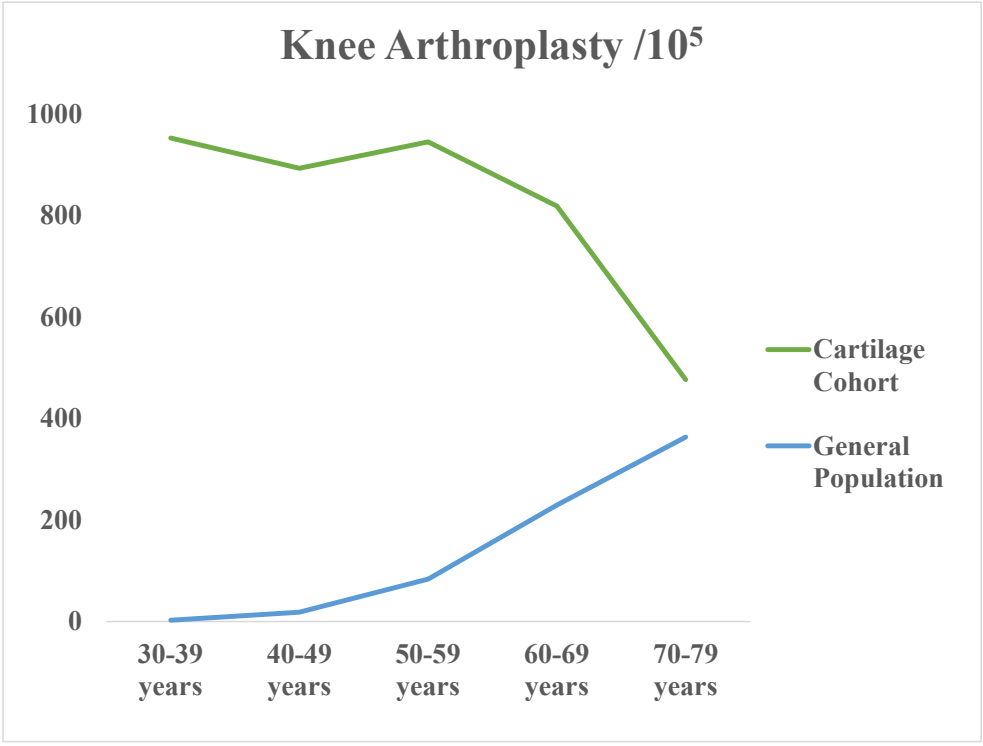



*Fig 4. The incidence of Knee Arthroplasty in 1999-2020 in the cartilage cohort and the general Norwegian population pr 100 000. Age at the time of knee arthroplasty surgery.*

Paper 2:

Patients with FCL in the knee, without undergoing subsequent KA or osteotomy procedures, had significantly better PROM at a mean of 19.8 years follow-up than preoperatively. At the final follow-up, 162 knees (49.4%) were classified as treatment failures, 59 patients had received knee arthroplasty, 4 had undergone osteotomy surgery and 99 patients had KOOS QoL subscore <50. The most important risk factors were: BMI 25-29 (OR 2.0, CI 1.1, 3.5 ) and BMI≥30 (OR 3.1, CI 1.6, 5.9), more than one cartilage lesion (OR 1.9, CI 1.1, 3.3), ICRS 3-4 lesions (OR 2.5, CI 1.3, 5.0) and lower level of education (OR 1.8, CI 1.1, 2.8). There were no statistically significant differences in mean KOOS-QoL subscore or the odds ratio of treatment failure between the non-surgically treated FCLs and the surgically treated lesions, except that ACI treatment was associated with significantly higher KOOS-QoL and decreased odds of treatment failure. Subsequent cartilage surgery had been performed in 47 (17,7%) knees as reported by the patients.

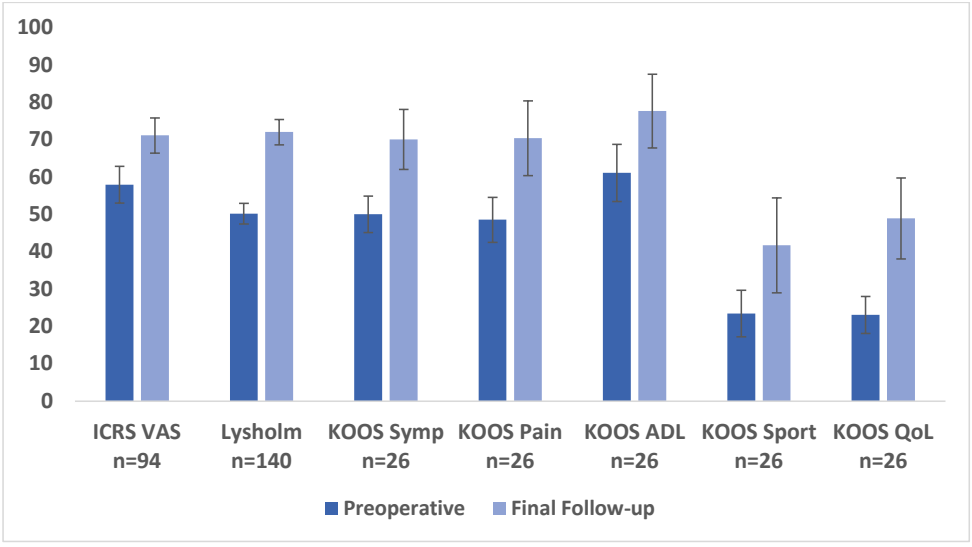



*Fig 5 Patient-reported outcome measures preoperatively at the time of index surgery and at the final follow-up. Bars presented with 95% confidence interval. ICRS VAS (Visual analogue scale) 100-no pain, 0-worst pain imaginable. N=Number of knees with this PROM registered preoperatively.*

Paper 3:

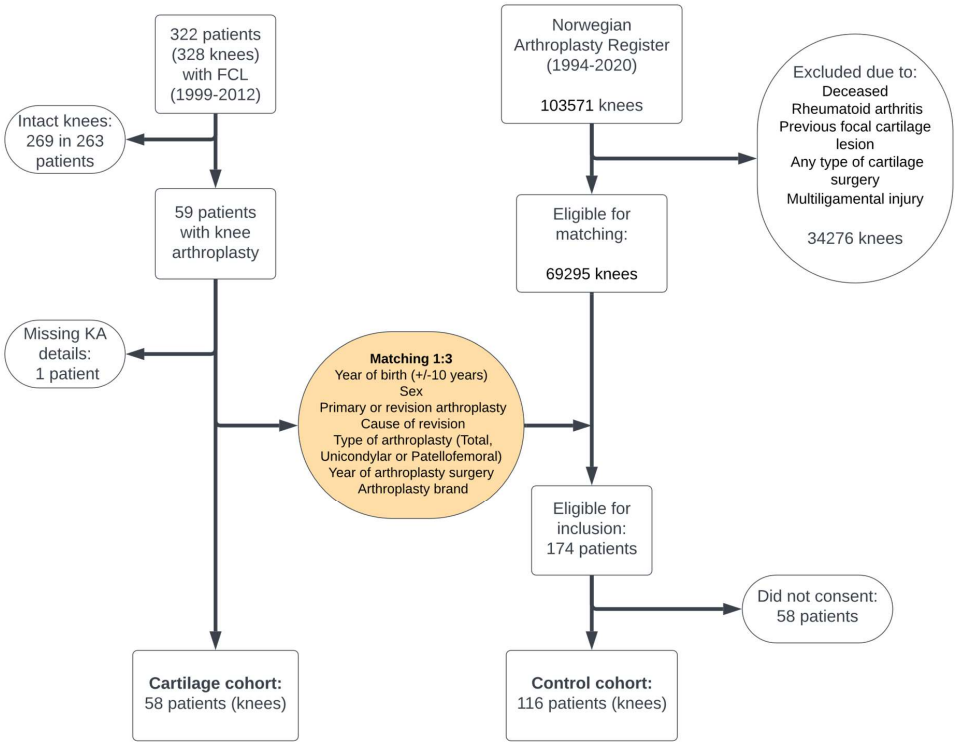



*Fig 6. Flowchart illustrating the inclusion process of the cartilage cohort and the control cohort in paper 3.* [117]

At an average of 8 years following knee arthroplasty, patients with a history of previous cartilage surgery demonstrated significantly lower scores for KOOS Symptoms (mean 8.4 points, CI 0.3, 16.4), Pain (mean 11.8 points, CI 2.2, 21.4), and QoL (mean 10.6 points, CI 0.2, 21.1) compared to the general population represented by a matched cohort from the NAR. Additionally, there were significantly lower odds of patients reaching the PASS threshold for the same KOOS subscores in the previous cartilage patients with Symptoms (OR 2.7, CI 1.2, 6.4), Pain (OR 3.0, CI 1.3, 7.0), and QoL (OR 2.4, CI 1.0, 5.5).

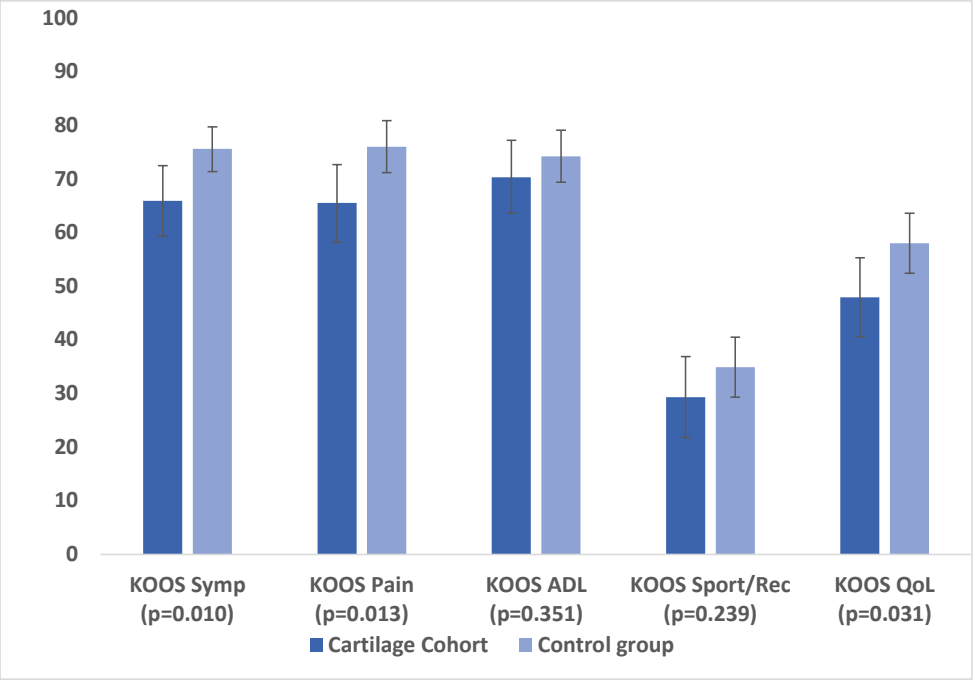



*Fig 7. KOOS score at final follow-up for the arthroplasty patients from the cartilage cohort and the control group. Mean score with 95% confidence intervals.*

# 11. Discussion

## 11.1 Study design

The studies included in the present thesis were retrospective cohort studies. However, several other study designs are available.

Randomised controlled trials (RCT) are at the highest levels of the scientific evidence pyramid and have been considered the gold standard for comparing treatments in medical science[118]. Randomisation ensures a more even distribution of potentially biasing factors between groups. However, RCTs also have several limitations, such as high cost, small sample size, and most often a shorter follow-up[119]. Owing to the strict inclusion criteria, concerns regarding the external validity of RCTs have been raised[119]. The reduced external validity of RCTs has also been demonstrated in cartilage patients[120]. Another problem in RCTs of cartilage patients is the choice of control treatment. Microfracture has been treated as the gold standard, despite the lack of

evidence for such a status, and has been used as the control group in several RCTs of newer treatment options[82]. To the best of our knowledge, there are no published RCTs comparing surgical treatment of cartilage lesions with non-operative treatment or sham surgery.

Register-based studies have good external validity and several advantages in evaluating rare outcomes or side effects[119, 121]. One disadvantage is that the ability to adjust for confounding factors is limited by the variables registered[119]. Cartilage registries, such as the German Cartilage Registry (KnorpelRegister DGOU)[122, 123], can be used to monitor outcomes after cartilage treatment. However, the KnorpelRegister only includes surgically treated lesions. Currently, there is no Norwegian Cartilage Registry. Any previous knee surgery should be reported to the Norwegian Arthroplasty Register (NAR); thus, NAR seems to be a good option for evaluating the risk of subsequent knee arthroplasty after an FCL. However, only 9 (15,3%) of the 59 patients with subsequent KA in the cartilage cohort of the present thesis were registered with previous cartilage surgery in the NAR. This suggests that NAR cannot be used to evaluate the risk of KA based on the indication for any previous knee surgery due to poor reporting completeness of this variable.

In this thesis, we used a retrospective cohort design to have a better chance of recruiting an adequate number of patients for the long-term follow-up of patients with arthroscopically verified focal cartilage lesions. The retrospective design also has several limitations, including selection and recall bias, as well as the limited number of variables registered at the time of index surgery as the most important[124]. Selection bias refers to the possibility that the patients responding to the questionnaire might not be representative of those who did not want to participate in the present study. Furthermore, recall bias might have occurred in the study cohort, as patients who underwent surgical cartilage treatment might be more likely to remember any subsequent cartilage treatment than those in the non-surgically treated group. Our study was also limited by the variables registered at index cartilage surgery. Information regarding BMI and level of activity at the time of surgery would have been valuable.

### 11.2 Cartilage cohort

In the present thesis, we recruited patients with arthroscopically verified FCLs of the knee who underwent surgery between 1999 and 2012. This timeframe was chosen for several reasons. First, we did not include patients who underwent surgery after 2012 in order to have a long-term follow-up. In long-term follow-up, there is always a risk that the treatment options used are no longer relevant as new treatment options have been introduced. In the 90's several of the modern cartilage treatment options was introduced, as described in the introduction[80, 92, 98]. The surgical procedures most frequently used in the cartilage cohort of the present thesis, debridement, Mfx, ACI, and mosaicplasty, are still regarded as valid options[125].

Furthermore, during this period, the collaborating six Norwegian hospitals conducted or participated in several clinical cartilage studies[15, 126-129]. Participating in clinical studies might increase the level of detail recorded regarding FCL size and depth, as well as recording a PROM. However, recruiting participants from the previous studies may have decreased the external validity of our study[120]. Engen et al.[21] identified 10830 knee cartilage surgeries in Norway between 2008 and 2011 in a study from the Norwegian Patient Registry. Thus, our cohort of 321 patients may not be representative of the average Norwegian cartilage patients. However, the undetailed inclusion and exclusion criteria of our study resulted in a heterogeneous cohort, which may have increased external validity.

There were no upper age limits in the inclusion criteria. Degenerative cartilage lesions and osteoarthritis occur more frequently in the older population. There is a risk of including patients with early osteoarthritis when participants over 50 years of age are included. Most patients in our cartilage cohort underwent preoperative radiography without radiographic signs of established osteoarthritis[116]. Further in Study 1, we also found a tendency, but not statistically significant, towards a decreased risk of KA in older patient groups compared to the age-matched general population[116]. A possible explanation is that older patients with an FCL have less cartilage changes than their peers at the same age. Thus, this finding might indicate that the treating surgeons' classification of the cartilage lesions as non-degenerative was correct even in older patients.

Body Mass Index (BMI) was registered during the index cartilage surgery in only 146 patients. Thus, the regression models could not be adjusted for BMI at index surgery but only for BMI at the final follow-up because of listwise deletion. This must be considered a limitation of the present study, as the BMI at index cartilage surgery is likely a more important factor in determining the outcome of cartilage treatment. It is possible that patients with poor knee function after the index cartilage treatment have been less active, which might have contributed to the higher BMI in the poor knee function group. In other words, it could be that poor knee function predicts a higher BMI and not vice versa. The proportion of both men and women with a BMI >25 has increased in the general Norwegian population from to 1999-2020[130]. Whether the same increase has occurred in the cartilage cohort remains unknown.

NAR does not include any details about BMI prior to 2021. Thus, knee arthroplasty patients in the general population could possibly have a significantly different BMI than those in our cohort. However, in 2021 84.1% of the knee arthroplasty patients reported in NAR[131] had a BMI >25 compared to 86.5% of the patients with subsequent knee arthroplasty in the cartilage cohort. Furthermore, in 2020, the mean BMI of Norwegian men were 26.5 kg/m$^2$ and women were 25.6 kg/m$^2$ [132]. A BMI >25 were found in 59% and 47% of male and female patients, respectively[132]. The corresponding numbers at the final follow-up in our cartilage cohort were BMI 28.1 for men and 26.4 for women, and BMI >25 was found in 78.1% and 53.6% of the patients, respectively. This suggests that the BMI in our cartilage cohort was slightly higher but still comparable to that of the general Norwegian population.

## 11.3 Strength of the study

The main advantage of the present study design was the inclusion of a large number of arthroscopically verified focal cartilage lesions. Furthermore, any concurrent meniscal or ligamentous lesion was registered during the index cartilage surgery, and the patients reported any subsequent ipsilateral knee surgery. Even though the exact alignment of the patient's leg remains unknown due to the lack of a standardised preoperative radiographic protocol, the included patients had < 5° malalignment due to

the inclusion criteria in previous clinical trials. A mean follow-up period of 20 years increased the ability to identify the long-term cumulative risk of knee arthroplasty. To our knowledge, this is the first long-term study outside an ACL cohort, including arthroscopically verified FCL patients undergoing no surgical cartilage treatment [133, 134] and comparing PROM between non-operative cartilage treatment and surgically treated lesions. This enhances our knowledge of the natural history of an FCL. NAR had a 97% completeness of reporting throughout the study period and as such the follow-up of knee arthroplasty procedures can be regarded as complete[131, 135].

### 11.4 Limitations of study design

This study has some limitations. First, 150 of the patients had participated in studies with previously published long-term results [94, 114, 115]. Thus, they may not be representative of an average patient with FCL[120]. Secondly a response rate of 65% might have introduced bias in the interpretation of the results. This is an observational study, and the differences in the final frequency of knee arthroplasty and PROM results should be interpreted with caution. The number of participants suggested by the power analysis was not met in all subgroups, increasing the risk of type-2 error. Several of the patients did not provide sufficient details of any subsequent cartilage treatment after the index surgery. Three different PROMs were used preoperatively, and none of the patients had more than one preoperative PROM. Owing to list-wise deletion, this limited the adjustment of the regression models based on PROM data. Furthermore, standardised preoperative radiographic images were unavailable. Owing to the study design and long-term follow-up, any association between the findings at index surgery and follow-up cannot be interpreted as a correlation[124].

### 11.5 Outcome evaluation

In a long-term follow-up of patients with a history of focal cartilage lesions in the knee, several outcomes could be registered. In this thesis, the primary outcomes were the need for a subsequent knee arthroplasty and the patient-reported KOOS subscores. Knee arthroplasty is the hallmark of end-stage symptomatic osteoarthritis and must be considered a failure after cartilage surgery. However, there is substantial variation in the frequency of knee arthroplasty between different geographical regions[136]. Thus,

there could be variations in defining the indications for knee arthroplasty between different hospitals. Including standardised radiographs at the follow-up could potentially have demonstrated a variation in the indication for knee arthroplasty and made adjustments in the statistical analysis possible. Standardised radiographs of a patient cohort from all over Norway would be a logistic challenge and have a high financial cost. The number of patients consenting to participate in the study would also likely have been lower. Furthermore, there seems to be a limited association between the severity of osteoarthritis and patient reported outcomes[137, 138]. Thus radiographs at follow-up was not included in the study protocol.

As outlined in the paragraph concerning PROMs in the introduction, there are several different PROMs available for the use in patients with knee conditions. These PROMs are frequently used to evaluate outcomes, even when there is a lack of validation in patients with that particular condition. KOOS is one of the few PROMs that has been validated in patients with focal cartilage lesions, osteoarthritis, as well as knee arthroplasty[45-48]. KOOS has been frequently used since it was first presented in 2003 and is currently the main PROM used by the Norwegian Knee Ligament Register and NAR. Thus, we chose the KOOS as the primary PROM in this study.

A statistically significant change in a PROM does not necessarily imply a clinically relevant change in experienced function of the knee by the patient. The importance of the minimal clinically important difference (MCID) and patient-acceptable symptom state (PASS) has been acknowledged in recent years[139]. A change in PROM above the MCID suggests that the patient perceives better or worse knee function after treatment, whereas any change below the MCID could be due to “measurement error” in PROM[139]. A PROM score above the PASS threshold suggests that the patient have a satisfactorily knee function. The PASS threshold must be established for each PROM, and for each knee condition in which it is intended to be used and may vary substantionally[139]. An analysis of the percentage of patients reaching the KOOS PASS threshold was thus included in both Papers 2 and 3 to evaluate whether the difference in PROM between the groups was clinically relevant.

## 11.6 Results

*Paper 1*

Apold et al. identified increased BMI and heavy labour as risk factors for KA in the Norwegian general population[29]. In a large cohort study including more than 4500 patients with osteoarthritis Salis et al[140]. demonstrated a linear (positive) association between weight loss and a decreased risk of KA. The risk of KA was reduced by 2% for every kg of weight loss. In our study, being overweight at follow-up was associated with an increased risk of having a knee replacement.

Several long-term clinical trials report subsequent KA after cartilage surgery[104, 141, 142]. Ogura et al. reported an incidence of 20% KA surgeries in a 20-year follow-up period of first generation ACI, which is consistent with our results[104]. Gobbi et al.[105] presented 15 years follow-up of FCL treated with microfracture in an athletic patient cohort. The authors reported progression of osteoarthritis in 40% of the knees, with 11% failures defined as subsequent surgeries at the final follow-up. Whether any of these were KA were not specified. Older age at the time of cartilage surgery and large or multiple lesions were the main risk factors for OA. Possible explanations for the high rate of KA in our study may be our somewhat older patient cohort (36.8 vs 31.4 years) as well as five years longer follow-up. Differences in KA frequencies at the population level between regions, as demonstrated by Ackerman[136], might also contribute to the differences in KA incidence.

In a study of 158 000 patients who had undergone chondroplasty in UK-NHS hospitals, Abram et al. demonstrated a higher risk of KA compared with the general British population[143]. The overall risk of KA within five years was 17.6%. Both age and sex were identified as risk factors for later KA. While Abram et al. did not have information on BMI, they found that a higher Charleston comorbidity index increased the risk of KA. The Abram patient cohort was older than our cohort, with a mean age 51.7 years. This is likely the reason for why the five-year risk of KA in the UK chondroplasty cohort was approximating the twenty-year risk in our study.

Both ACL injury and meniscal lesions are known to increase the risk of osteoarthritis and subsequently TKA[31, 101, 144-147]. Furthermore, in a meta-analysis by Whittaker et

al.[148] both cartilage lesions and concomitant meniscal resection were demonstrated to increase the risk of later KA in patients with previous ACL surgery. In the present cartilage cohort, meniscal resection and ACL surgery were not associated with an increased risk of KA. One possible reason could be that cartilage lesions increase the risk of KA to a greater extent than ACL and meniscal injuries, thereby obscuring the effect of the latter. Visnes et al. found that patients aged 30-39 years had a three-fold higher risk of KA after ACL surgery compared to the general population, while those aged 40-49 years had a doubled risk.[149]. In our cartilage cohort, the corresponding numbers were 416- and 49-times increase in risk. In a large registry study of 50 000 patients with knee osteoarthritis, Gustafson et al.[150] demonstrated an increased risk of KA in patients with previous knee surgery. Interestingly, Gustafson et al.[150] found a strong association between patients' desire for surgical treatment and subsequent KA. The patients in our cohort have had previous cartilage surgery and several of them additional knee surgery and as such might have a stronger believe in surgery. Thus, a stronger desire for a surgical solution for their knee condition might contribute to the increased risk of KA in the cartilage cohort.

In Paper 1, we found that ACI treatment of cartilage lesions increased the risk of subsequent KA by four times compared with no treatment. This finding was surprising because ACI treatment, in contrast to mosaicplasty and microfracture, does not violate the subchondral bone. ACI was performed as an open surgery and required two surgeries, which may increase the risk of knee arthroplasty[101, 145].

To reduce the risk of including asymptomatic lesions in the non-surgically treated group, we performed a subanalysis of patients without any concurrent procedures at the time of index surgery. The subanalysis revealed no significant differences between treatment groups. This might suggest that our finding of increased risk following ACI could be due to confounding factors. However, the subanalysis might be underpowered and thus prone to type 2 error. According to a Cochrane review, there is insufficient evidence of the superiority of ACI over other cartilage treatments[151]. In recent years, high-volume orthopaedic surgeries, such as meniscal surgery in middle-aged patients, have not been shown to be superior to sham surgery or nonoperative treatment[152, 153].

Consequently, we would suggest that future clinical trials on the treatment of FCL in the knee should include a control group treated non-operatively or preferably with sham surgery[154].

Paper 1 has several limitations. This is not a randomised trial, and the indications for different cartilage treatments might vary significantly. The ACI and several of the Mfx patients were, however, previous randomised trial participants which reduced the risk of selection bias. Patients undergoing cartilage surgery might have had more symptomatic lesions than those who were not surgically treated. There may also be unknown confounding factors that influence KA risk, such as genetic disposition[26]. There were few knee arthroplasties in the younger age groups, resulting in wide confidence intervals.

*Paper 2*

*Long-term PROM results*

In Paper 2, we found a mean KOOS-QoL of 58.1 at the final follow-up in patients without subsequent knee arthroplasty. In a series of 44 patients, Ossendorf et al[155] found a KOOS-QoL score of 49 in patients with 1st generation ACI treatment versus 64 in patients with microfractures. Furthermore, Kreuz et al[156] and Niemeyer et al. [157] found KOOS-QoL of 58.0 and 54.3 respectively, in their studies. Even though the present study has considerably longer follow-up, the PROM results are likely comparable as several previous studies have suggested stable results from mid- to long-term follow-up[94, 104, 115, 156]. In contrast, Gobbi et al[105] presented 15 years follow-up of 67 athletes with full-thickness lesions treated with microfractures, with a final KOOS-QoL of 82.2. The higher KOOS score might be due to the more active study population, as physical training has been shown to increase the KOOS score in patients with FCL[23]. Multiple lesions were associated with inferior KOOS QoL. A possible explanation could be that multiple lesions alter knee homeostasis more[158].

A lower education level was associated with inferior KOOS. A higher risk of heavy manual labour and a lower level of physical exercise may contribute to this.

Furthermore, a lower socioeconomic status is known to decrease self-reported general health[159].

Medial and lateral FCLs were associated with significantly better KOOS-QoL scores than retropatellar lesions. The inferior result in patellar lesions is consistent with previous studies[97, 160, 161]. Using the same regression model, a subgroup without PF lesions was analysed with the same overall results, indicating that the original statistical model was able to adjust for FCL location (Supplementary Table 2, Paper 2).

Seifeth et al.[162] presented a propensity matched study from the German Cartilage Register demonstrating that previous cartilage surgery was associated with decreased PROM within 3-years follow-up after ACI surgery. Any non-cartilage knee surgery did, however, not influence the patient reported outcome after ACI. The latter finding of Seifeth is consistent with the finding of no association between ACL and meniscal surgery and the KOOS QoL in the Paper 2 study.

In a systematic review of prognostic factors for the clinical outcome of FCLs in knees treated with microfracture, Van Tuijn et al.[163] identified several factors associated with inferior outcomes. Inferior PROM was found in older patients, patients with larger FCL size, previous or concomitant knee surgery such as meniscal resection or ACL reconstruction, and in patients with longer duration of symptoms preoperatively. There was, however, inconclusive data regarding the correlation between BMI and clinical outcomes. The findings of Van Tujin et al.[163] contradict the findings of Paper 2, where elevated BMI was strongly associated with inferior KOOS-QoL. Furthermore, there were no significant associations between patient-reported outcomes and lesion size, patient age, or any concomitant knee surgeries.

### *Subsequent cartilage surgery*

At the final follow-up, 47 knees (17.7%) had undergone subsequent cartilage surgery. Niemeyer et al[157] reported in a study of ACI patients that 28.6% required additional cartilage surgery. This is consistent with the findings of Ossendorf et al[155] with 34% of reoperations. In the present study, there was no significant difference in the rate of subsequent cartilage surgery between the treatment groups, although there was substantial variation. This finding suggests that the analysis was underpowered. We

did not have detailed data on the nature of subsequent cartilage surgery, and variations in the type of surgery between the groups could be substantial.

*Risk factors for treatment failure*

The failure rate, defined as KA, osteotomy, or KOOS-QoL score <50, was nearly 50%. Several other studies have defined any subsequent cartilage surgery as failure[104, 105, 114, 157]. From a 20-year perspective, any subsequent surgery might not be the best measure of failure. KA is the final outcome of end-stage osteoarthritis and must be considered a failure in cartilage surgery. However, the risk of undergoing a knee replacement may vary considerably between countries as well as regions of a country[108, 136]. To compensate for this, we also classified patients scoring <50 on the KOOS-QoL sub-score as treatment failure, as Chahal et al[112] demonstrated this to be the Patient Acceptable Symptom State (PASS) in patients with FCL. The failure rate of 50% seems high. Nonetheless, as previously discussed, the mean KOOS-QoL score in the present study is comparable to that of other long-term studies.

More than one FCL was associated with an increased odds of failure, consistent with the results of Gobbi et al[105]. Furthermore, an increased BMI is a known risk factor for both KA and lower KOOS-score even in the general population[50, 136].

*Long-term PROM and risk of failure in different Cartilage treatment strategies*

We found an increased KOOS-QoL score in ACI patients compared to other treatment strategies, including no surgical treatment. In contrast Ossendorf et al[155] found that microfracture patients had significantly higher scores than the ACI patients. However, their analysis was not fully adjusted for significantly larger defects in patients with ACI, which might introduce bias.

In the paper 1 study on the same cartilage cohort, we found that ACI treatment increased the risk of KA[116]. Considering this, it is notable that the ACI had the lowest overall risk of failure. Even though the higher risk of KA is concerning, the number of patients scoring themselves below PASS was considerably higher in the other treatment groups. Possibly the ACI patients have been more prone to receive a KA than the other patients. Cartilage allografts are not available in Norway, and revision

options in cases of a large failed ACI treatment may be limited. This may partly explain the higher KA rate.

This study included a heterogeneous cohort of patients. However, our findings highlight the need for long-term follow-up of RCTs**,** as also suggested in a review by Orth et al[164], as well as in cartilage registry studies. Furthermore, inclusion of a sham-surgery arm in future RCTs should be considered.

*Paper 3*

The principal findings of the present study were that, at an average of eight years following knee arthroplasty, patients with a history of previous cartilage surgery demonstrated significantly lower scores for KOOS Symptoms, Pain and QoL compared to a matched cohort from the Norwegian Arthroplasty Register. Additionally, there were significantly lower odds of reaching the PASS threshold for the same KOOS sub-scores in the patients with previous arthroscopically verified focal cartilage lesions.

Failure of FCL surgery with residual symptoms poses a clinical challenge[165]. In the absence of osteoarthritis, resurfacing with mini-implants has gained popularity and has been advocated in a recent consensus paper[165]. In the present study, all of the previous FCL patients were reported to have osteoarthritis at the time of knee arthroplasty by the treating surgeon. Preoperative radiographs were not available to the research group, but it is likely that the surgeon no longer considered the condition as a focal cartilage lesion, but rather as osteoarthritis in one or more knee compartments.

In a study of 972 patients from the NAR, Lygre et al[166] reported similar or slightly better KOOS sub-scores than in the control group in the present study. The tendency towards better KOOS scores in their study might be explained by an older patient population (76 years vs. 67 years in the control group in the present study), as younger age has been shown to predict poorer PROMs in knee arthroplasty patients[167]. Furthermore, Lygre et al. included only primary TKAs. Nevertheless, this might suggest that the KOOS sub-scores in the control group were representative of the average knee arthroplasty patients in Norway.

Several studies have reported no correlation between previous knee surgery and PROM scores in knee arthroplasty patients[168-170]. However, a recent meta-analysis by Zhang et al.[171] found that previous knee surgery had a negative effect on postoperative PROMs in patients undergoing knee arthroplasty. Furthermore, Khan et al.[172] demonstrated significantly lower KOOS JR, and lower odds for reaching both MCID and PASS in knee arthroplasty patients with previous meniscal resection compared to a cohort of patient without previous knee surgery. In a systematic review by Syrikas et al.[173] a negative association was demonstrated between fracture-related post-traumatic osteoarthritis and PROM following knee arthroplasty. These findings suggest a likely association between previous knee surgery and PROM after knee arthroplasty. In the present study, patients in the cartilage cohort underwent significantly more surgical procedures in addition to cartilage surgery than those in the control group. To account for possible confounding from these additional procedures in the analysis of the KOOS score, the regression models were adjusted for any additional surgical procedures apart from cartilage surgery and purely diagnostic arthroscopy. The sensitivity analysis (Paper 3, Supplementary Table 1) without this adjustment also demonstrated inferior results in the cartilage cohort for KOOS Symptoms and Pain, but not for QoL. This finding supports those of Zhang et al.[171].

There were also significantly more revision arthroplasties performed in the cartilage cohort. Although this variable was part of the matching procedure, a complete match was not achieved because of variations in response rates. Thus, the regression models were adjusted for primary versus revision arthroplasties. The sensitivity analysis, including only primary knee arthroplasty (Paper 3, Supplementary Table 2), showed results equivalent to those of the original analysis, indicating that the models were adequately adjusted for revision knee arthroplasty.

KOOS Symptoms-, Pain-, and QoL-subscore after knee arthroplasty were significantly lower in the previous cartilage cohort. This concurs with the findings of Ansari et al.[106] in a cohort of 21 previous microfracture patients, with a mean 7.8 points lower improvement in the Knee Society Score (KSS) in the cartilage cohort compared to a matched group of knee arthroplasty patients. However, the difference in KSS was below the clinically important difference demonstrated by Lizaur-Utrilla et al.[174].

Ansari et al.[106] did not report any power analysis prior to analysing the KSS results, and the power analysis in the present study suggests that the Ansari study was underpowered.
Frank et al.[107] presented 13 knee arthroplasty patients with previous chondral auto/allograft matched 1:1 to a cohort of knee arthroplasty patients with osteoarthrosis, finding a mean KSS improvement of 16 points lower in the cartilage cohort. However, they included patients with concomitant meniscal allografts in their cartilage cohort, which could have substantially confounded their results.

This is to the best of our knowledge the first study of patient-reported results in knee arthroplasty patients with previous cartilage lesions where PASS was reported. Reporting the percentage of patients who reached the PASS threshold offers several advantages, as outlined in a recent review by Mabrouk et al.[139]. This ensures that the identified differences are not only statistically significant but also clinically relevant. Significantly better odds of reaching the PASS threshold in the control group than in the cartilage cohort for KOOS Symptoms, Pain and QoL subscores were found, and PASS was not reached by two-thirds of the cartilage cohort. This supports the findings of lower KOOS sub-scores in the cartilage cohort.

The reason for the inferior results in the cartilage cohort remains unclear. However, several explanations for why previous focal cartilage lesions still seem to result in inferior patient satisfaction after knee arthroplasty could be considered. There is likely to be a substantial selection bias, in which cartilage patients require knee arthroplasty. Satisfied cartilage patients with an adequate knee function are not likely to require knee arthroplasty. Psychological factors have been shown to influence PROMs[175] and knee arthroplasty patients with failed cartilage surgery may have more psychological issues than average knee arthroplasty patients. In a recent review by Olsen et al.[176], preoperative pain catastrophising was associated with worse pain in patients who had undergone knee arthroplasty. Furthermore, Sellevold et al[177] found preoperative duration of pain, and psychological stress to be associated with less improvement after knee arthroplasty surgery. Arendt-Nielsen et al.[178] demonstrated central pain sensitisation to play an important role in the perception of pain in patients with severe

osteoarthritis. Again, the duration of chronic pain seems to be associated with increased central pain sensitisation[179]. The cartilage cohort may have experienced a longer duration of knee pain prior to knee arthroplasty than the control group. One or more FCLs have been shown to alter knee homeostasis[158], potentially reducing knee function even after knee arthroplasty.

The main strength of the present study was the large number of included patients with KA after a previous arthroscopically verified and symptomatic FCL in the ipsilateral knee. The follow-up after KA surgery was mid- to long-term, and several studies have shown stable PROMS from one year postoperative in KA patients[180-182], The previous FCL patients with patellofemoral or unicompartmental KA, had received KA in the same compartment as the previous FCL was located. This suggests that there may be a correlation between the FCL and later KA. The participants reported any additional ipsilateral knee surgeries in the questionnaire. This reduced the risk of not recording any additional surgeries performed at another hospital.

This study has several limitations. We failed to include the necessary number of FCL knees required by the pre-inclusion power analysis, falling six knees short. To reduce the risk of underpowered analysis, we included an analysis of whether or not the patients scored above the PASS threshold for KOOS subscores. This has been shown to be a robust strategy for demonstrating clinically important differences in a recent review by Mabrouk et al[139].

Furthermore, we did not have access to radiographs obtained before KA surgery, and there could be discrepancies in the degree of osteoarthritis in the FCL and control groups. Dowsey et al[137] however, found no association between the Kellgren-Lawrence score and preoperative PROM in patients with KA. Preoperative PROM was not available, which has been shown to be an important factor in determining postoperative PROM score[183-185]. There could have been a discrepancy in the preoperative KOOS scores between the groups. However, several studies have demonstrated that cartilage patients have similar KOOS QoL subscores to patients

awaiting KA [22, 186], indicating that preoperative PROM in the cartilage cohort might be similar to that in the control group.
Even though the control group was matched, there were differences in the distribution of age, education level, and revision TKA owing to uneven response rates in the matched control group. This resulted in unbalanced groups, necessitating adjustments using regression models.

Improvements in function and satisfaction are provided by knee arthroplasty, regardless of the type of implant, in patients with osteoarthrosis[187]. This seems to be true also in the context of previous FCL[107]. However, the present study suggests that both surgeons and patients should be aware of the lower improvement in PROMs after knee arthroplasty in cases with a history of previous focal cartilage lesions as part of shared decision-making.

## 11.7 General considerations of the thesis

Untreated cartilage injuries have limited healing potential and may progress to osteoarthritis, and reversing this process is often an aim in cartilage treatment[99, 103, 129]. However, scientific evidence for the ability of any cartilage treatment to stop or reverse the development of osteoarthritis is limited. In Paper 1, we demonstrated that there is a significant increase in the risk of receiving knee arthroplasty in patients with previous arthroscopically verified cartilage lesions compared with the general population. The risk of KA was particularly high in patients aged < 40 years. Furthermore, cartilage surgery does not seem to reduce the risk of subsequent arthroplasty compared with no surgical treatment. Previous studies have demonstrated a slight increase in the risk of osteoarthritis in patients with previous ACL reconstruction compared to that in patients with non-operative treatment[188]. The finding of no correlation between knee arthroplasty risk and operative vs. nonoperative treatment of FCLs suggests that the indication for any cartilage surgery should be based on the patients' current knee symptoms and not on the fear of any risk of later osteoarthritis.

As previously discussed in the introduction, focal cartilage lesions are frequently observed in the knees. In a study from the American College of Surgeons National Surgical Quality Improvement Program database, Gowd et al.[189] demonstrated a significant increase in cartilage surgeries in the US between 2010 and 2016 (4.4% per year). In contrast Engen et al[21]. found a slight decrease in cartilage surgeries in Norway in 2008-2011 but the incidence of cartilage surgery in Norway seemed to be only slightly lower than that in the US at that time point. Gowd et al[189]. found a particular increase in more advanced cartilage procedures, such as arthroscopic osteochondral allograft and ACI, with an increase of > 600% for both procedures during that period. However, there was no significant increase in the prevalence of chondroplasty or microfractures. Advanced cartilage surgeries, such as allografts and ACI, are substantially more expensive than microfractures or debridements. Although most available surgical cartilage procedures are cost effective[190], Aae et al[81]. demonstrated that ACI are less cost-effective than microfractures in a review of Level 1 and 2 studies. Thus, it is interesting that the increase in cartilage surgery seems to be entirely in the more advanced and expensive procedures. However, this is consistent with recent literature recommending microfracture in only smaller cartilage lesions[191-194].

Currently, there is no scientific evidence for the optimal treatment of focal cartilage lesions. Several authors, such as Brittberg[191] and Hinckel et al.[125], have proposed guidelines for the treatment of cartilage lesions based on available literature.

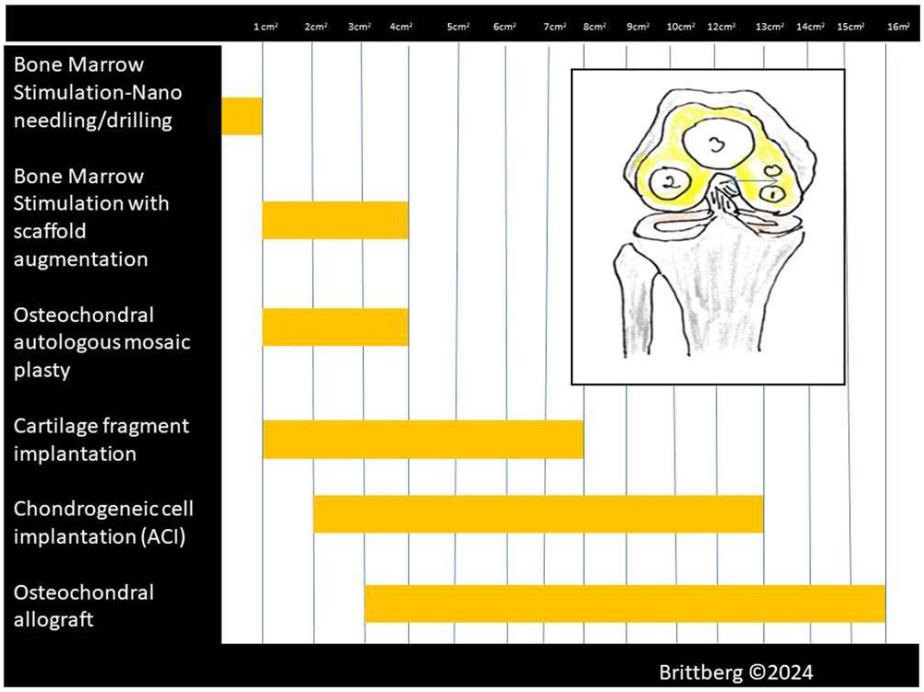



*Fig 8 Proposed treatment algorithm related to cross-section area of the lesions by Brittberg 2024[191]. Reprinted with permission.*

Additionally, focal inlay implants may be an alternative to failed biological cartilage treatments. In a recent consensus paper from the German Knee Society and ESSKA[165], there was a high degree of consensus in the international expert group that focal metal inlay implants are a treatment option for full-thickness cartilage lesions that have failed previous conservative or surgical treatments. However, there are concerns regarding the revision rates in the Australian Joint Replacement Registry, with revision rates as high as 38.8% after ten years. In contrast, Christensen et al.[195] reported a more acceptable 80% survival rate after 10 years in the Danish Knee Arthroplasty Registry, and Megaloikonomos et al.[196] reported 96% survival at 10-years. Furthermore, Stålman et al.[197] demonstrated no implant migration in a study using radiostereometric analysis (RSA) of a novel customised focal metal inlay implant.

In our studies, we could not find any correlation between lesion size and PROM or risk of subsequent arthroplasty. This finding is consistent with that of a recent study from

the German Cartilage Registry, which demonstrated no correlation between patient satisfaction and lesion size[198]. Furthermore, in the largest randomised controlled trial comparing ACI with other treatments, Snow et al[129]., failed to demonstrate the superiority of ACI. A detrimental effect of previous microfracture was demonstrated in the 5-years results of ACI patients, but not in those receiving other cartilage surgeries after failed microfracture. Several other randomised trials have also failed to demonstrate any clinically relevant differences between ACI and microfractures after five years of follow-up[199, 200]. On the other hand, Kon et al[201]., demonstrated clinical relevant superior IKDC and return to sports in ACI patients compared to microfracture patients, consistent with the SUMMIT study by Brittberg et al. with superior KOOS score after 5-years[99]. However, the latter study was not manufacture-independent. Concerns regarding declining long-term results after microfracture have been raised[192, 193, 202]. However, Knutsen et al.[114] did not find any difference in Lysholm scores for ACI and microfracture procedures at 16-years postoperatively in their RCT. The findings of Knutsen et al. are interesting, as most of the ACI patients included in this thesis were the same as those in the Knutsen study. In paper 2, a clinically relevant and significantly better KOOS QoL score was found in ACI patients compared to those without surgical cartilage treatment and microfracture. A possible explanation could be the superior quality of cartilage after ACI, even though there does not appear to be a correlation between repair cartilage quality and clinical outcomes[191, 198, 203, 204]. Microfracture has been regarded as the "golden standard" in surgical cartilage treatment and several comparative studies includes a microfracture group, but the evidence for such a status is scarce[82]. Microfracture has never been demonstrated to be superior to debridement or non-operative treatment of cartilage lesions[81]. In a recent randomised study from the Norwegian Cartilage Project, debridement achieved equivalent or superior PROM scores compared with ACI in lesions > 2 $cm^2$ at a 2-years follow-up[205]. In paper 2 we used non-surgically treated lesions as reference in the regression models. Few studies have compared cartilage surgery with non-surgical treatment. In a study from the Norwegian Knee Ligament Register, Røtterud et al.[206] demonstrated inferior results for microfracture compared to non-surgical treatment at 2 years following concomitant ACL surgery. In Paper 2, there was a tendency towards

inferior KOOS in the microfracture group compared to the non-surgical treatment group, although the difference was not statistically significant. In addition to the current literature, this further emphasises that less invasive or non-operative treatment might serve better as a control group in comparative cartilage studies.

One concern regarding non-operative cartilage treatment is that several studies suggest that a prolonged delay from symptom onset to cartilage surgery is negatively correlated with the extent of cartilage injury and the PROM postoperatively[199, 207]. This might suggest that a preliminary period of non-operation could negatively affect the outcome of any later cartilage surgery. However, two large studies including more than 2800 and 6000 patients, respectively, from the German Cartilage Registry found no effect of symptom duration on either the preoperative or postoperative PROM scores in cartilage patients[198, 208]. Furthermore, the knowledge regarding the natural history of cartilage lesions and which lesions that remain symptomatic after the initial trauma is limited[69, 193, 208, 209]. Thus, an initial period of exploratory non-operative treatment might be advisable for symptomatic cartilage lesions.

However, the optimal non-operative treatment for focal cartilage lesions remains unknown[210, 211]. While there are several studies on the importance of physical training in osteoarthritis[210-212], only one study has focused on physiotherapy in focal cartilage patients[23]. Wondrasch et al[23]. demonstrated the feasibility of a 3-month rehabilitation program focusing on neuromuscular and progressive resistance training in patients scheduled for focal cartilage surgery. The patients experienced significant and clinically relevant improvement in knee function and 65% of them cancelled their scheduled cartilage surgery.

Several studies have been conducted on orthobiologics in knee osteoarthritis, and ESSKA has recently endorsed the use of both PRP and cell-based (mesenchymal stem cell) injections in the treatment of osteoarthritis[213, 214]. Orthobiologics in osteoarthritis are, however, still controversial, and several internationally recognised guidelines recommend not using them due to the lack of high-quality evidence of clinically meaningful effects[215, 216]. In the treatment of focal cartilage lesions, there is currently limited evidence regarding the effect of orthobiolgics[191].

There are no nerve endings in the cartilage, the source of pain in patients with cartilage lesions remains elusive[192], and there is limited knowledge regarding the natural history of focal cartilage lesions[69]. Two models have been proposed to explain the cause of pain in cartilage lesions[186, 217]: synovitis and breaching of the subchondral bone plate, causing fluid under pressure to enter the highly innervated subchondral osteons[217]. In Paper 3, we demonstrated inferior patient-reported outcomes after knee arthroplasty in patients with pervious arthroscopically verified focal cartilage lesions. One of the reasons for persistent pain in patients with knee arthroplasty might be a higher degree of persistent synovitis, as focal cartilage lesions are known to substantially impair joint homeostasis[158]. The patients in our cohort have first had a period with a symptomatic cartilage lesion and then likely a period with symptomatic osteoarthritis before they underwent knee arthroplasty surgery. Thus, the degree of synovitis and altered joint homeostasis may be more profound than in patients with knee arthroplasty after idiopathic osteoarthritis. The likely prolonged period of symptoms before knee arthroplasty in the cartilage patients may also have led to a sensitisation to pain. A longer duration of preoperative pain has been shown to predict less improvement in pain after knee arthroplasty[185]. Furthermore, preoperative pain catastrophising is associated with increased pain in patients with knee arthroplasty[176]. Chronic pain may also be associated with symptoms of depression, which have been demonstrated to be correlated with inferior patient satisfaction in arthroplasty patients[177, 218]. Additionally, high preoperative expectations are associated with less patient satisfaction postoperatively[218]. With pain from cartilage injury, patients in our cohort might have had higher expectations for an arthroplasty procedure that removed all the cartilage.

There is conflicting evidence in the current literature regarding whether there is any correlation between the degree of preoperative osteoarthritis and patient satisfaction after knee arthroplasty. Dowsey et al.[137] demonstrated no correlation between preoperative KL grade and knee function in arthroplasty patients; however, Hoorntje et al.[219], Sauder et al.[220], Rehman et al.[221], and Olsen et al.[185] reported that severe preoperative osteoarthritis was associated with better patient satisfaction after knee arthroplasty. Preoperative radiographs were not available in our cohort of patients who underwent knee arthroplasty. As patients with focal cartilage have similar KOOS QoL

as patients scheduled for knee arthroplasty[22, 186], it is possible that patients with previous cartilage lesions had less severe preoperative osteoarthritis compared to the control group from NAR.

It does not seem to be a correlation in the cartilage quality or thickness and knee function neither in focal cartilage lesions nor osteoarthritis[156, 198, 222]. Faber et al.[198], in a large study from the German Cartilage Registry, did not find any correlation between cartilage repair quality on MRI and patient satisfaction. Faber et al.[198], thus suggest that PROM should be the "golden standard" when reporting results in cartilage studies. Bacon et al.[222] demonstrated that, although statistically significant, the correlation between cartilage thickness and pain in osteoarthritis patients were weak. In a randomised, placebo-controlled study, Hochberg et al[223]. demonstrated a significant and substantial effect of Sprifermin on cartilage thickness in osteoarthritis. The significant effect on the cartilage were, however, not correlated with any improvement in pain. Based on their own findings and those of Hochberg et al.[223], Bacon et al.[222] concluded that, at least in osteoarthritis, no treatment focused on improving cartilage thickness would be able to achieve any clinically relevant effect on patient satisfaction.

## 12. Future perspectives

- RCTs on cartilage surgeries involving a sham surgery arm should be performed to demonstrate that the effect on patient-reported outcomes is not purely placebo. The importance of a sham-surgery control group has been highlighted by Moseley et al.[224] in osteoarthritis and by Sihvonen et al.[225] in degenerative menisci.
- The natural history of focal cartilage lesions should be better understood. The reasons for why some cartilage lesions remain asymptomatic while others are detrimental to knee function needs to be investigated.
- The optimal nonoperative treatment of patients with focal cartilage lesions should be investigated and most likely applied before surgical treatment is considered.
- Several studies have investigated the sources of pain in osteoarthritis.[179] The sources of pain in knees with focal cartilage lesions should be studied.

- Future cartilage treatment modalities should target the sources of symptoms in addition to the cartilage lesion itself.
- Cartilage treatment registries or large cohort studies are needed to monitor rare but potentially serious adverse effects as well as that novel treatment options do not underperform.
- PROM should be the primary outcome of prospective cartilage studies as suggested by the German Cartilage Registry[198], and cartilage repair quality assessed by MRI or histology should only be secondary outcomes.

# 13. Conclusion and clinical implications

This thesis, with its nearly 20-years follow up of a cohort of patients with arthroscopically verified focal cartilage lesions, provides new knowledge of their long-term prognosis. Additionally, it provides new insights into the long-term outcomes of nonsurgical treatment of focal cartilage lesions. These are important factors in the shared decision-making process of choosing the optimal treatment for a patient with a focal cartilage lesion.

Focal cartilage lesions increased the risk of requiring a later knee arthroplasty, especially in the younger population. Surgical treatment of cartilage lesions does not seem to reduce the risk of knee arthroplasty, suggesting that fear of subsequent osteoarthritis may not be an indication for cartilage surgery. The only modifiable risk factor for knee arthroplasty we found was the patient's Body Mass Index. This finding suggests that the guidance of patients with FCLs regarding lifestyle changes may be important.

Patients with focal cartilage lesions in the knee did, however, report improved outcomes at long-term follow-up compared to what they had reported before index cartilage surgery, regardless of treatment strategy. However, patients treated with Autologous Chondrocyte Implantation reported significantly and clinically relevant better KOOS QoL than those treated with other treatment strategies. They also had lower odds of treatment failure, despite an increased risk of knee arthroplasty.

Patients who had undergone knee arthroplasty surgery after a previous focal cartilage lesion reported significantly and clinically relevant lower KOOS at mid-term follow-up. They also had a significantly lower odds of achieving the Patient Acceptable Symptom State threshold than the matched knee arthroplasty cohort. These findings may be important factors to consider in shared decision making in patients eligible for knee arthroplasty and the adjustment of preoperative expectations.

# 14. References


1. Nasiri N, Taheri S, Hosseini S, et al. Introduction to Cartilage Tissue: Development, Structure, and Functions. Springer Nature Singapore, 2023, pp.1-20.
2. Camarero-Espinosa S, Rothen-Rutishauser B, Foster EJ, et al. Articular cartilage: from formation to tissue engineering. *Biomater Sci* 2016; 4: 734-767. 20160229. DOI: 10.1039/c6bm00068a.
3. Benjamin M and Ralphs JR. Biology of fibrocartilage cells. *Int Rev Cytol* 2004; 233: 1-45. DOI: 10.1016/s0074-7696(04)33001-9.
4. Sophia Fox AJ, Bedi A and Rodeo SA. The Basic Science of Articular Cartilage: Structure, Composition, and Function. *Sports Health: A Multidisciplinary Approach* 2009; 1: 461-468. DOI: 10.1177/1941738109350438.
5. Goldring MB, Culley KL and Otero M. Pathogenesis of Osteoarthritis in General. Springer International Publishing, 2017, pp.1-25.
6. Aspberg A. Cartilage Proteoglycans. Springer International Publishing, 2016, pp.1-22.
7. Grässel S. Collagens in Hyaline Cartilage. Springer International Publishing, 2016, pp.23-53.
8. Eyre DR. The collagens of articular cartilage. *Semin Arthritis Rheum* 1991; 21: 2-11. DOI: 10.1016/0049-0172(91)90035-x.
9. Zaucke F. Cartilage Glycoproteins. Springer International Publishing, 2016, pp.55-81.
10. Roughley PJ and Mort JS. The role of aggrecan in normal and osteoarthritic cartilage. *Journal of Experimental Orthopaedics* 2014; 1. DOI: 10.1186/s40634-014-0008-7.
11. Wang X, Chan WC and Chan D. Joint Development. Springer International Publishing, 2016, pp.169-189.
12. Widuchowski W, Widuchowski J and Trzaska T. Articular cartilage defects: Study of 25,124 knee arthroscopies. *The Knee* 2007; 14: 177-182. DOI: http://dx.doi.org/10.1016/j.knee.2007.02.001.
13. Curl WW, Krome J, Gordon ES, et al. Cartilage injuries: a review of 31,516 knee arthroscopies. *Arthroscopy* 1997; 13: 456-460. DOI: 10.1016/s0749-8063(97)90124-9.
14. Hjelle K, Solheim E, Strand T, et al. Articular cartilage defects in 1,000 knee arthroscopies. *Arthroscopy: The Journal of Arthroscopic & Related Surgery* 2002; 18: 730-734. DOI: http://dx.doi.org/10.1053/jars.2002.32839.
15. Aroen A, Loken S, Heir S, et al. Articular cartilage lesions in 993 consecutive knee arthroscopies. *Am J Sports Med* 2004; 32: 211-215.
16. Ding C, Garnero P, Cicuttini F, et al. Knee cartilage defects: association with early radiographic osteoarthritis, decreased cartilage volume, increased joint surface area and type II collagen breakdown. *Osteoarthritis Cartilage* 2005; 13: 198-205. DOI: 10.1016/j.joca.2004.11.007.
17. Brennan SL, Cicuttini FM, Pasco JA, et al. Does an increase in body mass index over 10 years affect knee structure in a population-based cohort study of adult women? *Arthritis Res Ther* 2010; 12: R139. DOI: 10.1186/ar3078.
18. Zanetti M, Pfirrmann CWA, Schmid MR, et al. Patients with Suspected Meniscal Tears: Prevalence of Abnormalities Seen on MRI of 100 Symptomatic and 100 Contralateral Asymptomatic Knees. *American Journal of Roentgenology* 2003; 181: 635-641. DOI: 10.2214/ajr.181.3.1810635.
19. Whittaker JL, Toomey CM, Woodhouse LJ, et al. Association between MRI-defined osteoarthritis, pain, function and strength 3–10 years following knee joint injury in youth sport. *Br J Sports Med* 2018; 52: 934-939. DOI: 10.1136/bjsports-2017-097576.
20. Pappas GP, Vogelsong MA, Staroswiecki E, et al. Magnetic Resonance Imaging of Asymptomatic Knees in Collegiate Basketball Players. *Clin J Sport Med* 2016; 26: 483-489. DOI: 10.1097/jsm.0000000000000283.
21. Engen CN, Aroen A and Engebretsen L. Incidence of knee cartilage surgery in Norway, 2008-2011. *BMJ Open* 2015; 5: e008423. 2015/12/02. DOI: 10.1136/bmjopen-2015-008423.
22. Heir S, Nerhus TK, Rotterud JH, et al. Focal cartilage defects in the knee impair quality of life as much as severe osteoarthritis: a comparison of knee injury and osteoarthritis outcome score in 4

patient categories scheduled for knee surgery. *Am J Sports Med* 2010; 38: 231-237. 2010/01/01. DOI: 10.1177/0363546509352157.
23. Wondrasch B, Aroen A, Rotterud JH, et al. The feasibility of a 3-month active rehabilitation program for patients with knee full-thickness articular cartilage lesions: the Oslo Cartilage Active Rehabilitation and Education Study. *J Orthop Sports Phys Ther* 2013; 43: 310-324. DOI: 10.2519/jospt.2013.4354.
24. Saris DBF, Vanlauwe J, Victor J, et al. Characterized Chondrocyte Implantation Results in Better Structural Repair when Treating Symptomatic Cartilage Defects of the Knee in a Randomized Controlled Trial versus Microfracture. *The American Journal of Sports Medicine* 2008; 36: 235-246. DOI: 10.1177/0363546507311095.
25. Ismail HM and Vincent TL. Cartilage Injury and Osteoarthritis. Springer International Publishing, 2017, pp.27-40.
26. Magnusson K, Scurrah K, Ystrom E, et al. Genetic factors contribute more to hip than knee surgery due to osteoarthritis - a population-based twin registry study of joint arthroplasty. *Osteoarthritis Cartilage* 2017; 25: 878-884. 20161213. DOI: 10.1016/j.joca.2016.12.015.
27. Gauci SJ, Stanton H, Little CB, et al. Proteoglycan and Collagen Degradation in Osteoarthritis. Springer International Publishing, 2017, pp.41-61.
28. Favero M, Giusti A, Geusens P, et al. OsteoRheumatology: a new discipline? *RMD Open* 2015; 1: e000083. DOI: 10.1136/rmdopen-2015-000083.
29. Apold H, Meyer HE, Nordsletten L, et al. Risk factors for knee replacement due to primary osteoarthritis, a population based, prospective cohort study of 315,495 individuals. *BMC Musculoskelet Disord* 2014; 15: 217. 2014/06/25. DOI: 10.1186/1471-2474-15-217.
30. Blagojevic M, Jinks C, Jeffery A, et al. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 2010; 18: 24-33. DOI: 10.1016/j.joca.2009.08.010.
31. Poulsen E, Goncalves GH, Bricca A, et al. Knee osteoarthritis risk is increased 4-6 fold after knee injury – a systematic review and meta-analysis. *Br J Sports Med* 2019; 53: 1454-1463. DOI: 10.1136/bjsports-2018-100022.
32. Rongen JJ, Rovers MM, Van Tienen TG, et al. Increased risk for knee replacement surgery after arthroscopic surgery for degenerative meniscal tears: a multi-center longitudinal observational study using data from the osteoarthritis initiative. *Osteoarthritis Cartilage* 2017; 25: 23-29. DOI: 10.1016/j.joca.2016.09.013.
33. Lysholm J and Gillquist J. Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. *Am J Sports Med* 1982; 10: 150-154. DOI: 10.1177/036354658201000306.
34. Tegner Y and Lysholm J. Rating systems in the evaluation of knee ligament injuries. *Clin Orthop Relat Res* 1985: 43-49.
35. Kocher MS, Steadman JR, Briggs KK, et al. Reliability, validity, and responsiveness of the Lysholm knee scale for various chondral disorders of the knee. *J Bone Joint Surg Am* 2004; 86-A: 1139-1145.
36. Collins NJ, Misra D, Felson DT, et al. Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). *Arthritis Care Res (Hoboken)* 2011; 63: S208-S228. DOI: 10.1002/acr.20632.
37. Dawson J, Fitzpatrick R, Murray D, et al. Questionnaire on the perceptions of patients about total knee replacement. *J Bone Joint Surg Br* 1998; 80: 63-69. DOI: 10.1302/0301-620x.80b1.7859.
38. Murray DW, Fitzpatrick R, Rogers K, et al. The use of the Oxford hip and knee scores. *J Bone Joint Surg Br* 2007; 89: 1010-1014. DOI: 10.1302/0301-620x.89b8.19424.

39. Vilchez F, Lara J, Álvarez-Lozano E, et al. Knee chondral lesions treated with autologous chondrocyte transplantation in a tridimensional matrix: clinical evaluation at 1-year follow-up. *J Orthop Traumatol* 2009; 10: 173-177. DOI: 10.1007/s10195-009-0069-z.
40. Harris K, Lim CR, Dawson J, et al. The Oxford knee score and its subscales do not exhibit a ceiling or a floor effect in knee arthroplasty patients: an analysis of the National Health Service PROMs data set. *Knee Surg Sports Traumatol Arthrosc* 2017; 25: 2736-2742. DOI: 10.1007/s00167-015-3788-0.
41. Shelbourne KD and Nitz P. Accelerated rehabilitation after anterior cruciate ligament reconstruction. *Am J Sports Med* 1990; 18: 292-299. DOI: 10.1177/036354659001800313.
42. Barber-Westin SD, Noyes FR and McCloskey JW. Rigorous Statistical Reliability, Validity, and Responsiveness Testing of the Cincinnati Knee Rating System in 350 Subjects with Uninjured, Injured, or Anterior Cruciate Ligament-Reconstructed Knees. *The American Journal of Sports Medicine* 1999; 27: 402-416. DOI: doi:10.1177/03635465990270040201.
43. Marx RG, Jones EC, Allen AA, et al. Reliability, validity, and responsiveness of four knee outcome scales for athletic patients. *J Bone Joint Surg Am* 2001; 83: 1459-1469. DOI: 10.2106/00004623-200110000-00001.
44. Agel J and LaPrade RF. Assessment of differences between the modified Cincinnati and International Knee Documentation Committee patient outcome scores: a prospective study. *Am J Sports Med* 2009; 37: 2151-2157. 20090724. DOI: 10.1177/0363546509337698.
45. Roos EM and Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes* 2003; 1: 64. DOI: 10.1186/1477-7525-1-64.
46. Engelhart L, Nelson L, Lewis S, et al. Validation of the Knee Injury and Osteoarthritis Outcome Score subscales for patients with articular cartilage lesions of the knee. *Am J Sports Med* 2012; 40: 2264-2272. DOI: 10.1177/0363546512457646.
47. Roos EM, Engelhart L, Ranstam J, et al. ICRS Recommendation Document: Patient-Reported Outcome Instruments for Use in Patients with Articular Cartilage Defects. *Cartilage* 2011; 2: 122-136. DOI: 10.1177/1947603510391084.
48. Roos EM and Toksvig-Larsen S. Knee injury and Osteoarthritis Outcome Score (KOOS) - validation and comparison to the WOMAC in total knee replacement. *Health Qual Life Outcomes* 2003; 1: 17. 20030525. DOI: 10.1186/1477-7525-1-17.
49. Baldwin JN, McKay MJ, Simic M, et al. Self-reported knee pain and disability among healthy individuals: reference data and factors associated with the Knee injury and Osteoarthritis Outcome Score (KOOS) and KOOS-Child. *Osteoarthritis Cartilage* 2017; 25: 1282-1290. DOI: 10.1016/j.joca.2017.03.007.
50. Marot V, Murgier J, Carrozzo A, et al. Determination of normal KOOS and WOMAC values in a healthy population. *Knee Surg Sports Traumatol Arthrosc* 2019; 27: 541-548. 2018/09/27. DOI: 10.1007/s00167-018-5153-6.
51. Perruccio AV, Stefan Lohmander L, Canizares M, et al. The development of a short measure of physical function for knee OA KOOS-Physical Function Shortform (KOOS-PS) – an OARSI/OMERACT initiative. *Osteoarthritis Cartilage* 2008; 16: 542-550. DOI: 10.1016/j.joca.2007.12.014.
52. Davis AM, Perruccio AV, Canizares M, et al. Comparative, validity and responsiveness of the HOOS-PS and KOOS-PS to the WOMAC physical function subscale in total joint replacement for Osteoarthritis. *Osteoarthritis Cartilage* 2009; 17: 843-847. DOI: 10.1016/j.joca.2009.01.005.
53. Örtqvist M, Roos EM, Broström EW, et al. Development of the Knee Injury and Osteoarthritis Outcome Score for Children (KOOS-Child). *Acta Orthop* 2012; 83: 666-673. DOI: 10.3109/17453674.2012.747921.
54. Örtqvist M, Iversen MD, Janarv P-M, et al. Psychometric properties of the Knee injury and Osteoarthritis Outcome Score for Children (KOOS-Child) in children with knee disorders. *Br J Sports Med* 2014; 48: 1437-1446. DOI: 10.1136/bjsports-2013-093164.
55. Gandek B, Roos EM, Franklin PD, et al. A 12-item short form of the Knee injury and Osteoarthritis Outcome Score (KOOS-12): tests of reliability, validity and responsiveness. *Osteoarthritis Cartilage* 2019; 27: 762-770. DOI: 10.1016/j.joca.2019.01.011.

56. International Cartilage Repair Society The cartilage standard evaluation form/knee.ICRS Newsletter, spring 1998. 1998.
57. Irrgang JJ, Anderson AF, Boland AL, et al. Development and validation of the international knee documentation committee subjective knee form. *Am J Sports Med* 2001; 29: 600-613.
58. Greco NJ, Anderson AF, Mann BJ, et al. Responsiveness of the International Knee Documentation Committee Subjective Knee Form in comparison to the Western Ontario and McMaster Universities Osteoarthritis Index, modified Cincinnati Knee Rating System, and Short Form 36 in patients with focal articular cartilage defects. *Am J Sports Med* 2010; 38: 891-902. DOI: 10.1177/0363546509354163.
59. Grevnerts HT, Terwee CB and Kvist J. The measurement properties of the IKDC-subjective knee form. *Knee Surg Sports Traumatol Arthrosc* 2015; 23: 3698-3706. DOI: 10.1007/s00167-014-3283-z.
60. Kocher MS, Smith JT, Iversen MD, et al. Reliability, validity, and responsiveness of a modified International Knee Documentation Committee Subjective Knee Form (Pedi-IKDC) in children with knee disorders. *Am J Sports Med* 2011; 39: 933-939. 20101110. DOI: 10.1177/0363546510383002.
61. Outerbridge RE. The etiology of chondromalacia patellae. *J Bone Joint Surg Br* 1961; 43-b: 752-757. DOI: 10.1302/0301-620x.43b4.752.
62. Cameron ML, Briggs KK and Steadman JR. Reproducibility and Reliability of the Outerbridge Classification for Grading Chondral Lesions of the Knee Arthroscopically. *The American Journal of Sports Medicine* 2003; 31: 83-86. DOI: 10.1177/03635465030310012601.
63. Brittberg M and Winalski CS. Evaluation of cartilage injuries and repair. *J Bone Joint Surg Am* 2003; 85-A Suppl 2: 58-69.
64. Dwyer T, Martin CR, Kendra R, et al. Reliability and Validity of the Arthroscopic International Cartilage Repair Society Classification System: Correlation With Histological Assessment of Depth. *Arthroscopy* 2017; 33: 1219-1224. 20170202. DOI: 10.1016/j.arthro.2016.12.012.
65. Årøen A, Røtterud JH and Sivertsen EA. Agreement in Arthroscopic and Arthrotomy Assessment of Full-Thickness Articular Cartilage Lesions of the Knee in a Clinical Setting in 33 Consecutive Patients. *CARTILAGE* 2013; 4: 214-218. DOI: 10.1177/1947603513483546.
66. Flanigan DC, Carey JL, Brophy RH, et al. Interrater and Intrarater Reliability of Arthroscopic Measurements of Articular Cartilage Defects in the Knee. *J Bone Joint Surg* 2017; 99: 979-988. DOI: 10.2106/jbjs.16.01132.
67. Fransen M, McConnell S, Harmer AR, et al. Exercise for osteoarthritis of the knee. *Cochrane Database Syst Rev* 2015. DOI: 10.1002/14651858.CD004376.pub3.
68. Messner K and Maletius W. The long-term prognosis for severe damage to weight-bearing cartilage in the knee: a 14-year clinical and radiographic follow-up in 28 young athletes. *Acta Orthop Scand* 1996; 67: 165-168. 1996/04/01. DOI: 10.3109/17453679608994664.
69. Widuchowski W, Widuchowski J, Faltus R, et al. Long-term clinical and radiological assessment of untreated severe cartilage damage in the knee: a natural history study. *Scand J Med Sci Sports* 2011; 21: 106-110. 2010/02/09. DOI: 10.1111/j.1600-0838.2009.01062.x.
70. Shahid M and Kundra R. Platelet-rich plasma (PRP) for knee disorders. *EFORT Open Reviews* 2017; 2: 28-34. DOI: 10.1302/2058-5241.2.160004.
71. Marmotti A, Rossi R, Castoldi F, et al. PRP and Articular Cartilage: A Clinical Update. *BioMed Research International* 2015; 2015: 1-19. DOI: 10.1155/2015/542502.
72. *Platelet-rich plasma injections for osteoarthritis of the knee*. 2014. NICE.
73. Bhandari M, Bannuru RR, Babins EM, et al. Intra-articular hyaluronic acid in the treatment of knee osteoarthritis: a Canadian evidence-based perspective. *Ther Adv Musculoskelet Dis* 2017; 9: 231-246. DOI: 10.1177/1759720x17729641.
74. Leopold SS. Editorial: Getting Evidence Into Practice - or Not: The Case of Viscosupplementation. *Clin Orthop Relat Res* 2016; 474: 285-288. DOI: 10.1007/s11999-015-4632-z.
75. Hunter DJ. Viscosupplementation for osteoarthritis of the knee. *N Engl J Med* 2015; 372: 1040-1047. DOI: 10.1056/NEJMct1215534.

76. Anderson DE, Rose MB, Wille AJ, et al. Arthroscopic Mechanical Chondroplasty of the Knee Is Beneficial for Treatment of Focal Cartilage Lesions in the Absence of Concurrent Pathology. *Orthopaedic Journal of Sports Medicine* 2017; 5: 232596711770721. DOI: 10.1177/2325967117707213.
77. Barber FA and Iwasko NG. Treatment of grade III femoral chondral lesions: mechanical chondroplasty versus monopolar radiofrequency probe. *Arthroscopy* 2006; 22: 1312-1317. DOI: 10.1016/j.arthro.2006.06.008.
78. Grieshober JA, Stanton M and Gambardella R. Debridement of Articular Cartilage: The Natural Course. *Sports Med Arthrosc* 2016; 24.
79. PROCEEDINGS AND REPORTS OF UNIVERSITIES COLLEGES, COUNCILS AND ASSOCIATIONS. *The Journal of Bone and Joint Surgery British volume* 1959; 41-B: 616-639. DOI: 10.1302/0301-620x.41b3.616.
80. Steadman JR, Rodkey WG, Singleton SB, et al. Microfracture technique forfull-thickness chondral defects: Technique and clinical results. *Oper Tech Orthop* 1997; 7: 300-304. DOI: https://doi.org/10.1016/S1048-6666(97)80033-X.

81. Aae TF, Randsborg PH, Breen AB, et al. Norwegican Cartilage Project - a study protocol for a double-blinded randomized controlled trial comparing arthroscopic microfracture with arthroscopic debridement in focal cartilage defects in the knee. *BMC Musculoskelet Disord* 2016; 17: 292. DOI: 10.1186/s12891-016-1156-y.

82. Erggelet C and Vavken P. Microfracture for the treatment of cartilage defects in the knee joint – A golden standard? *Journal of Clinical Orthopaedics and Trauma* 2016; 7: 145-152. DOI: 10.1016/j.jcot.2016.06.015.

83. Steadman JR, Briggs KK, Rodrigo JJ, et al. Outcomes of microfracture for traumatic chondral defects of the knee: average 11-year follow-up. *Arthroscopy* 2003; 19: 477-484. 2003/05/02. DOI: 10.1053/jars.2003.50112.

84. Devitt BM, Bell SW, Webster KE, et al. Surgical treatments of cartilage defects of the knee: Systematic review of randomised controlled trials. *The Knee* 2017; 24: 508-517. DOI: https://doi.org/10.1016/j.knee.2016.12.002.

85. Oliver-Welsh L, Griffin JW, Meyer MA, et al. Deciding How Best to Treat Cartilage Defects. *Orthopedics* 2016; 39: 343-350. 2016/11/29. DOI: 10.3928/01477447-20161020-03.

86. Benthien JP and Behrens P. The treatment of chondral and osteochondral defects of the knee with autologous matrix-induced chondrogenesis (AMIC): method description and recent developments. *Knee Surg Sports Traumatol Arthrosc* 2011; 19: 1316-1319. DOI: 10.1007/s00167-010-1356-1.

87. Piontek T, Ciemniewska-Gorzela K, Szulc A, et al. All-arthroscopic AMIC procedure for repair of cartilage defects of the knee. *Knee Surg Sports Traumatol Arthrosc* 2012; 20: 922-925. DOI: 10.1007/s00167-011-1657-z.

88. Gille J, Behrens P, Volpi P, et al. Outcome of Autologous Matrix Induced Chondrogenesis (AMIC) in cartilage knee surgery: data of the AMIC Registry. *Arch Orthop Trauma Surg* 2013; 133: 87-93. DOI: 10.1007/s00402-012-1621-5.

89. Anders S, Volz M, Frick H, et al. A Randomized, Controlled Trial Comparing Autologous Matrix-Induced Chondrogenesis (AMIC®) to Microfracture: Analysis of 1- and 2-Year Follow-Up Data of 2 Centers. *The Open Orthopaedics Journal* 2013; 7: 133-143. DOI: 10.2174/1874325001307010133.

90. Fossum V, Hansen AK, Wilsgaard T, et al. Collagen-Covered Autologous Chondrocyte Implantation Versus Autologous Matrix-Induced Chondrogenesis: A Randomized Trial Comparing 2

Methods for Repair of Cartilage Defects of the Knee. *Orthop J Sports Med* 2019; 7: 2325967119868212. 2019/09/27. DOI: 10.1177/2325967119868212.

91. Bobić V. Arthroscopic osteochondral autograft transplantation in anterior cruciate ligament reconstruction: A preliminary clinical study. *Knee Surg Sports Traumatol Arthrosc* 1996; 3: 262-264. DOI: 10.1007/bf01466630.

92. Hangody L, Kish G, Kárpáti Z, et al. Arthroscopic autogenous osteochondral mosaicplasty for the treatment of femoral condylar articular defects. A preliminary report. *Knee Surg Sports Traumatol Arthrosc* 1997; 5: 262-267. 1997/01/01. DOI: 10.1007/s001670050061.

93. Hangody L, Ráthonyi GK, Duska Z, et al. Autologous Osteochondral Mosaicplasty: Surgical Technique. *JBJS* 2004; 86: 65-72.

94. Solheim E, Hegna J, Oyen J, et al. Results at 10 to 14 years after osteochondral autografting (mosaicplasty) in articular cartilage defects in the knee. *Knee* 2013; 20: 287-290. DOI: 10.1016/j.knee.2013.01.001.

95. MCDERMOTT AGP, LANGER F, PRITZKER KPH, et al. Fresh Small-Fragment Osteochondral Allografts: Long-term Follow-up Study on First 100 Cases. *Clinical Orthopaedics and Related Research®* 1985; 197: 96-102.

96. LaPrade RF, Botker J, Herzog M, et al. Refrigerated Osteoarticular Allografts to Treat Articular Cartilage Defects of the Femoral Condyles: A Prospective Outcomes Study. *JBJS* 2009; 91: 805-811. DOI: 10.2106/jbjs.H.00703.

97. Familiari F, Cinque ME, Chahla J, et al. Clinical Outcomes and Failure Rates of Osteochondral Allograft Transplantation in the Knee: A Systematic Review. *Am J Sports Med* 2018; 46: 3541-3549. 20171017. DOI: 10.1177/0363546517732531.

98. Brittberg M, Lindahl A, Nilsson A, et al. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N Engl J Med* 1994; 331: 889-895. 1994/10/06. DOI: 10.1056/nejm199410063311401.

99. Brittberg M, Recker D, Ilgenfritz J, et al. Matrix-Applied Characterized Autologous Cultured Chondrocytes Versus Microfracture: Five-Year Follow-up of a Prospective Randomized Trial. *Am J Sports Med* 2018; 46: 1343-1351. 2018/03/23. DOI: 10.1177/0363546518756976.

100. Hunziker EB, Lippuner K, Keel MJ, et al. An educational review of cartilage repair: precepts & practice--myths & misconceptions--progress & prospects. *Osteoarthritis Cartilage* 2015; 23: 334-350. 2014/12/24. DOI: 10.1016/j.joca.2014.12.011.

101. Brophy RH, Gray BL, Nunley RM, et al. Total knee arthroplasty after previous knee surgery: expected interval and the effect on patient age. *J Bone Joint Surg Am* 2014; 96: 801-805. DOI: 10.2106/JBJS.M.00105.

102. Demey G, Magnussen RA, Lustig S, et al. Total knee arthroplasty for advanced osteoarthritis in the anterior cruciate ligament deficient knee. *Int Orthop* 2012; 36: 559-564. DOI: 10.1007/s00264-011-1306-7.

103. Pareek A, Reardon PJ, Maak TG, et al. Long-term Outcomes After Osteochondral Autograft Transfer: A Systematic Review at Mean Follow-up of 10.2 Years. *Arthroscopy: The Journal of Arthroscopic & Related Surgery* 2016; 32: 1174-1184. DOI: https://doi.org/10.1016/j.arthro.2015.11.037.

104. Ogura T, Mosier BA, Bryant T, et al. A 20-Year Follow-up After First-Generation Autologous Chondrocyte Implantation. *The American Journal of Sports Medicine* 2017; 45: 2751-2761. DOI: 10.1177/0363546517716631.

105. Gobbi A, Karnatzikos G and Kumar A. Long-term results after microfracture treatment for full-thickness knee chondral lesions in athletes. *Knee Surg Sports Traumatol Arthrosc* 2014; 22: 1986-1996. 2013/09/21. DOI: 10.1007/s00167-013-2676-8.

106. Ansari MH, Pareek A, Johnson NR, et al. Clinical Outcome of Total Knee Arthroplasty After Prior Microfracture: A Matched Cohort Study. *Orthopedics* 2017; 40: e473-e478. 20170228. DOI: 10.3928/01477447-20170223-02.

107. Frank RM, Della Valle CJ, Plummer DR, et al. Does Prior Cartilage Restoration Impact Outcomes Following Knee Arthroplasty? *Orthop Clin North Am* 2017; 48: 265-273. 20170405. DOI: 10.1016/j.ocl.2017.03.001.

108. Norwegian. The Norwegian Arthroplasty Register Annual Report. National Advisory Unit on Arthroplasty and Hip Fractures., 2020.

109. Furnes O, Espehaug B, Lie SA, et al. Early failures among 7,174 primary total knee replacements: a follow-up study from the Norwegian Arthroplasty Register 1994-2000. *Acta Orthop Scand* 2002; 73: 117-129. 2002/06/25. DOI: 10.1080/000164702753671678.

110. Kaplan EL and Meier P. Nonparametric Estimation from Incomplete Observations. *Journal of the American Statistical Association* 1958; 53: 457-481. DOI: 10.1080/01621459.1958.10501452.

111. Westreich D and Greenland S. The Table 2 Fallacy: Presenting and Interpreting Confounder and Modifier Coefficients. *Am J Epidemiol* 2013; 177: 292-298. DOI: 10.1093/aje/kws412.

112. Chahal J, Lansdown DA, Davey A, et al. The Clinically Important Difference and Patient Acceptable Symptomatic State for Commonly Used Patient-Reported Outcomes After Knee Cartilage Repair. *Am J Sports Med* 2021; 49: 193-199. 2020/11/24. DOI: 10.1177/0363546520969883.

113. Connelly JW, Galea VP, Rojanasopondist P, et al. Patient Acceptable Symptom State at 1 and 3 Years After Total Knee Arthroplasty: Thresholds for the Knee Injury and Osteoarthritis Outcome Score (KOOS). *J Bone Joint Surg Am* 2019; 101: 995-1003. 2019/06/07. DOI: 10.2106/jbjs.18.00233.

114. Knutsen G, Drogset JO, Engebretsen L, et al. A Randomized Multicenter Trial Comparing Autologous Chondrocyte Implantation with Microfracture: Long-Term Follow-up at 14 to 15 Years. *J Bone Joint Surg Am* 2016; 98: 1332-1339. 2016/08/19. DOI: 10.2106/jbjs.15.01208.

115. Solheim E, Hegna J, Inderhaug E, et al. Results at 10-14 years after microfracture treatment of articular cartilage defects in the knee. *Knee Surg Sports Traumatol Arthrosc* 2016; 24: 1587-1593. DOI: 10.1007/s00167-014-3443-1.

116. Birkenes T, Furnes O, Laastad Lygre SH, et al. The Long-Term Risk of Knee Arthroplasty in Patients with Arthroscopically Verified Focal Cartilage Lesions: A Linkage Study with the Norwegian Arthroplasty Register, 1999 to 2020. *J Bone Joint Surg Am* 2023; 105: 951-961. 20230427. DOI: 10.2106/JBJS.22.01174.

117. Birkenes T, Furnes O, Lygre SHL, et al. Previous cartilage surgery is associated with inferior patient-reported outcomes after knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc* 2024; 32: 361-370. 20240131. DOI: 10.1002/ksa.12050.

118. Bothwell LE, Greene JA, Podolsky SH, et al. Assessing the Gold Standard — Lessons from the History of RCTs. *N Engl J Med* 2016; 374: 2175-2181. DOI: 10.1056/nejmms1604593.

119. Frieden TR. Evidence for Health Decision Making — Beyond Randomized, Controlled Trials. *N Engl J Med* 2017; 377: 465-475. DOI: 10.1056/NEJMra1614394.

120. Engen CN, Engebretsen L and Årøen A. Knee Cartilage Defect Patients Enrolled in Randomized Controlled Trials Are Not Representative of Patients in Orthopedic Practice. *Cartilage* 2010; 1: 312-319. DOI: 10.1177/1947603510373917.

121. Maret-Ouda J, Tao W, Wahlin K, et al. Nordic registry-based cohort studies: Possibilities and pitfalls when combining Nordic registry data. *Scandinavian Journal of Public Health* 2017; 45: 14-19. DOI: 10.1177/1403494817702336.

122. Maurer J, Grotejohann B, Jenkner C, et al. A Registry for Evaluation of Efficiency and Safety of Surgical Treatment of Cartilage Defects: The German Cartilage Registry (KnorpelRegister DGOU). *JMIR Res Protoc* 2016; 5: e122. 20160629. DOI: 10.2196/resprot.5895.

123. Bumberger A, Rupp MC, Lattermann C, et al. Increased risk of reoperation and failure to attain clinically relevant improvement following autologous chondrocyte implantation of the knee in female patients and individuals with previous surgeries: a time-to-event analysis based on the German cartilag. *Knee Surg Sports Traumatol Arthrosc* 2023; 31: 5837-5847. DOI: 10.1007/s00167-023-07615-5.

124. Sedgwick P. Retrospective cohort studies: advantages and disadvantages. *BMJ* 2014; 348: g1072-g1072. DOI: 10.1136/bmj.g1072.

125. Hinckel BB, Thomas D, Vellios EE, et al. Algorithm for Treatment of Focal Cartilage Defects of the Knee: Classic and New Procedures. *CARTILAGE* 2021; 13: 473S-495S. DOI: 10.1177/1947603521993219.

126. Knutsen G, Engebretsen L, Ludvigsen TC, et al. Autologous chondrocyte implantation compared with microfracture in the knee. A randomized trial. *J Bone Joint Surg Am* 2004; 86-A: 455-464.

127. Solheim E, Hegna J, Oyen J, et al. Osteochondral autografting (mosaicplasty) in articular cartilage defects in the knee: results at 5 to 9 years. *Knee* 2010; 17: 84-87. DOI: 10.1016/j.knee.2009.07.007.

128. Solheim E, Oyen J, Hegna J, et al. Microfracture treatment of single or multiple articular cartilage defects of the knee: a 5-year median follow-up of 110 patients. *Knee Surg Sports Traumatol Arthrosc* 2010; 18: 504-508. DOI: 10.1007/s00167-009-0974-y.

129. Snow M, Middleton L, Mehta S, et al. A Randomized Trial of Autologous Chondrocyte Implantation Versus Alternative Forms of Surgical Cartilage Management in Patients With a Failed Primary Treatment for Chondral or Osteochondral Defects in the Knee. *The American Journal of Sports Medicine* 2023; 51: 367-378. DOI: 10.1177/03635465221141907.

130. Health NIoP. Public health report: Overweight and obesity in adults, https://www.fhi.no/en/he/hin/health-disease/overweight-and-obesity-in-norway---/?term=#overweight-and-obesity-in-adults (2024, accessed 30.04.2024 2024).

131. The Norwegian Arthroplasty Register Annual Report, https://www.helse-bergen.no/4ad4ab/contentassets/9f19d57711ee4e60815d6b89e8e8472b/report2023.pdf (2023, accessed 10.06.2023).

132. Abel MH. *Diet and self-reported weight and weight-change based on data from the National Public Health Survey 2020.* 2021. Norwegian Institute of Public Health.

133. Shelbourne KD, Jari S and Gray T. Outcome of untreated traumatic articular cartilage defects of the knee: a natural history study. *J Bone Joint Surg Am* 2003; 85-A Suppl 2: 8-16.

134. Widuchowski W, Widuchowski J, Koczy B, et al. Untreated asymptomatic deep cartilage lesions associated with anterior cruciate ligament injury: results at 10- and 15-year follow-up. *Am J Sports Med* 2009; 37: 688-692. 20090203. DOI: 10.1177/0363546508328104.

135. Espehaug B, Furnes O, Havelin LI, et al. Registration completeness in the Norwegian Arthroplasty Register. *Acta Orthop* 2006; 77: 49-56. 2006/03/15. DOI: 10.1080/17453670610045696.

136. Ackerman IN, Bohensky MA, de Steiger R, et al. Substantial rise in the lifetime risk of primary total knee replacement surgery for osteoarthritis from 2003 to 2013: an international, population-level analysis. *Osteoarthritis Cartilage* 2016. DOI: 10.1016/j.joca.2016.11.005.

137. Dowsey MM, Dieppe P, Lohmander S, et al. The association between radiographic severity and pre-operative function in patients undergoing primary knee replacement for osteoarthritis. *Knee* 2012; 19: 860-865. 20120323. DOI: 10.1016/j.knee.2012.02.007.

138. Son KM, Hong JI, Kim D-H, et al. Absence of pain in subjects with advanced radiographic knee osteoarthritis. *BMC Musculoskelet Disord* 2020; 21. DOI: 10.1186/s12891-020-03647-x.

139. Mabrouk A, Nwachukwu B, Pareek A, et al. MCID and PASS in Knee Surgeries. Theoretical Aspects and Clinical Relevance References. *Knee Surg Sports Traumatol Arthrosc* 2023; 31: 2060-2067. DOI: 10.1007/s00167-023-07359-2.

140. Salis Z, Sainsbury A, I. Keen H, et al. Weight loss is associated with reduced risk of knee and hip replacement: a survival analysis using Osteoarthritis Initiative data. *Int J Obes* 2022; 46: 874-884. DOI: 10.1038/s41366-021-01046-3.

141. Minas T, Von Keudell A, Bryant T, et al. The John Insall Award: A minimum 10-year outcome study of autologous chondrocyte implantation. *Clinical orthopaedics and related research* 2014; 472: 41-51. 2013/08/28. DOI: 10.1007/s11999-013-3146-9.

142. Sanders TL, Pareek A, Obey MR, et al. High Rate of Osteoarthritis After Osteochondritis Dissecans Fragment Excision Compared With Surgical Restoration at a Mean 16-Year Follow-up. *Am J Sports Med* 2017; 45: 1799-1805. 2017/04/19. DOI: 10.1177/0363546517699846.

143. Abram SGF, Palmer AJR, Judge A, et al. Rates of knee arthroplasty in patients with a history of arthroscopic chondroplasty: results from a retrospective cohort study utilising the National Hospital Episode Statistics for England. *BMJ Open* 2020; 10: e030609. 2020/04/19. DOI: 10.1136/bmjopen-2019-030609.

144. Lindanger L, Strand T, Mølster AO, et al. Predictors of Osteoarthritis Development at a Median 25 Years After Anterior Cruciate Ligament Reconstruction Using a Patellar Tendon Autograft. *Am J Sports Med* 2022: 3635465221079327. 20220302. DOI: 10.1177/03635465221079327.

145. Enweze LC, Varshneya K, Sherman SL, et al. Risk of Subsequent Knee Arthroplasty After Sports Medicine Procedures. *J Am Acad Orthop Surg Glob Res Rev* 2020; 4: e20.00125. 2020/08/28. DOI: 10.5435/JAAOSGlobal-D-20-00125.

146. Everhart JS, Magnussen RA, Abouljoud MM, et al. Meniscus tears accelerate joint space loss and lateral meniscal extrusion increases risk of knee arthroplasty in middle-aged adults. *J Orthop Res* 2020; 38: 2495-2504. 2020/03/30. DOI: 10.1002/jor.24672.

147. Abram SGF, Judge A, Khan T, et al. Rates of knee arthroplasty in anterior cruciate ligament reconstructed patients: a longitudinal cohort study of 111,212 procedures over 20 years. *Acta Orthop* 2019; 90: 568-574. 2019/07/11. DOI: 10.1080/17453674.2019.1639360.

148. Whittaker JL, Losciale JM, Juhl CB, et al. Risk factors for knee osteoarthritis after traumatic knee injury: a systematic review and meta-analysis of randomised controlled trials and cohort studies for the OPTIKNEE Consensus. *Br J Sports Med* 2022; 56: 1406-1421. DOI: 10.1136/bjsports-2022-105496.

149. Visnes H, Gifstad T, Persson A, et al. ACL Reconstruction Patients Have Increased Risk of Knee Arthroplasty at 15 Years of Follow-up: Data from the Norwegian Knee Ligament Register and the Norwegian Arthroplasty Register from 2004 to 2020. *JBJS Open Access* 2022; 7: e22.00023. DOI: 10.2106/jbjs.Oa.22.00023.

150. Gustafsson K, Kvist J, Zhou C, et al. Progression to arthroplasty surgery among patients with hip and knee osteoarthritis. *The Bone & Joint Journal* 2022; 104-B: 792-800. DOI: 10.1302/0301-620x.104b7.bjj-2021-1766.r1.

151. Vasiliadis HS and Wasiak J. Autologous chondrocyte implantation for full thickness articular cartilage defects of the knee. *Cochrane Database Syst Rev* 2010; 2010: Cd003323. 2010/10/12. DOI: 10.1002/14651858.CD003323.pub3.

152. Sihvonen R, Paavola M, Malmivaara A, et al. Arthroscopic partial meniscectomy for a degenerative meniscus tear: a 5 year follow-up of the placebo-surgery controlled FIDELITY (Finnish Degenerative Meniscus Lesion Study) trial. *Br J Sports Med* 2020; 54: 1332-1339. 2020/08/29. DOI: 10.1136/bjsports-2020-102813.

153. Kise NJ, Risberg MA, Stensrud S, et al. Exercise therapy versus arthroscopic partial meniscectomy for degenerative meniscal tear in middle aged patients: randomised controlled trial with two year follow-up. *BMJ* 2016; 354: i3740. 2016/07/22. DOI: 10.1136/bmj.i3740.

154. Beard DJ, Campbell MK, Blazeby JM, et al. Placebo comparator group selection and use in surgical trials: the ASPIRE project including expert workshop. *Health Technol Assess* 2021; 25: 1-52. DOI: 10.3310/hta25530.

155. Ossendorff R, Franke K, Erdle B, et al. Clinical and radiographical ten years long-term outcome of microfracture vs. autologous chondrocyte implantation: a matched-pair analysis. *Int Orthop* 2019; 43: 553-559. 2018/06/18. DOI: 10.1007/s00264-018-4025-5.

156. Kreuz PC, Kalkreuth RH, Niemeyer P, et al. Long-Term Clinical and MRI Results of Matrix-Assisted Autologous Chondrocyte Implantation for Articular Cartilage Defects of the Knee. *Cartilage* 2019; 10: 305-313. 2018/02/13. DOI: 10.1177/1947603518756463.

157. Niemeyer P, Porichis S, Steinwachs M, et al. Long-term Outcomes After First-Generation Autologous Chondrocyte Implantation for Cartilage Defects of the Knee. *The American Journal of Sports Medicine* 2013; 42: 150-157. DOI: 10.1177/0363546513506593.

158. Saris DB, Dhert WJ and Verbout AJ. Joint homeostasis. The discrepancy between old and fresh defects in cartilage repair. *J Bone Joint Surg Br* 2003; 85: 1067-1076. DOI: 10.1302/0301-620x.85b7.13745.

159. Lindström C, Rosvall M and Lindström M. Socioeconomic status, social capital and self-reported unmet health care needs: A population-based study. *Scand J Public Health* 2017; 45: 212-221. 20170308. DOI: 10.1177/1403494816689345.

160. Pánics G, Hangody LR, Baló E, et al. Osteochondral Autograft and Mosaicplasty in the Football (Soccer) Athlete. *CARTILAGE* 2012; 3: 25S-30S. DOI: 10.1177/1947603511408286.

161. Peterson L, Vasiliadis HS, Brittberg M, et al. Autologous Chondrocyte Implantation: A Long-term Follow-up. *The American Journal of Sports Medicine* 2010; 38: 1117-1124. DOI: 10.1177/0363546509357915.

162. Seiferth NL, Faber SO, Angele P, et al. Effect of Previous Knee Surgery on Clinical Outcome After ACI for Knee Cartilage Defects: A Propensity Score-Matched Study Based on the German Cartilage Registry (KnorpelRegister DGOU). *Am J Sports Med* 2022; 50: 994-1005. DOI: 10.1177/03635465211070536.

163. Van Tuijn IM, Emanuel KS, Van Hugten PPW, et al. Prognostic Factors for the Clinical Outcome after Microfracture Treatment of Chondral and Osteochondral Defects in the Knee Joint: A Systematic Review. *CARTILAGE* 2023; 14: 5-16. DOI: 10.1177/19476035221147680.

164. Orth P, Gao L and Madry H. Microfracture for cartilage repair in the knee: a systematic review of the contemporary literature. *Knee Surg Sports Traumatol Arthrosc* 2020; 28: 670-706. DOI: 10.1007/s00167-019-05359-9.

165. Becher C, Megaloikonomos PD, Lind M, et al. High degree of consensus amongst an expert panel regarding focal resurfacing of chondral and osteochondral lesions of the femur with mini-implants. *Knee Surg Sports Traumatol Arthrosc* 2023; 31: 4027-4034. DOI: 10.1007/s00167-023-07450-8.

166. Lygre SH, Espehaug B, Havelin LI, et al. Does patella resurfacing really matter? Pain and function in 972 patients after primary total knee arthroplasty. *Acta Orthop* 2010; 81: 99-107. 2010/02/18. DOI: 10.3109/17453671003587069.

167. Jiang Y, Sanchez-Santos MT, Judge AD, et al. Predictors of Patient-Reported Pain and Functional Outcomes Over 10 Years After Primary Total Knee Arthroplasty: A Prospective Cohort Study. *J Arthroplasty* 2017; 32: 92-100. DOI: 10.1016/j.arth.2016.06.009.

168. Issa K, Naziri Q, Johnson AJ, et al. TKA results are not compromised by previous arthroscopic procedures. *J Knee Surg* 2012; 25: 161-164. DOI: 10.1055/s-0032-1313755.

169. Rothermich MA, Nam D, Brophy RH, et al. The Impact of Prior Surgery after Total Knee Arthroplasty. *J Knee Surg* 2017; 30: 57-62. 2016/03/10. DOI: 10.1055/s-0036-1579666.

170. Viste A, Abdel MP, Ollivier M, et al. Prior Knee Arthroscopy Does Not Influence Long-Term Total Knee Arthroplasty Outcomes and Survivorship. *J Arthroplasty* 2017; 32: 3626-3631. DOI: https://doi.org/10.1016/j.arth.2017.06.052.

171. Zhang LY, Cui CM, Min JK, et al. Does prior arthroscopic procedure impact outcomes of knee arthroplasty? A systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci* 2021; 25: 4459-4469. DOI: 10.26355/eurrev_202107_26237.

172. Khan IA, Desimone CA, Sonnier JH, et al. Prior Meniscectomy in Patients Undergoing Primary Total Knee Arthroplasty is Associated With Worse Short-Term Outcomes. *The Journal of Arthroplasty* 2023; 38: S187-S193. DOI: 10.1016/j.arth.2023.01.062.

173. Syrikas I, Engbäck C, Tsikandylakis G, et al. Increased complications rates and inferior patient reported outcomes following total knee arthroplasty due to post-traumatic osteoarthritis with previous fracture treatment: a systematic review. *Knee Surg Sports Traumatol Arthrosc* 2023; 31: 4124-4141. DOI: 10.1007/s00167-023-07407-x.

174. Lizaur-Utrilla A, Gonzalez-Parreño S, Martinez-Mendez D, et al. Minimal clinically important differences and substantial clinical benefits for Knee Society Scores. *Knee Surg Sports Traumatol Arthrosc* 2020; 28: 1473-1478. DOI: 10.1007/s00167-019-05543-x.

175. Mawarikado Y, Inagaki Y, Fujii T, et al. Preoperative Factors Affecting Patient-reported Outcome Measures for Total Knee Arthroplasty. *Prog Rehabil Med* 7. DOI: 10.2490/prm.20220049.

176. Olsen U, Lindberg MF, Rose C, et al. Factors correlated with pain after total knee arthroplasty: A systematic review and meta-analysis. *PLoS One* 18: e0283446. DOI: 10.1371/journal.pone.0283446.

177. Sellevold VB, Olsen U, Lindberg MF, et al. "I am accustomed to something in my body causing pain": a qualitative study of knee replacement non-improvers' stories of previous painful and stressful experiences. *BMC Musculoskelet Disord* 2023; 24: 305. 20230418. DOI: 10.1186/s12891-023-06423-9.

178. Arendt-Nielsen L, Nie H, Laursen MB, et al. Sensitization in patients with painful knee osteoarthritis. *Pain* 2010; 149: 573-581. DOI: 10.1016/j.pain.2010.04.003.

179. Arendt-Nielsen L. Joint pain: more to it than just structural damage? *Pain* 2017; 158 Suppl 1: S66-s73. DOI: 10.1097/j.pain.0000000000000812.

180. Nerhus TK, Heir S, Thornes E, et al. Time-dependent improvement in functional outcome following LCS rotating platform knee replacement. *Acta Orthop* 2010; 81: 727-732. DOI: 10.3109/17453674.2010.533929.

181. Lee H-J, Jung H-J, Jung Y-B, et al. Time-Dependent Clinical Results of Rotating-Platform Total Knee Arthroplasty According to Mechanical Axis Deviation. *Knee Surgery & Related Research* 2014; 26: 141-148. DOI: 10.5792/ksrr.2014.26.3.141.

182. Sebastia-Forcada E, Ruiz-Lozano M, Perez-Aznar A, et al. Functional Outcome Change Over 10 Years After Primary Total Knee Arthroplasty. A Prospective Longitudinal Cohort Study. *J Arthroplasty* 2023 20230818. DOI: 10.1016/j.arth.2023.08.042.

183. Martin RK, Wastvedt S, Pareek A, et al. Predicting subjective failure of ACL reconstruction: a machine learning analysis of the Norwegian Knee Ligament Register and patient reported outcomes. *Journal of ISAKOS* 2022; 7: 1-9. DOI: 10.1016/j.jisako.2021.12.005.

184. Scott CEH, Oliver WM, Macdonald D, et al. Predicting dissatisfaction following total knee arthroplasty in patients under 55 years of age. *The Bone & Joint Journal* 2016; 98-B: 1625-1634. DOI: 10.1302/0301-620x.98b12.bjj-2016-0375.r1.

185. Olsen U, Lindberg MF, Rose C, et al. Factors Correlated With Physical Function 1 Year After Total Knee Arthroplasty in Patients With Knee Osteoarthritis: A Systematic Review and Meta-analysis. *JAMA Netw Open* 5: e2219636. DOI: 10.1001/jamanetworkopen.2022.19636.

186. Randsborg PH, Årøen A and Owesen C. The Effect of Lesion Size on Pain and Function in Patients Scheduled for Cartilage Surgery of the Knee. *Cartilage* 2022; 13: 43-49. DOI: 10.1177/19476035221109242.

187. Kahlenberg CA, Lyman S, Joseph AD, et al. Comparison of patient-reported outcomes based on implant brand in total knee arthroplasty: a prospective cohort study. *Bone Joint J* 2019; 101-b: 48-54. DOI: 10.1302/0301-620x.101b7.Bjj-2018-1382.R1.

188. Lien-Iversen T, Morgan DB, Jensen C, et al. Does surgery reduce knee osteoarthritis, meniscal injury and subsequent complications compared with non-surgery after ACL rupture with at least 10 years follow-up? A systematic review and meta-analysis. *Br J Sports Med* 2020; 54: 592-598. DOI: 10.1136/bjsports-2019-100765.

189. Gowd AK, Cvetanovich GL, Liu JN, et al. Management of Chondral Lesions of the Knee: Analysis of Trends and Short-Term Complications Using the National Surgical Quality Improvement Program Database. *Arthroscopy* 2019; 35: 138-146. 20181122. DOI: 10.1016/j.arthro.2018.07.049.

190. Everhart JS, Campbell AB, Abouljoud MM, et al. Cost-efficacy of Knee Cartilage Defect Treatments in the United States. *Am J Sports Med* 2020; 48: 242-251. 20190430. DOI: 10.1177/0363546519834557.

191. Brittberg M. Treatment of knee cartilage lesions in 2024: From hyaluronic acid to regenerative medicine. *Journal of Experimental Orthopaedics* 2024; 11. DOI: 10.1002/jeo2.12016.

192. Abraamyan T, Johnson AJ, Wiedrick J, et al. Marrow Stimulation Has Relatively Inferior Patient-Reported Outcomes in Cartilage Restoration Surgery of the Knee: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *The American Journal of Sports Medicine* 2022; 50: 858-866. DOI: 10.1177/03635465211003595.

193. Zamborsky R and Danisovic L. Surgical Techniques for Knee Cartilage Repair: An Updated Large-Scale Systematic Review and Network Meta-analysis of Randomized Controlled Trials. *Arthroscopy: The Journal of Arthroscopic & Related Surgery* 2020; 36: 845-858. DOI: https://doi.org/10.1016/j.arthro.2019.11.096.

194. Na Y, Shi Y, Liu W, et al. Is implantation of autologous chondrocytes superior to microfracture for articular-cartilage defects of the knee? A systematic review of 5-year follow-up data. *Int J Surg* 2019; 68: 56-62. 20190618. DOI: 10.1016/j.ijsu.2019.06.007.

195. Christensen BB, El-Galaly A, Laursen JO, et al. Eighty Percent Survival of Resurfacing Implants in the Knee After 10 Years: A Nationwide Cohort Study on 379 Procedures from the Danish Knee Arthroplasty Registry. *CARTILAGE* 2021; 13: 900S-906S. DOI: 10.1177/19476035211030983.

196. Megaloikonomos PD, Becher C, Van Der Stok J, et al. Femoral condyle resurfacing using an inlay metal implant: low revision rate of 266 patients in a 5–10 years follow-up. *Arch Orthop Trauma Surg* 2021; 143: 1243-1251. DOI: 10.1007/s00402-021-04251-x.

197. Stålman A, Sköldenberg O, Martinez-Carranza N, et al. No implant migration and good subjective outcome of a novel customized femoral resurfacing metal implant for focal chondral lesions. *Knee Surg Sports Traumatol Arthrosc* 2018; 26: 2196-2204. DOI: 10.1007/s00167-017-4805-2.

198. Faber S, Seiferth N, Angele P, et al. Factors correlating with patients' satisfaction after undergoing cartilage repair surgery—data from the German Cartilage Registry (KnorpelRegister DGOU). *Int Orthop* 2022; 46: 457-464. DOI: 10.1007/s00264-021-05274-0.

199. Vanlauwe J, Saris DBF, Victor J, et al. Five-Year Outcome of Characterized Chondrocyte Implantation Versus Microfracture for Symptomatic Cartilage Defects of the Knee. *The American Journal of Sports Medicine* 2011; 39: 2566-2574. DOI: doi:10.1177/0363546511422220.

200. Lim H-C, Bae J-H, Song S-H, et al. Current Treatments of Isolated Articular Cartilage Lesions of the Knee Achieve Similar Outcomes. *Clin Orthop Relat Res* 2012; 470: 2261-2267. DOI: 10.1007/s11999-012-2304-9.

201. Kon E, Gobbi A, Filardo G, et al. Arthroscopic Second-Generation Autologous Chondrocyte Implantation Compared with Microfracture for Chondral Lesions of the Knee:Prospective Nonrandomized Study at 5 Years. *The American Journal of Sports Medicine* 2009; 37: 33-41. DOI: 10.1177/0363546508323256.

202. Kreuz PC, Steinwachs MR, Erggelet C, et al. Results after microfracture of full-thickness chondral defects in different compartments in the knee. *Osteoarthritis Cartilage* 2006; 14: 1119-1125. DOI: 10.1016/j.joca.2006.05.003.

203. Knutsen G, Drogset JO, Engebretsen L, et al. A randomized trial comparing autologous chondrocyte implantation with microfracture. Findings at five years. *J Bone Joint Surg Am* 2007; 89: 2105-2112. DOI: 10.2106/JBJS.G.00003.

204. Saris D, Price A, Widuchowski W, et al. Matrix-Applied Characterized Autologous Cultured Chondrocytes Versus Microfracture: Two-Year Follow-up of a Prospective Randomized Trial. *Am J Sports Med* 2014; 42: 1384-1394. 2014/04/10. DOI: 10.1177/0363546514528093.

205. Randsborg P-H, Brinchmann JE, Owesen C, et al. Autologous Chondrocyte Implantation Is Not Better Than Arthroscopic Debridement for the Treatment of Symptomatic Cartilage Lesions of the Knee: Two-Year Results From a Randomized-Controlled Trial. *Arthroscopy, Sports Medicine, and Rehabilitation* 2024; 6. DOI: 10.1016/j.asmr.2024.100909.

206. Røtterud JH, Sivertsen EA, Forssblad M, et al. Effect on Patient-Reported Outcomes of Debridement or Microfracture of Concomitant Full-Thickness Cartilage Lesions in Anterior Cruciate Ligament-Reconstructed Knees: A Nationwide Cohort Study From Norway and Sweden of 357 Patients With 2-Year Follow-up. *Am J Sports Med* 2016; 44: 337-344. 20151211. DOI: 10.1177/0363546515617468.

207. de Windt TS, Bekkers JEJ, Creemers LB, et al. Patient Profiling in Cartilage Regeneration: Prognostic Factors Determining Success of Treatment for Cartilage Defects. *The American Journal of Sports Medicine* 2009; 37: 58-62. DOI: 10.1177/0363546509349765.

208. Hochrein A, Zinser W, Spahn G, et al. What parameters affect knee function in patients with untreated cartilage defects: baseline data from the German Cartilage Registry. *Int Orthop* 2019; 43: 1107-1112. DOI: 10.1007/s00264-018-4125-2.

209. Walczak BE, McCulloch PC, Kang RW, et al. Abnormal findings on knee magnetic resonance imaging in asymptomatic NBA players. *J Knee Surg* 2008; 21: 27-33. DOI: 10.1055/s-0030-1247788.

210. Hirschmüller A, Schoch W, Baur H, et al. Rehabilitation before regenerative cartilage knee surgery: a new prehabilitation guideline based on the best available evidence. *Arch Orthop Trauma Surg* 2019; 139: 217-230. 2018/08/23. DOI: 10.1007/s00402-018-3026-6.

211. Hanaoka C, Fausett C and Jayabalan P. Nonsurgical Management of Cartilage Defects of the Knee: Who, When, Why, and How? *The journal of knee surgery* 2020; 33: 1078-1087. 2020/07/14. DOI: 10.1055/s-0040-1713813.

212. Juhl C, Christensen R, Roos EM, et al. Impact of Exercise Type and Dose on Pain and Disability in Knee Osteoarthritis: A Systematic Review and Meta-Regression Analysis of Randomized Controlled Trials. *Arthritis & Rheumatology* 2014; 66: 622-636. DOI: 10.1002/art.38290.

213. de Girolamo L. ESSKA European consensus; The use of injectable Orthobiologics for knee osteoarthritis: Part 1 - Blood-derived Products (PRP), https://cdn.ymaws.com/www.esska.org/resource/resmgr/docs/consensus_projects/FINAL_document_ORBIT_long.pdf (2022, accessed 12.05.2024 2024).

214. de Girolamo L. ESSKA European (Title) Consensus: The use of injectable Orthobiologics for knee osteoarthritis: Part 2 – Cell-Based Therapy (CBT), https://cdn.ymaws.com/www.esska.org/resource/resmgr/docs/consensus_projects/2024_orbit_complete_report.pdf (2024, accessed 12.05.2024 2024).

215. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage* 2019; 27: 1578-1589. DOI: 10.1016/j.joca.2019.06.011.

216. NICE guideline: Osteoarthritis in over 16s: diagnosis and management, https://www.nice.org.uk/guidance/ng226 (2022, accessed 08.04.2024 2024).

217. Van Dijk CN, Reilingh ML, Zengerink M, et al. Osteochondral defects in the ankle: why painful? *Knee Surg Sports Traumatol Arthrosc* 2010; 18: 570-580. DOI: 10.1007/s00167-010-1064-x.

218. Nakano N, Shoman H, Olavarria F, et al. Why are patients dissatisfied following a total knee replacement? A systematic review. *Int Orthop* 2020; 44: 1971-2007. DOI: 10.1007/s00264-020-04607-9.

219. Hoorntje A, Witjes S, Koenraadt KLM, et al. More Severe Preoperative Kellgren-Lawrence Grades of Knee Osteoarthritis were Partially Associated with Better Postoperative Patient-Reported Outcomes in TKA Patients. *J Knee Surg* 2019; 32: 211-217. 20180228. DOI: 10.1055/s-0038-1635114.

220. Sauder N, Galea VP, Rojanasopondist P, et al. Regional differences between the US, Scandinavia, and South Korea in patient demographics and patient-reported outcomes for primary total knee arthroplasty. *Arch Orthop Trauma Surg* 2020; 140: 93-108. 20191024. DOI: 10.1007/s00402-019-03286-5.

221. Rehman Y, Lindberg MF, Arnljot K, et al. More Severe Radiographic Osteoarthritis Is Associated With Increased Improvement in Patients' Health State Following a Total Knee Arthroplasty. *The Journal of Arthroplasty* 2020; 35: 3131-3137. DOI: 10.1016/j.arth.2020.06.025.

222. Bacon K, LaValley MP, Jafarzadeh SR, et al. Does cartilage loss cause pain in osteoarthritis and if so, how much? *Ann Rheum Dis* 2020; 79: 1105-1110. DOI: 10.1136/annrheumdis-2020-217363.

223. Hochberg MC, Guermazi A, Guehring H, et al. Effect of Intra-Articular Sprifermin vs Placebo on Femorotibial Joint Cartilage Thickness in Patients With Osteoarthritis. *JAMA* 2019; 322: 1360. DOI: 10.1001/jama.2019.14735.

224. Moseley JB, O'Malley K, Petersen NJ, et al. A Controlled Trial of Arthroscopic Surgery for Osteoarthritis of the Knee. *N Engl J Med* 2002; 347: 81-88. DOI: 10.1056/nejmoa013259.

225. Sihvonen R, Paavola M, Malmivaara A, et al. Arthroscopic partial meniscectomy versus placebo surgery for a degenerative meniscus tear: a 2-year follow-up of the randomised controlled trial. *Ann Rheum Dis* 2018; 77: 188-195. 2017/05/20. DOI: 10.1136/annrheumdis-2017-211172.

# 15. Appendix

# Paper I

# The Long-Term Risk of Knee Arthroplasty in Patients with Arthroscopically Verified Focal Cartilage Lesions

## A Linkage Study with the Norwegian Arthroplasty Register, 1999 to 2020

Thomas Birkenes, MD, Ove Furnes, MD, PhD, Stein Haakon Laastad Lygre, PhD, Eirik Solheim, MD, PhD, Asbjorn Aaroen, MD, PhD, Gunnar Knutsen, MD, PhD, Jon Olav Drogset, MD, PhD, Stig Heir, MD, PhD, Lars Engebretsen, MD, PhD, Sverre Loken, MD, PhD, and Haavard Visnes, MD, PhD



**Background:** Focal cartilage lesions are common in the knee. The risk of later ipsilateral knee arthroplasty remains unknown. The purposes of the present study were to evaluate the long-term cumulative risk of knee arthroplasty after arthroscopic identification of focal cartilage lesions in the knee, to investigate the risk factors for subsequent knee arthroplasty, and to estimate the subsequent cumulative risk of knee arthroplasty compared with that in the general population.

**Methods:** Patients who had undergone surgical treatment of focal cartilage lesions at 6 major Norwegian hospitals between 1999 and 2012 were identified. The inclusion criteria were an arthroscopically classified focal cartilage lesion in the knee, an age of ≥18 years at the time of surgery, and available preoperative patient-reported outcomes (PROMs). The exclusion criteria were osteoarthritis or "kissing lesions" at the time of surgery. Demographic data, later knee surgery, and PROMs were collected with use of a questionnaire. A Cox regression model was used to adjust for and investigate the impact of risk factors, and Kaplan-Meier analysis was performed to estimate cumulative risk. The risk of knee arthroplasty in the present cohort was compared with that in the age-matched general Norwegian population.

**Results:** Of the 516 patients who were eligible, 322 patients (328 knees) consented to participate. The mean age at the time of the index procedure was 36.8 years, and the mean duration of follow-up was 19.8 years. The 20-year cumulative risk of knee arthroplasty in the cartilage cohort was 19.1% (95% CI, 14.6% to 23.6%). Variables that had an impact on the risk of knee arthroplasty included an ICRS grade of 3 to 4 (hazard ratio [HR], 3.1; 95% CI, 1.1 to 8.7), an age of ≥40 years at time of cartilage surgery (HR, 3.7; 95% CI, 1.8 to 7.7), a BMI of 25 to 29 kg/m$^2$ (HR, 3.9; 95% CI, 1.7 to 9.0), a BMI of ≥30 kg/m$^2$ (HR, 5.9; 95% CI, 2.4 to 14.3) at the time of follow-up, autologous chondrocyte implantation (ACI) at the time of the index procedure (HR, 3.4; 95% CI, 1.0 to 11.4), >1 focal cartilage lesion (HR, 2.1; 95% CI, 1.1 to 3.7), and a high preoperative visual analog scale (VAS) score for pain at the time of the index procedure (HR, 1.1; 95% CI, 1.0 to 1.1). The risk ratio of later knee arthroplasty in the cartilage cohort as compared with the age-matched general Norwegian population was 415.7 (95% CI, 168.8 to 1,023.5) in the 30 to 39-year age group.

**Conclusions:** In the present study, we found that the 20-year cumulative risk of knee arthroplasty after a focal cartilage lesion in the knee was 19%. Deep lesions, higher age at the time of cartilage surgery, high BMI at the time of follow-up, ACI, and >1 cartilage lesion were associated with a higher risk of knee arthroplasty.

**Level of Evidence:** Prognostic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Focal cartilage lesions are common in the knee and represent a clinical challenge[1-3]. In the study by Heir et al., patients who were scheduled for cartilage surgery reported Knee Injury and Osteoarthritis Outcome Score Quality of Life (KOOS QoL) subscores similar to those of patients scheduled for knee arthroplasty[4]. The intra-articular hyaline cartilage is unable to heal naturally[5]. Several treatment options (including microfracture, autologous chondrocyte implantation [ACI], and mosaicplasty) are available, but the optimum treatment has yet to be determined[6,7]. Furthermore, no treatment has been proven to restore hyaline cartilage or decrease the risk of osteoarthritis[5].

**Disclosure:** The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJS/H503).

Patients who have had previous knee surgery undergo knee arthroplasty at a significantly younger age than those who have not[8]. Several factors have been reported to increase the lifetime risk of knee arthroplasty, including age, body mass index (BMI), body height, sex, manual labor, knee injury, and family history[9,10].

Long-term articular cartilage studies have shown that the rate of knee arthroplasty has ranged from 0% to 17% following regenerative cartilage surgical procedures such as microfracture, ACI, chondroplasty, or mosaicplasty[11-14]. The relative risk of knee arthroplasty in patients with a previous focal cartilage lesion versus the general population remains unknown. Thus, the purposes of the present study were to (1) evaluate the long-term cumulative risk of knee arthroplasty in patients with arthroscopically verified focal cartilage lesions in the knee, (2) to investigate the risk factors for knee arthroplasty in patients with cartilage lesions, and (3) to estimate the relative risk of knee arthroplasty in patients with arthroscopically verified focal cartilage lesions as compared with the risk in the general population.

## Materials and Methods

### *Patients and Methods*

We identified patients with arthroscopically verified focal cartilage lesions that had been treated at 6 major Norwegian hospitals between 1999 and 2012 (Fig. 1). These hospitals were chosen because they had participated in several prospective clinical cartilage trials in the contemporary period[15-18].

The inclusion criteria in this study were (1) an arthroscopically verified and classified focal cartilage lesion in the knee and (2) an age of ≥18 years at the time of surgery. At least 1 preoperative patient-reported outcome measure (PROM) score had to be available. Exclusion criteria were cartilage lesions that were assessed as being osteoarthritis or "kissing lesions" intraoperatively by the surgeon (Fig. 1).

Patients who were found to be eligible for inclusion were contacted by mail. Patients who were listed in the Norwegian Population Register as emigrated or deceased were excluded. Informed consent was obtained. Each patient received a questionnaire regarding their current height, weight, level of education, knee function, additional knee surgery, and level of activity. The

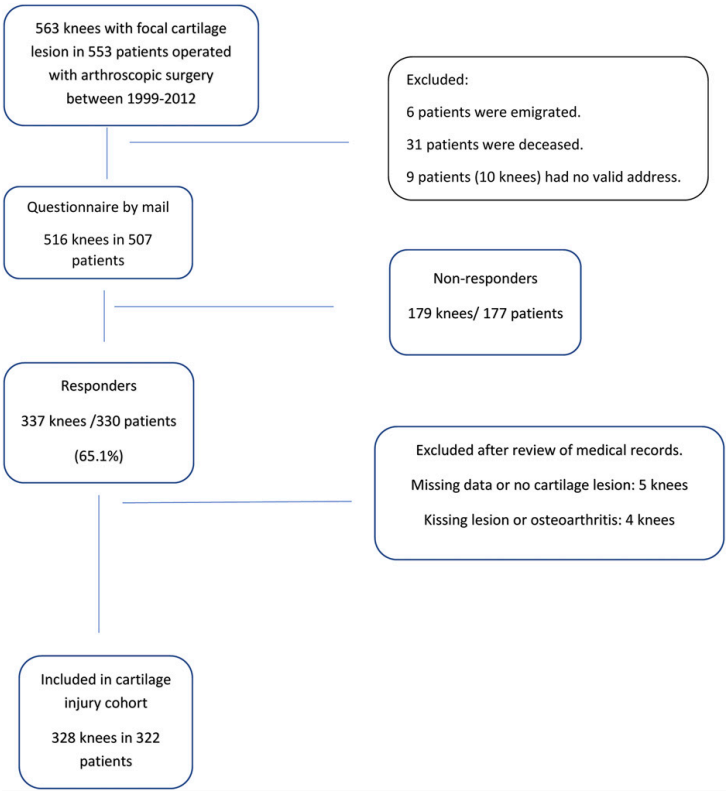



Fig. 1

Flowchart illustrating the inclusion of patients in the cartilage cohort.

PROMs that had been previously used were the KOOS score[19], Lysholm score[20], and International Cartilage Regeneration & Joint Preservation Society (ICRS) visual analog scale (VAS) for knee pain[21].

After informed consent had been obtained, the surgical report and/or trial data for each participant were made available to the main investigator (T.B.). The variables of interest included any previous cartilage surgery; the location, size, and ICRS classification of the cartilage lesions; the type of operative treatment; any additional procedures; and preoperative PROMs. Nine knees in 8 patients who met the exclusion criteria at the time of surgery were then identified and excluded (Fig. 1).

The Norwegian Arthroplasty Register (NAR) has captured data on knee arthroplasty interventions and outcomes in Norway since 1994 and has >95% completeness of reporting[22,23]. The patients in the current study and in the NAR are identified by their Norwegian unique identification number. Data from the NAR included the date of knee arthroplasty, surgeon-reported cause of knee arthroplasty (i.e., osteoarthritis, posttraumatic arthritis, inflammatory arthritis), type of prothesis, and laterality.

A patient was registered as having a knee arthroplasty when (1) the patient reported an ipsilateral knee arthroplasty in the questionnaire and/or (2) the ipsilateral knee was registered in the NAR.

The study was approved by the Regional Ethics Committee (2017/1387).

### *Statistical Analysis*

The data were analyzed with use of SPSS Statistics (version 26; IBM). The level of significance was set at $p < 0.05$.

The cumulative risk of knee arthroplasty was estimated with use of the Kaplan-Meier method[24]. Cox regression models were used to investigate risk factors for knee arthroplasty in the study population. A graphical causal model (www.dagitty.net/dags.html) was used to identify variables to adjust for, as suggested by Westreich and Greenland[25]. Preoperative Lysholm and ICRS VAS pain scores were registered for 185 and 114 patients, respectively, and no patient had recorded >1 preoperative PROM. The linear assumption of the Cox model was confirmed for the preoperative VAS pain score with use of the Box-Tidwell procedure. Survival times were calculated as the time between cartilage surgery and knee arthroplasty or the end of the study on December 31, 2020. The proportional hazards assumption was fulfilled for all variables that were investigated except for BMI group and anterior cruciate ligament (ACL) surgery (yes or no). On the basis of a visual inspection of the Kaplan-Meier plot, both variables were analyzed separately according to the duration of follow up (<12 or ≥12 years).

A subgroup of patients without any concomitant procedures at the time of the index procedure were analyzed with use of the same Cox model as described above.

The relative risk of knee arthroplasty after a cartilage injury as compared with the risk in the age-matched general population was estimated. The absolute risk of knee arthroplasty in the cartilage injury cohort was estimated by dividing the number of knee arthroplasties by the total number of knees with cartilage injury in each age-matched group. For the general population, the numerator was the number of all other patients undergoing knee arthroplasty without inflammatory arthritis or previous cartilage surgery as reported to the NAR between January 1, 1999, and December 31, 2020. The denominator was the average number of Norwegian citizens in the same period, retrieved from Statistics Norway. The results were stratified in 10-year groups based on the age at the time of knee arthroplasty.

To further aid the clinical interpretation of the relative risk of knee arthroplasty in the cartilage injury cohort as compared with the general population, we also stratified each 10-year age group at the time of knee arthroplasty according to when the patient underwent the index cartilage procedure. For the general population, the absolute risk was estimated as described in the previous paragraph. In the cartilage injury cohort, the numerator was the number of knee arthroplasties in each 10-year age group (at the time of cartilage surgery) and the denominator was the total number of patients with cartilage injury in the same age group.

A power analysis was performed prior to inclusion. In order to achieve an 80% chance of detecting a 4-times higher rate of knee arthroplasty in the focal cartilage lesion cohort as compared with the general population, we needed to include at least 181 participants.

### *Source of Funding*

The present study was funded by the Norwegian Research Council through the Norwegian Cartilage Project.

## Results

Of the 553 patients (563 knees) who were identified, 507 patients (516 knees) were eligible, and, of those, 322 patients (328 knees) consented to participate (Fig. 1). One hundred and sixty-four patients (169 knees) had participated in studies with previously published intermediate to long-term results[26–28]. Most patients had a pre-enrollment radiograph that did not show any joint-space narrowing. The demographic characteristics of the patients are summarized in Table I. At baseline, there were no significant differences between the responders and nonresponders apart from the responders being a mean of 3.0 years older ($p = 0.002$).

The 20-year cumulative risk of knee arthroplasty after arthroscopic verification of a focal cartilage lesion was 19.1% (95% confidence interval [CI], 14.6% to 23.6%). The mean age at the index procedure for the treatment of the focal cartilage lesion was 36.8 years, and the mean duration of follow-up was 19.8 years. The results of the Cox regression model are summarized in Table II. The BMI classifications of overweight and obese at the time of follow-up were the 2 most important risk factors for knee arthroplasty, with an adjusted hazard ratio (aHR) of 3.9 (95% CI, 1.7 to 9.0) and 5.9 (95% CI, 2.4 to 14.3), respectively. The size of the cartilage lesion did not significantly influence the risk of later knee arthroplasty, but ICRS grade-3 and 4 lesions did increase the risk of knee arthroplasty (aHR, 3.1; 95% CI, 1.1 to 8.7). ACI treatment increased the risk of knee arthroplasty (aHR, 3.4; 95% CI, 1.0 to 11.4) compared

**TABLE I Demographic and Descriptive Characteristics of 328 Knees with Focal Cartilage Lesions Treated with Arthroscopic Surgery in 6 Norwegian Hospitals Between 1999 and 2012***

| | |
|---|---|
| No. of knees | 328 |
| Sex (male/female) *(no. of knees)* | 188 (57%)/140 (43%) |
| Side (right/left) *(no. of knees)* | 174 (53%)/154 (47%) |
| Age at time of surgery† *(yr)* | 36.8 (35.6-38.0) |
| Time from index procedure to end of study† *(yr)* | 19.8 (19.4-20.2) |
| ICRS grade *(no. of knees)* | |
| 1-2 | 52 (15.9%) |
| 3-4 | 276 (84.1%) |
| Size of cartilage lesion† *($mm^2$)* | 201.3 (178.9-223.7) |
| Preop. Lysholm score (n = 184)† | 49.4 (46.9-51.8) |
| Preop. VAS pain score (n = 105)† | 44.3 (39.6-49.0) |
| Location of cartilage lesion *(no. of knees)* | |
| Patellofemoral | 73 (22.3%) |
| Medial | 204 (62.2%) |
| Lateral | 51 (15.5%) |
| Type of cartilage lesion *(no. of knees)* | |
| Traumatic | 125 (38.1%) |
| OCD | 17 (5.2%) |
| Degenerative | 4 (1.2%) |
| Not reported | 182 (55.5%) |
| Type of treatment *(no. of knees)* | |
| No cartilage treatment | 93 (28.4%) |
| Microfracture | 124 (37.8%) |
| Debridement | 12 (3.0%) |
| ACI/MACI | 30 (9.1%) |
| Mosaicplasty | 53 (16.2%) |
| Other | 16 (4.9%) |
| Level of education *(no. of knees)* | |
| High school | 155 (47.3%) |
| Bachelor's/Master's degree | 164 (50.0%) |
| Missing information | 9 (2.7%) |
| BMI at end of study† *($kg/m^2$)* | 27.4 (26.9-27.9) |
| BMI category at end of study *(no. of knees)* | |
| <25 $kg/m^2$ | 100 (30.5%) |
| 25-29 $kg/m^2$ | 137 (41.8%) |
| ≥30 $kg/m^2$ | 75 (22.9%) |
| Missing information | 16 (4.9%) |
| Ipsilateral ACL reconstruction *(no. of knees)* | 50 (15.2%) |
| At index surgery | 15 (4.6%) |
| Before or after index surgery | 35 (10.7%) |
| None | 278 (84.8%) |
| Ipsilateral meniscal resection *(no. of knees)* | 100 (30.5%) |
| At index surgery | 46 (14.0%) |
| Before or after index surgery | 54 (16.5%) |
| None | 228 (69.5%) |
| Knee arthroplasty *(no. of knees)* | 59 (18.0%) |
| Male patients (n=188) | 30 (16.0%) |
| Female patients (n=140) | 29 (20.7%) |
| Knee arthroplasty procedures *(no. of knees)* | 59 (18.0%) |
| Total knee arthroplasty (n = 59) | 48 (81.4%) |
| Unicompartmental knee arthroplasty (n = 59) | 8 (13.6%) |
| Patellofemoral knee arthroplasty | 3 (5.1%) |
| Age at the time of knee arthroplasty† *(yr)* | |
| Male patients | 56.4 (53.1-59.7) |
| Female patients | 51.9 (47.6-56.1) |
| Time from index cartilage surgery to knee arthroplasty† *(yr)* | |
| Male patients | 13.9 (11.9-16.0) |
| Female patients | 11.4 (9.0-13.8) |

*N = 328 unless indicated otherwise. ICRS = International Cartilage Repair & Joint Preservation Society, VAS = visual analog scale, OCD = osteochondritis dissecans, ACI = autologous chondrocyte implantation, MACI = matrix-induced ACI, ACL = anterior cruciate ligament. †The values are given as the mean, with the 95% CI in parenthesis.

with no cartilage treatment at index surgery. The preoperative Lysholm and VAS pain scores were analyzed as continuous variables. A low preoperative Lysholm score did not significantly increase the risk of knee arthroplasty, whereas a high preoperative VAS pain score did and was found to be linearly correlated with the risk. ACL reconstruction was not a risk factor for total knee arthroplasty (TKA) at the time of the latest follow-up, but there was an increased risk in the <12-year follow-up group (aHR, 3.2; 95% CI, 1.4 to 7.3) (subanalysis not presented). Increased BMI was a significant risk factor only in the ≥12-year follow-up group.

The subanalysis of patients without any concomitant procedures at the time of the index procedure demonstrated no significant difference in the risk of knee arthroplasty between the treatment groups (see Appendix). Furthermore, an additional Cox analysis including the time period of the index operation (1999 to 2004 or 2005 to 2012) did not alter our findings.

The Cox adjusted survival curves of the knees with a cartilage lesion, with knee arthroplasty as the end point, are presented in Figures 2-A through 2-D. The survival curves

**TABLE II Twenty-Year Cumulative Risk (1 − Kaplan-Meier Survival) and Risk Factors Associated with Knee Arthroplasty After Cartilage Injury, 1999 to 2020, in a Focal Cartilage Lesion Cohort Linked to the Norwegian Arthroplasty Register§§§**

| | No. of Knees | No. of Knee Arthroplasties | No of Knee Arthroplasties (TKAs/ UKAs/PFs) | 20-Year Cumulative Risk (95% CI) | Crude HR* (95% CI) | Adjusted HR† (95% CI) |
|---|---|---|---|---|---|---|
| Total | 328 | 59 (18.0%) of 328 | | 19.1 (14.6-23.6) | | |
| Age at time of surgery† *(no. of knees)* | | | | | | |
| 18-29 yr | 83 (25.3%) | 9 (10.8%) of 83 | 9 (7/0/2) | 13.8 (9.7-17.9) | 1 | |
| 30-39 yr | 128 (39.0%) | 14 (10.9%) of 128 | 14 (12/2/0) | 12.0 (5.7-18.3) | 1.08 (0.47-2.50) | |
| ≥40 yr | 117 (35.7%) | 36 (30.8%) of 117 | 36 (29/6/1) | 32.2 (23.2-41.2) | 3.69 (1.78-7.67) | |
| Sex† *(no. of knees)* | | | | | | |
| Male | 188 (57.3%) | 30 (16.0%) of 188 | 30 (25/5/0) | 14.1 (8.8-19.4) | 1 | |
| Female | 140 (42.7%) | 29 (20.7%) of 140 | 29 (23/3/3) | 22.8 (15.4-30.3) | 1.38 (0.83-2.30) | |
| BMI at end of study§ *(no. of knees)* | | | | | | |
| <25 kg/m$^2$ | 100 (30.5%) | 7 (7.0%) of 100 | 7 (5/1/1) | 7.2 (2.1-12.3) | 1 | 1 |
| 25-29 kg/m$^2$ | 137 (41.8%) | 27 (19.7%) of 137 | 27 (20/6/1) | 22.2 (14.6-29.8) | 3.07 (1.34-7.06) | 3.86 (1.65-9.00) |
| ≥30 kg/m$^2$ | 75 (22.9%) | 19 (25.3%) of 75 | 19 (17/1/1) | 27.1 (16.3-37.9) | 4.1 (1.74-9.88) | 5.90 (2.43-14.32) |
| Size of lesion# *(no. of knees)* | | | | | | |
| <200 mm$^2$ | 214 (65.2%) | 40 (18.7%) of 214 | 40 (32/5/3) | 20.3 (14.6-26.0) | 1 | 1 |
| ≥200 mm$^2$ | 114 (34.8%) | 19 (16.7%) of 114 | 19 (16/3/0) | 16.1 (8.8-23.4) | 0.92 (0.53-1.59) | 0.99 (0.55-1.78) |
| ICRS grade# *(no. of knees)* | | | | | | |
| 1-2 | 52 (15.9%) | 4 (7.7%) of 52 | 4 (4/0/0) | 7.7 (0.4-15.0) | 1 | 1 |
| 3-4 | 276 (84.1%) | 55 (19.9%) of 276 | 55 (44/8/3) | 21.5 (16.2-26.8) | 3.35 (1.21-9.27) | 3.09 (1.10-8.70) |
| Level of education** *(no. of knees)* | | | | | | |
| High school | 155 (47.3%) | 33 (21.3%) of 155 | 33 (24/6/3) | 20.8 (14.1-27.5) | 1 | 1 |
| Bachelor's/ Master's degree | 164 (50.0%) | 22 (13.4%) of 164 | 22 (20/2/0) | 15.8 (9.7-21.9) | 0.62 (0.36-1.06) | 0.60 (0.35-1.02) |
| ACL reconstructed at any time†† *(no. of knees)* | | | | | | |
| No | 278 (84.8%) | 50 (18.0%) of 278 | 50 (39/8/3) | 19.1 (14.2-24.0) | 1 | 1 |
| Yes | 50 (15.2%) | 9 (18.0%) of 50 | 9 (9/0/0) | 19.1 (7.1-31.1) | 0.94 (0.46-1.91) | 1.62 (0.76-3.47) |
| Meniscal resection at any time†† *(no. of knees)* | | | | | | |
| Yes | 100 (30.5%) | 18 (18.0%) of 100 | 18 (18/0/0) | 21.3 (12.5-30.1) | 1 | 1 |
| No | 228 (69.5%) | 41 (18%) of 228 | 41 (30/8/3) | 18.1 (12.8-23.4) | 1.0 (0.58-1.75) | 0.96 (0.53-1.73) |
| Location of cartilage lesion§§ *(no. of knees)* | | | | | | |
| Patellofemoral | 73 (22.3%) | 9 (12.3%) of 73 | 9 (7/0/2) | 13.5 (5.3-21.7) | 1 | 1 |
| Medial | 204 (62.2%) | 38 (18.6%) of 204 | 38 (29/8/1) | 19.7 (13.8-25.6) | 1.53 (0.74-3.17) | 1.27 (0.58-2.78) |
| Lateral | 51 (15.5%) | 12 (23.5%) of 51 | 12 (12/0/0) | 23.3 (11.1-35.5) | 1.8 (0.74-4.30) | 1.40 (0.55-3.57) |

*continued*

**TABLE II (*continued*)**

| | No. of Knees | No. of Knee Arthroplasties | No of Knee Arthroplasties (TKAs/ UKAs/PFs) | 20-Year Cumulative Risk (95% CI) | Crude HR* (95% CI) | Adjusted HR† (95% CI) |
|---|---|---|---|---|---|---|
| Cartilage lesions## *(no. of knees)* | | | | | | |
| 1 lesion | 244 (74.4%) | 33 (13.5%) of 244 | 33 (24/6/3) | 14.2 (9.5-18.9) | 1 | 1 |
| >1 lesion | 84 (25.6%) | 26 (31.0%) of 84 | 26 (24/2/0) | 31.2 (21.2-41.2) | 2.25 (1.34-3.76) | 2.05 (1.13-3.71) |
| Treatment at index operation*** *(no. of knees)* | | | | | | |
| No cartilage treatment | 93 (28.4%) | 13 (14.0%) of 93 | 13 (11/1/1) | 14.2 (7.1-21.3) | 1 | 1 |
| Debridement/ microfracture | 136 (41.5%) | 28 (20.6%) of 136 | 28 (23/3/2) | 22.1 (14.5-29.7) | 1.8 (0.95-3.56) | 1.61 (0.70-3.70) |
| ACI | 30 (9.1%) | 7 (23.3%) of 30 | 7 (5/2/0) | 21.0 (5.9-36.1) | 2.0 (0.78-5.01) | 3.43 (1.03-11.39) |
| OATS | 53 (16.2%) | 11 (20.8%) of 53 | 11 (9/2/0) | 21.1 (9.9-32.3) | 1.65 (0.74-3.69) | 1.95 (0.67-5.69) |
| Other | 16 (4.9%) | 0 | 0 | 0 | 0.0 (0-3.89 × $10^{295}$) | 0.0 (0.0) |
| Preop. VAS pain score†††,‡‡‡ | 105 (32.0%) | 14 (13.3%) of 105 | | | 1.03 (1.01-1.06) | 1.08 (1.03-1.14) |
| Preop. Lysholm score†††,‡‡‡ | 18 (56.1%) | 42 (22.8%) of 184 | | | 0.99 (0.97-1.00) | 1.0 (0.98-1.02) |

§§§TKA = total knee arthroplasty, UKA = unicompartmental knee arthroplasty, PF = patellofemoral knee arthroplasty, CR = cumulative risk, CI = confidence interval, BMI = body mass index, ICRS = International Cartilage Repair & Joint Preservation Society, ACL = anterior cruciate ligament, ACI = autologous chondrocyte implantation, OATS = osteochondral autograft transplantation system (mosaicplasty), VAS = visual analog scale. *HR = hazard rate ratio from Cox analysis. †Cox-adjusted for variables according to a graphical causal model ‡Not adjusted. §Adjusted for age at time of surgery, sex, level of education. #Adjusted for age at time of surgery, BMI, meniscal resection. **Adjusted for sex. ††Adjusted for age at time of surgery, BMI, sex, level of education. ‡‡Adjusted for ACL reconstruction, age at time of surgery, BMI, sex, level of education. §§Adjusted for ACL reconstruction, age at time of surgery, sex, meniscal resection. ##Adjusted for ACL reconstruction, age at time of surgery, BMI, sex, level of education, meniscal resection, size of lesion. ***Adjusted for age at time of surgery, ICRS grade, level of education, location of lesion, number of lesions, size of lesion. †††Adjusted for ACL reconstruction, age at time of surgery, BMI, sex, ICRS grade, level of education, location of lesion, meniscal resection, number of lesions, size of lesion. ‡‡‡Adjusted for VAS pain and Lysholm scores analyzed as continuous variables.



are adjusted for the same covariates as in the Cox regression model.

Table III summarizes the risk of knee arthroplasty in the cartilage cohort as compared with that in the age-matched general population. Table IV summarizes the subsequent risk of knee arthroplasty according to age at the time of cartilage surgery. The risk ratio of subsequent knee arthroplasty in the cartilage cohort versus the age-matched general Norwegian population ranged from 3.6 in the 60 to 69-year age group to 415.7 in the 30 to 39-year age group.

The rate of knee arthroplasty was significantly increased in all age groups except the 70 to 79-year age group, ranging from 819 to 952 of 100,000 in the cartilage cohort as compared with 2.3 to 229 of 100,000 in the general population (Table III).

Table V summarizes the number of concomitant surgical procedures at the time of the index procedure.

## Discussion

### *Principal Findings*

Patients with an arthroscopically verified focal cartilage lesion in the knee had a 19.1% 20-year cumulative risk of knee arthroplasty and a significantly increased risk of knee arthroplasty compared with the general population. The relative risk was particularly elevated in the younger population. The factors that were associated with an increased risk of subsequent knee arthroplasty included an older age at the time of arthroscopy, ACI treatment of the cartilage lesion, the depth of the cartilage lesion, a higher VAS pain score at the time of the index procedure, and a higher BMI at the time of follow-up.

### *Strengths and Limitations*

The main strength of the present study is that all focal cartilage lesions in the knee were evaluated arthroscopically. Furthermore, any concurrent meniscal or ligamentous lesions were registered. The patients in the present study had no malalignment (>5°) because of the inclusion criteria in the previous clinical trials[15,17,18]. The mean duration of follow-up of 20 years increases the ability to identify the long-term cumulative risk of knee arthroplasty. To our knowledge, this is the first long-term study outside of an ACL cohort that has included patients with arthroscopically verified focal cartilage lesions who have undergone no cartilage treatment[29,30]. As such, the findings of

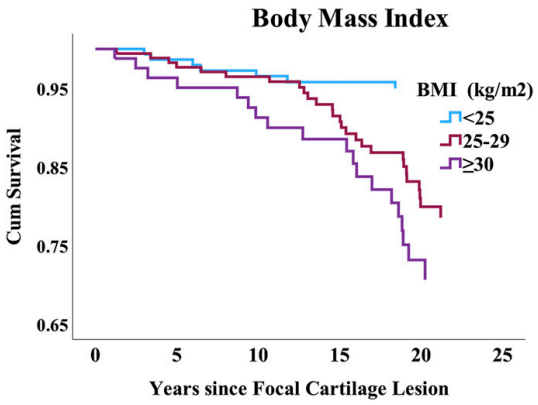



Fig. 2-A

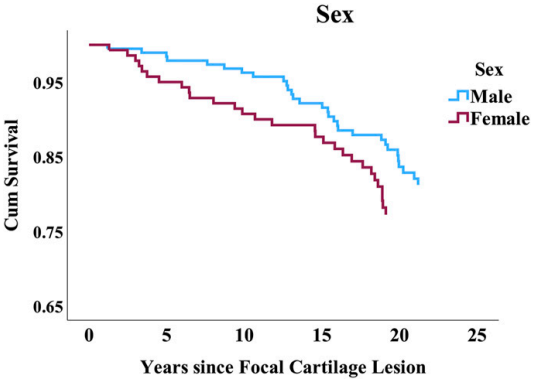



Fig. 2-B

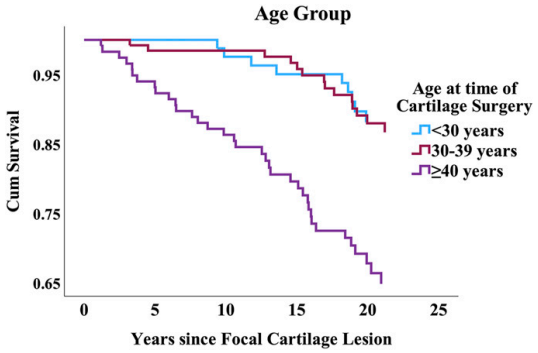



Fig. 2-C

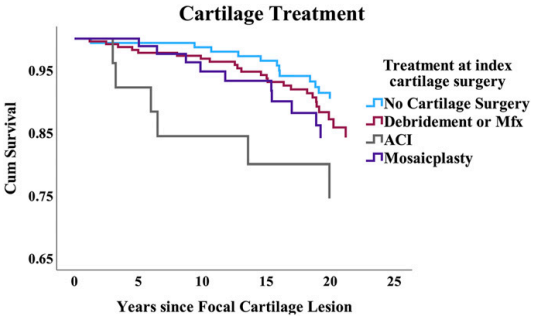



Fig. 2-D

**Fig. 2-A through 2-D** Cox adjusted survival curves of knees with focal cartilage lesions by World Health Organization BMI classes (adjusted for age at time of surgery, sex, and level of education) (**Fig. 2-A**), sex (unadjusted) (**Fig. 2-B**), age group at index surgery (unadjusted) (**Fig. 2-C**), and cartilage treatment (adjusted for age at time of surgery, ICRS grade, level of education, location of lesion, number of lesions, and size of lesion) (**Fig. 2-D**), with knee arthroplasty as the end point. Adjustment based on graphical causal model. Mfx = microfracture.

**TABLE III Risk Ratio of Knee Arthroplasty in Cartilage Cohort Versus General Norwegian Population***

| Cartilage Cohort | | | | Age-Matched General Population† | |
|---|---|---|---|---|---|
| Age at Knee Arthroplasty | No. of Knee Arthroplasties | No. of Patients in Age Group | No. of Knee Arthroplasties, 1999-2020 *(per $10^5$)* | No. of Knee Arthroplasties, 1999-2019 *(per $10^5$)* | Risk Ratio (95% CI) |
| 30-39 yr | 4 | 20 | 952.4 | 2.3 | 415.69 (168.83-1,023.49) |
| 40-49 yr | 15 | 80 | 892.9 | 18.1 | 49.42 (31.01-78.76) |
| 50-59 yr | 25 | 126 | 944.8 | 83.3 | 11.35 (7.93-16.24) |
| 60-69 yr | 11 | 64 | 818.5 | 229.0 | 3.57 (2.07-6.17) |
| 70-79 yr | 3 | 31 | 460.8 | 363.4 | 1.27 (0.43-3.76) |

*The relative risk of knee arthroplasty after a cartilage injury as compared with the general population. The absolute risk of knee arthroplasty in the cartilage cohort was estimated by dividing the number of knee arthroplasties by the total number of knees with cartilage injury in each group. For the general population, the numerator was all other patients with knee arthroplasty without inflammatory arthritis or previous cartilage surgery on the ipsilateral side as reported to the NAR between January 1, 1999, and December 31, 2020. The denominator was the average number of Norwegian citizens in the same period, retrieved from population data from Statistics Norway. One patient was 81 years old at the time of knee arthroplasty and was excluded. †General population excluded patients with previous cartilage surgery.

**TABLE IV Risk Ratio of Knee Arthroplasty After Cartilage Surgery in Specific Age Ranges Versus Age-Matched General Norwegian Population***

| Cartilage Cohort | | | | | Age-Matched General Population† | |
|---|---|---|---|---|---|---|
| Age at Cartilage Surgery | Age at Knee Arthroplasty | No. of Knee Arthroplasties | No. of Patients in Age Group | No. of Knee Arthroplasties, 1999-2020 *(per $10^5$)* | No. of Knee Arthroplasties, 1999-2019 *(per $10^5$)* | Risk Ratio (95% CI) |
| 20-29 yr | | | | | | |
| | 30-39 yr | 2 | 68 | 140.1 | 2.3 | 61.1 (15.5-240.6) |
| | 40-49 yr | 7 | 66 | 505.1 | 18.1 | 28.0 (13.8-56.6) |
| 30-39 yr | | | | | | |
| | 30-39 yr | 2 | 128 | 74.4 | 2.3 | 32.5 (8.2-129.0) |
| | 40-49 yr | 2 | 126 | 75.6 | 18.1 | 4.2 (1.1-16.6) |
| | 50-59 yr | 7 | 124 | 268.8 | 83.3 | 3.2 (1.6-6.6) |
| 40-49 yr | | | | | | |
| | 40-49 yr | 6 | 78 | 366.3 | 18.1 | 20.3 (9.4-43.9) |
| | 50-59 yr | 13 | 72 | 859.8 | 83.3 | 10.3 (6.3-17.0) |
| | 60-69 yr | 8 | 59 | 645.7 | 229.0 | 2.8 (1.5-5.4) |
| 50-59 yr | | | | | | |
| | 50-59 yr | 2 | 34 | 280.1 | 83.3 | 3.4 (0.9-12.9) |
| | 60-69 yr | 3 | 32 | 446.4 | 229.0 | 1.9 (0.7-5.8) |
| | 70-79 yr | 1 | 29 | 164.2 | 363.4 | 0.5 (0.1-3.1) |

*The relative risk of knee arthroplasty in the cartilage cohort as compared with the general population, stratified in 10-year age groups at the time index cartilage procedure. For the general population, the absolute risk was estimated as described in Table III. In the cartilage cohort, the numerator was the number of knee arthroplasties in each 10-year age group (at the time of cartilage surgery) and the denominator was the total number of patients with a cartilage injury in the same age group. †General population excluded patients with previous cartilage surgery.

the present study enhance our knowledge of the natural history of focal cartilage lesions.

The present study had several limitations. The included patients were predominantly participants in previous clinical trials and may not be representative of the average patient with a focal cartilage lesion[31]. The follow-up rate of 65.1% may have introduced bias to the interpretation of the results, although the nonresponders had the same demographic characteristics as the responders, with the exception that they were a mean of 3 years younger. Patients with poor knee function or knee arthroplasty might have been more prone to participate in the study, thus leading to an overestimated risk of knee arthroplasty. Although the participants were asked if they had undergone additional surgery, we did not have complete

**TABLE V Number of Additional Surgical Procedures at Time of Index Cartilage Procedure***

| Index Cartilage Treatment | ACL Reconstruction | Meniscal Resection | Meniscal Suture | Lateral Release | Diagnostic Arthroscopy | Loose Body Removal | Total |
|---|---|---|---|---|---|---|---|
| No surgical treatment of cartilage (n = 93) | 12 | 39 | 2 | 2 | 36 | 2 | 93 |
| Microfracture/debridement (n = 136) | 2 | 6 | 0 | 0 | 0 | 0 | 8 |
| ACI/MACI (n = 30) | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Mosaicplasty (n = 53) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Other (n = 16) | 0 | 1 | 0 | 0 | 0 | 0 | 1 |

*ACL = anterior cruciate ligament, ACI = autologous chondrocyte implantation, MACI = matrix-induced ACI, Other = MaioRegen (Finceramica, Italy), Cartipatch (Xizia, Hong Kong), or TruFit (Smith & Nephew, USA).

medical records regarding later knee surgery. There were few knee arthroplasties in the younger age groups, which could have introduced bias.

The NAR does not include any details on BMI, and thus patients undergoing knee arthroplasty in the general population could have a significantly different BMI than those in our cohort. However, in 2020, the mean BMI values for Norwegian men and women were 26.5 and 25.6 kg/m$^2$, respectively, with a BMI value of >30 kg/m$^2$ reported for 59% and 47% of men and women, respectively[32]. These findings suggest that the BMI for our cartilage cohort was comparable with that the general Norwegian population. Three different PROMs were used preoperatively, and no patient had >1 preoperative PROM, limiting the ability to adjust on the basis of PROM data in the Cox model.

The present study was not a randomized trial, and the indications for the different cartilage treatments might have varied substantially. However, the patients who underwent ACI and several of those who underwent microfracture were participants in previous randomized trials, reducing the risk of selection bias. Patients who underwent cartilage surgery might have had more symptomatic lesions than those who did not. There also may have been unknown confounding factors (e.g., genetic disposition) that influenced the risk of knee arthroplasty[10].

### *Risk of Arthroplasty*

Apold et al. identified increased BMI and heavy labor as risk factors for knee arthroplasty in the Norwegian general population[9]. In the present study, being overweight at the time of follow-up was associated with an increased risk of knee arthroplasty.

Several long-term clinical trials have investigated knee arthroplasty after cartilage surgery[12,33,34]. Ogura et al. reported a 20% rate of knee arthroplasty in a 20-year follow-up of first-generation ACI, which is in line with our results[12]. Gobbi et al. presented the 15-year results for focal cartilage lesions that had been treated with microfracture in an athletic patient cohort[13]. Those authors reported progression of osteoarthritis in 40% of the knees, with an 11% rate of failure (defined as subsequent surgery by the time of the latest follow-up); however, they did not report whether any of the subsequent procedures were knee arthroplasties. Older age at the time of cartilage surgery and large or multiple lesions were found to be the main risk factors for osteoarthritis. Possible explanations for the high rate of knee arthroplasty in our study may have been our somewhat older patient cohort (mean, 36.8 versus 31.4 years) as well as the 5-year-longer follow-up as compared with the study by Gobbi et al. Differences in the frequency of knee arthroplasty at a population level between regions, as demonstrated by Ackerman et al.[35], also might have contributed to the difference in the rate of knee arthroplasty.

Abram et al., in a study of almost 158,000 patients who had undergone previous chondroplasty in U.K. National Health Service (NHS) hospitals, found an increased risk of knee arthroplasty compared with that in the general British population[14]. The overall risk of knee arthroplasty within 8 years was 17.6%. Both sex and age were identified as risk factors for later knee arthroplasty. Abram et al. provided no information on BMI but found that an increased Charlson Comorbidity Index increased the risk of knee arthroplasty. The cohort in that study (mean age, 51.7 years) was older than our cohort. This is most likely the explanation why the 8-year risk of knee arthroplasty in the U.K. chondroplasty cohort approximated the 20-year risk in our study.

Both ACL injury and meniscal lesions are known to increase the risk of osteoarthritis and subsequent TKA[8,36-40]. In the present cartilage cohort, neither meniscal resection nor ACL surgery was associated with an increased risk of knee arthroplasty. A possible explanation could be that the cartilage lesion increases the risk of knee arthroplasty substantially more than ACL and meniscal injury do, thereby limiting the functional impact of the latter. Visnes et al. found a 3-times increased risk of knee arthroplasty in 30 to 39-year-old patients and a doubled risk in 40 to 49-year-old patients after ACL surgery compared with the general population[41]. In our cartilage cohort, the corresponding values were a 416-times increased risk and a 49-times increased risk, respectively. However, we do not have any information regarding nonoperative ACL treatment. Another possibility is that the surgeons might have misclassified arthritic lesions as focal cartilage lesions. We found that the oldest patients in our cartilage cohort had a tendency toward a decreased risk of subsequent knee arthroplasty (although this finding was not significant). This finding might be indicative that patients with arthritic lesions were excluded even in the older patient group.

In the present study, we found that treatment of the cartilage lesion with ACI increased the risk of subsequent knee arthroplasty by 3.4 times as compared with no treatment. To reduce the risk of including asymptomatic lesions in the nonoperatively treated group, we performed a subanalysis of the patients without any concomitant procedures at the time of the index procedure. The subanalysis revealed no significant difference between the treatment groups, suggesting that our finding of increased risk following ACI could have been due to confounding factors. Vasiliadis and Wasiak, in a Cochrane review, found that there is insufficient evidence of the superiority of ACI compared with other cartilage treatments[42]. In recent years, high-volume orthopaedic procedures such as meniscal surgery in middle-aged patients have been shown not to be superior to sham surgery or nonoperative treatment[43,44]. Consequently, we suggest that future clinical trials on the treatment of focal cartilage lesions in the knee should include a control group that is treated nonoperatively or with sham surgery[45].

### *Conclusions*

In this study, the 20-year cumulative risk of knee arthroplasty after focal cartilage lesion in the knee was 19%. We found an up to 416-times increased risk of knee arthroplasty in patients with a focal cartilage lesion as compared with the general population.

Deep lesions, older age at the time of cartilage surgery, high BMI at the time of follow-up, ACI, and >1 cartilage lesion were associated with a higher risk of knee arthroplasty. Surgical treatment of cartilage lesions does not seem to decrease the risk of subsequent knee arthroplasty compared with no surgical cartilage treatment. Our findings should be viewed as hypothesis-generating and support the need for prospective randomized clinical trials including a sham surgery arm.

## Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/H504). ■

Thomas Birkenes, MD[1,2,3]
Ove Furnes, MD, PhD[1,2,4]
Stein Haakon Laastad Lygre, PhD[4,5]
Eirik Solheim, MD, PhD[1]
Asbjorn Aaroen, MD, PhD[6,7,8]
Gunnar Knutsen, MD, PhD[9]
Jon Olav Drogset, MD, PhD[10,11,12]
Stig Heir, MD, PhD[13]
Lars Engebretsen, MD, PhD[6,8,14]
Sverre Loken, MD, PhD[14]
Haavard Visnes, MD, PhD[8,12,15]

[1]Department of Clinical Medicine, University of Bergen, Bergen, Norway

[2]Department of Orthopaedic Surgery, Haukeland University Hospital, Bergen, Norway

[3]Sports Traumatology and Arthroscopy Research Group, Bergen, Norway

[4]Norwegian Arthroplasty Register, Department of Orthopaedic Surgery, Haukeland University Hospital, Bergen, Norway

[5]Department of Occupational Medicine, Haukeland University Hospital, Bergen, Norway

[6]University of Oslo, Oslo, Norway

[7]Akershus University Hospital, Lorenskog, Norway

[8]Oslo Sports Trauma Research Center, Oslo, Norway

[9]University Hospital of North Norway, Tromsoe, Norway

[10]Trondheim University Hospital, Trondheim, Norway

[11]Norwegian University of Science and Technology, Trondheim, Norway

[12]Norwegian Knee Ligament Register, Department of Orthopaedic Surgery, Haukeland University Hospital, Bergen, Norway

[13]Martina Hansen Hospital, Baerum, Norway

[14]Oslo University Hospital, Oslo, Norway

[15]Hospital of Southern Norway, Kristiansand, Norway

Email for corresponding author: thbirkenes@hotmail.com

## References

**1.** Hjelle K, Solheim E, Strand T, Muri R, Brittberg M. Articular cartilage defects in 1,000 knee arthroscopies. Arthroscopy. 2002 Sep;18(7):730-4.
**2.** Engen CN, Årøen A, Engebretsen L. Incidence of knee cartilage surgery in Norway, 2008-2011. BMJ Open. 2015 Nov 30;5(11):e008423.
**3.** Widuchowski W, Widuchowski J, Trzaska T. Articular cartilage defects: study of 25,124 knee arthroscopies. Knee. 2007 Jun;14(3):177-82.
**4.** Heir S, Nerhus TK, Røtterud JH, Løken S, Ekeland A, Engebretsen L, Arøen A. Focal cartilage defects in the knee impair quality of life as much as severe osteoarthritis: a comparison of knee injury and osteoarthritis outcome score in 4 patient categories scheduled for knee surgery. Am J Sports Med. 2010 Feb;38(2):231-7.
**5.** Hunziker EB, Lippuner K, Keel MJ, Shintani N. An educational review of cartilage repair: precepts & practice—myths & misconceptions—progress & prospects. Osteoarthritis Cartilage. 2015;23(3):334-50.
**6.** Devitt BM, Bell SW, Webster KE, Feller JA, Whitehead TS. Surgical treatments of cartilage defects of the knee: Systematic review of randomised controlled trials. Knee. 2017 Jun;24(3):508-17.
**7.** Bekkers JE, Inklaar M, Saris DB. Treatment selection in articular cartilage lesions of the knee: a systematic review. Am J Sports Med. 2009 Nov;37(Suppl 1):148S-55S.
**8.** Brophy RH, Gray BL, Nunley RM, Barrack RL, Clohisy JC. Total knee arthroplasty after previous knee surgery: expected interval and the effect on patient age. J Bone Joint Surg Am. 2014 May 21;96(10):801-5.
**9.** Apold H, Meyer HE, Nordsletten L, Furnes O, Baste V, Flugsrud GB. Risk factors for knee replacement due to primary osteoarthritis, a population based, prospective cohort study of 315,495 individuals. BMC Musculoskelet Disord. 2014 Jun 23;15:217.
**10.** Magnusson K, Scurrah K, Ystrom E, Ørstavik RE, Nilsen T, Steingrímsdóttir ÓA, et al. Genetic factors contribute more to hip than knee surgery due to osteoarthritis - a population-based twin registry study of joint arthroplasty. Osteoarthritis Cartilage. 2017;25(6):878-84.
**11.** Pareek A, Reardon PJ, Maak TG, Levy BA, Stuart MJ, Krych AJ. Long-term Outcomes After Osteochondral Autograft Transfer: A Systematic Review at Mean Follow-up of 10.2 Years. Arthroscopy. 2016 Jun;32(6):1174-84.
**12.** Ogura T, Mosier BA, Bryant T, Minas T. A 20-Year Follow-up After First-Generation Autologous Chondrocyte Implantation. Am J Sports Med. 2017 Oct;45(12):2751-61.
**13.** Gobbi A, Karnatzikos G, Kumar A. Long-term results after microfracture treatment for full-thickness knee chondral lesions in athletes. Knee Surg Sports Traumatol Arthrosc. 2014 Sep;22(9):1986-96.
**14.** Abram SGF, Palmer AJR, Judge A, Beard DJ, Price AJ. Rates of knee arthroplasty in patients with a history of arthroscopic chondroplasty: results from a retrospective cohort study utilising the National Hospital Episode Statistics for England. BMJ Open. 2020 Apr 16;10(4):e030609.
**15.** Knutsen G, Engebretsen L, Ludvigsen TC, Drogset JO, Grøntvedt T, Solheim E, Strand T, Roberts S, Isaksen V, Johansen O. Autologous chondrocyte implantation compared with microfracture in the knee. A randomized trial. J Bone Joint Surg Am. 2004 Mar;86(3):455-64.
**16.** Arøen A, Løken S, Heir S, Alvik E, Ekeland A, Granlund OG, Engebretsen L. Articular cartilage lesions in 993 consecutive knee arthroscopies. Am J Sports Med. 2004 Jan-Feb;32(1):211-5.
**17.** Solheim E, Øyen J, Hegna J, Austgulen OK, Harlem T, Strand T. Microfracture treatment of single or multiple articular cartilage defects of the knee: a 5-year median follow-up of 110 patients. Knee Surg Sports Traumatol Arthrosc. 2010 Apr;18(4):504-8.
**18.** Solheim E, Hegna J, Oyen J, Austgulen OK, Harlem T, Strand T. Osteochondral autografting (mosaicplasty) in articular cartilage defects in the knee: results at 5 to 9 years. Knee. 2010 Jan;17(1):84-7.
**19.** Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual Life Outcomes. 2003 Nov 3;1:64.
**20.** Lysholm J, Gillquist J. Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. Am J Sports Med. 1982 May-Jun;10(3):150-4.
**21.** International Cartilage Repair Society. The cartilage standard evaluation form/knee. ICRS Newsletter, spring 1998.
**22.** The Norwegian National Advisory Unit. Norwegian National Advisory Unit on Arthroplasty and Hip Fractures. 2020. Accessed 2023 Mar 27. http://nrlweb.ihelse.net/eng/Rapporter/Report2020_english.pdf

**23.** Furnes O, Espehaug B, Lie SA, Vollset SE, Engesaeter LB, Havelin LI. Early failures among 7,174 primary total knee replacements: a follow-up study from the Norwegian Arthroplasty Register 1994-2000. Acta Orthop Scand. 2002 Apr;73(2):117-29.

**24.** Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. J Am Stat Assoc. 1958;53(282):457-81.

**25.** Westreich D, Greenland S. The table 2 fallacy: presenting and interpreting confounder and modifier coefficients. Am J Epidemiol. 2013 Feb 15;177(4):292-8.

**26.** Knutsen G, Drogset JO, Engebretsen L, Grøntvedt T, Ludvigsen TC, Løken S, Solheim E, Strand T, Johansen O. A Randomized Multicenter Trial Comparing Autologous Chondrocyte Implantation with Microfracture: Long-Term Follow-up at 14 to 15 Years. J Bone Joint Surg Am. 2016 Aug 17;98(16):1332-9.

**27.** Solheim E, Hegna J, Inderhaug E, Øyen J, Harlem T, Strand T. Results at 10-14 years after microfracture treatment of articular cartilage defects in the knee. Knee Surg Sports Traumatol Arthrosc. 2016 May;24(5):1587-93.

**28.** Solheim E, Hegna J, Øyen J, Harlem T, Strand T. Results at 10 to 14 years after osteochondral autografting (mosaicplasty) in articular cartilage defects in the knee. Knee. 2013 Aug;20(4):287-90.

**29.** Shelbourne KD, Jari S, Gray T. Outcome of untreated traumatic articular cartilage defects of the knee: a natural history study. J Bone Joint Surg Am. 2003;85-A(Suppl 2):8-16.

**30.** Widuchowski W, Widuchowski J, Koczy B, Szyluk K. Untreated asymptomatic deep cartilage lesions associated with anterior cruciate ligament injury: results at 10- and 15-year follow-up. Am J Sports Med. 2009 Apr;37(4):688-92.

**31.** Engen CN, Engebretsen L, Årøen A. Knee Cartilage Defect Patients Enrolled in Randomized Controlled Trials Are Not Representative of Patients in Orthopedic Practice. Cartilage. 2010 Oct;1(4):312-9.

**32.** Abel MH. Diet and self-reported weight and weight-change based on data from the National Public Health Survey 2020. Norwegian Institute of Public Health.; 2021. https://www.fhi.no/globalassets/dokumenterfiler/rapporter/2021/rapport-nhus-2020.pdf

**33.** Minas T, Von Keudell A, Bryant T, Gomoll AH. The John Insall Award: A minimum 10-year outcome study of autologous chondrocyte implantation. Clin Orthop Relat Res. 2014 Jan;472(1):41-51.

**34.** Sanders TL, Pareek A, Obey MR, Johnson NR, Carey JL, Stuart MJ, Krych AJ. High Rate of Osteoarthritis After Osteochondritis Dissecans Fragment Excision Compared With Surgical Restoration at a Mean 16-Year Follow-up. Am J Sports Med. 2017 Jul;45(8):1799-805.

**35.** Ackerman IN, Bohensky MA, de Steiger R, Brand CA, Eskelinen A, Fenstad AM, Furnes O, Garellick G, Graves SE, Haapakoski J, Havelin LI, Mäkelä K, Mehnert F, Pedersen AB, Robertsson O. Substantial rise in the lifetime risk of primary total knee replacement surgery for osteoarthritis from 2003 to 2013: an international, population-level analysis. Osteoarthritis Cartilage. 2017 Apr;25(4):455-61.

**36.** Lindanger L, Strand T, Mølster AO, Solheim E, Fischer-Bredenbeck C, Ousdal OT, Inderhaug E. Predictors of Osteoarthritis Development at a Median 25 Years After Anterior Cruciate Ligament Reconstruction Using a Patellar Tendon Autograft. Am J Sports Med. 2022 Apr;50(5):1195-204.

**37.** Poulsen E, Goncalves GH, Bricca A, Roos EM, Thorlund JB, Juhl CB. Knee osteoarthritis risk is increased 4-6 fold after knee injury - a systematic review and meta-analysis. Br J Sports Med. 2019 Dec;53(23):1454-63.

**38.** Enweze LC, Varshneya K, Sherman SL, Safran MR, Abrams GD. Risk of Subsequent Knee Arthroplasty After Sports Medicine Procedures. J Am Acad Orthop Surg Glob Res Rev. 2020 Aug;4(8):00125.

**39.** Everhart JS, Magnussen RA, Abouljoud MM, Regalado LE, Kaeding CC, Flanigan DC. Meniscus tears accelerate joint space loss and lateral meniscal extrusion increases risk of knee arthroplasty in middle-aged adults. J Orthop Res. 2020 Nov;38(11):2495-504.

**40.** Abram SGF, Judge A, Khan T, Beard DJ, Price AJ. Rates of knee arthroplasty in anterior cruciate ligament reconstructed patients: a longitudinal cohort study of 111,212 procedures over 20 years. Acta Orthop. 2019 Dec;90(6):568-74.

**41.** Visnes H, Gifstad T, Persson A, Lygre SHL, Engebretsen L, Drogset JO, Furnes O. ACL Reconstruction Patients Have Increased Risk of Knee Arthroplasty at 15 Years of Follow-up: Data from the Norwegian Knee Ligament Register and the Norwegian Arthroplasty Register from 2004 to 2020. JB JS Open Access. 2022 Jun 21;7(2):e22.00023.

**42.** Vasiliadis HS, Wasiak J. Autologous chondrocyte implantation for full thickness articular cartilage defects of the knee. Cochrane Database Syst Rev. 2010 Oct 6;2010(10):CD003323.

**43.** Sihvonen R, Paavola M, Malmivaara A, Itälä A, Joukainen A, Kalske J, Nurmi H, Kumm J, Sillanpää N, Kiekara T, Turkiewicz A, Toivonen P, Englund M, Taimela S, Järvinen TLN; FIDELITY (Finnish Degenerative Meniscus Lesion Study) Investigators. Arthroscopic partial meniscectomy for a degenerative meniscus tear: a 5 year follow-up of the placebo-surgery controlled FIDELITY (Finnish Degenerative Meniscus Lesion Study) trial. Br J Sports Med. 2020 Nov;54(22):1332-9.

**44.** Kise NJ, Risberg MA, Stensrud S, Ranstam J, Engebretsen L, Roos EM. Exercise therapy versus arthroscopic partial meniscectomy for degenerative meniscal tear in middle aged patients: randomised controlled trial with two year follow-up. BMJ. 2016 Jul 20;354:i3740.

**45.** Beard DJ, Campbell MK, Blazeby JM, Carr AJ, Weijer C, Cuthbertson BH, Buchbinder R, Pinkney T, Bishop FL, Pugh J, Cousins S, Harris I, Lohmander LS, Blencowe N, Gillies K, Probst P, Brennan C, Cook A, Farrar-Hockley D, Savulescu J, Huxtable R, Rangan A, Tracey I, Brocklehurst P, Ferreira ML, Nicholl J, Reeves BC, Hamdy F, Rowley SC, Lee N, Cook JA. Placebo comparator group selection and use in surgical trials: the ASPIRE project including expert workshop. Health Technol Assess. 2021 Sep;25(53):1-52.

http://dx.doi.org/10.2106/JBJS.22.01174


**The following content was supplied by the authors as supporting material and has not been copy-edited or verified by JBJS.**

Table Supplement 1. Risk factors associated with knee arthroplasty (KA) after a cartilage injury 1999-2020. A focal cartilage lesion cohort without any concomitant procedures at index cartilage surgery.

| | number of knee arthroplasties (%) | Crude HR[1] | | Adjusted HR[2] | |
|---|---|---|---|---|---|
| | | HR | (95% CI) | HR | (95% CI) |
| Total | 50(19.6%) | | | | |
| Age at time of surgery(years)[3] | | | | | |
| *18-29* | 8 (11.6%) | 1 | | 1 | |
| *30-39* | 13 (13.1%) | 1.3 | (0.5-3.1) | 1.3 | (0.5-3.1) |
| *>40* | 29 (33.3%) | 4.1 | (1.9-9.0) | 4.1 | (1.9-9.0) |
| Gender[3] | | | | | |
| *Male* | 27 (19.3%) | 1 | | 1 | |
| *Female* | 23 (20.0%) | 1.1 | (0.6-1.9) | 1.1 | (0.6-1.9) |
| BMI[4] | | | | | |
| <25 | 6 (7.9%) | 1 | | 1 | |
| 25-29 | 23 (22.1%) | 3.1 | (1.2-7.5) | 3.6 | (1.4-8.9) |
| >30 | 16 (25.8%) | 3.8 | (1.5-9.7) | 5.5 | (2.1-14-7) |
| Size of lesion($mm^2$)[5] | | | | | |
| <200 $mm^2$ | 36 (21.6%) | 1 | | 1 | |
| ≥200 $mm^2$ | 14 (15.9%) | 0.7 | (0.4-1.3) | 0.7 | (0.4-1.4) |
| ICRS grade[5] | | | | | |
| 1-2 | 2 (10.5%) | 1 | | 1 | |
| 3-4 | 48 (20.3%) | 2.5 | (0.6-10.5) | 2.6 | (0.6-10.1) |
| Level of education[6] | | | | | |
| High school | 28 (22.6%) | 1 | | 1 | |
| Bachelor/Master | 18 (14.5%) | 0.6 | (0.4-1.1) | 0.6 | (0.3-1.1) |
| ACL reconstructed at any time[7] | | | | | |
| No | 43 (18.9%) | 1 | | 1 | |
| Yes | 7 (25.9%) | 1.4 | (0.6-3.0) | 1.9 | (0.8-4.6) |
| Meniscal resection at any time[8] | | | | | |
| Yes | 11 (22.4%) | 1 | | 1 | |
| No | 39(18.9%) | 1.4 | (0.7-2.7) | 1.1 | (0.5-2.3) |
| Location of cartilage lesion[9] | | | | | |
| Patellofemoral | 9 (14.8%) | 1 | | 1 | |
| Medial | 32 (20.4%) | 1.3 | (0.6-2.8) | 1.2 | (0.6-2.7) |
| Lateral | 9 (24.3%) | 1.5 | (0.6-3.8) | 1.2 | (0.4-3.4) |
| Number of cartilage lesions[10] | | | | | |
| 1 | 30 (16.0%) | 1 | | 1 | |
| >1 | 19 (38.0%) | 2.6 | (1.5-4.7) | 2.6 | (1.4-4.9) |
| Treatment at index operation[11] | | | | | |
| No cartilage treatment | 6 (19.4%) | 1 | | 1 | |
| Debridement/Mfx | 26 (20.5%) | 1.3 | (0.5-3.1) | 0.6 | (0.2-1.8) |
| ACI | 7 (24.1%) | 1.5 | (0.5-4.4) | 1.8 | (0.5-6.7) |
| OATS | 11 (20.8%) | 1.2 | (0.4-3.2) | 0.7 | (0.2-2.5) |
| Other | 0 (0 %) | | | | |
| VAS Pain preoperative[12,13] | | 1.04 | (0.99-1.08) | 1.49 | (0.33-6.52) |
| Lysholm preoperative[12,13] | | 0.99 | (0.99-1.00) | 0.99 | (0.97-1.02) |

*[1] HR=Hazard rate ratio from Cox analysis [2]Cox-adjusted for variables according to graphical causal model [3]Not adjusted. [4] Adjusted for Age at time of surgery, Gender, Level of Education. [5] Adjusted for Age at time of surgery, BMI, Meniscal resection. [6] Adjusted for Gender.[7] Adjusted for Age at time of surgery, BMI, Gender, Level of Education. [8] Adjusted for ACL reconstructed, Age at time of surgery, BMI, Gender, Level of Education. [9] Adjusted for ACL reconstructed, Age at time of surgery, Gender, Meniscal resection. [10] Adjusted for ACL reconstructed, Age at time of surgery, BMI, Gender, Level of Education, Meniscal resection, Size of lesion. [11] Adjusted for Age at time of surgery, ICRS grade, Level of Education, Location of lesion, Number of lesions, Size of lesion. [12] Adjusted for ACL reconstructed, Age at time of surgery, BMI, Gender, ICRS grade, Level of Education, Location of lesion, , Meniscal resection, Number of lesions, Size of lesion. [13] Adjusted for VAS pain and Lysholm analysed as continuous variables.*

http://dx.doi.org/10.2106/JBJS.22.01174


KA-Knee Arthroplasty, UKA- Unicompartmental Knee Arthroplasty, PF-Patellofemoral Knee Arthroplasty, CR-Cumulative Risk, BMI- Body Mass Index, ICRS- International Cartilage Repair Society, ACL- Anterior Cruciate ligament, Mfx- Microfracture, ACI-Autologous Cartilage Implantation, OATS-Osteochondral Autograft Transplantation System (Mosaicplasty), VAS- Visual Analogue Scale

# Paper II

# Long term results after arthroscopically verified focal cartilage lesion in the knee. A 20-year multicentre follow-up with patient reported outcome

Birkenes T, Furnes O, Laastad Lygre SH, Solheim E, Aaroen A, Knutsen G, Drogset JO, Heir S, Engebretsen L, Løken S, and Visnes H.

## Abstract

### Introduction

Focal cartilage lesions (FCL) are frequently found in knee arthroscopies and may impair quality of life (QoL) significantly. Several treatment options with good short-term results are available. The natural history without any treatment is largely unknown. The aim of this study was to evaluate the patient satisfaction, need of further cartilage surgery and the risk of treatment failure 20-years after a FCL in the knee.

### Methods

Patients were identified in six major Norwegian hospitals undergoing any FCL-surgery between 1999-2012. Inclusion criteria: Arthroscopically classified FCL in the knee, Patient >18-years at surgery and any preoperative patient reported outcome (PROM). Exclusion criteria: Osteoarthritis or “kissing-lesions” at surgery. Demographic data, later knee-surgery and PROM were collected by questionnaire. Regression models were used to adjust for and evaluate the factors impacting the long-term PROM and risk-factors for treatment failure (knee arthroplasty, osteotomy or KOOS-QoL<50).

### Results

322 patients(328 knees) of 553 eligible consented to participate. The mean follow-up was 19.1 years and mean age at index FCL-surgery was 36.8(CI 35.6-38.0) years. The patients without knee arthroplasty(KA) or osteotomy, had significantly better mean PROM(Pain, Lysholm and KOOS) at final follow-up than preoperatively. At follow-up 17.7% of the knees had undergone subsequent cartilage surgery. Nearly 50% of the patients had treatment failure and the main risk factors were body mass index >25 with odds ratio 2.0(CI 1.1-3.6), >1 FCL OR 1.9(CI 1.1-3.3), full-thickness lesions OR 2.5(CI 1.3-5.0), and lower level of education OR 1.8(Cl 1.1-2.8). Autologous Chondrocyte Implantation(ACI) was associated with

significantly higher KOOS-QoL at 17.5(CI 3.2-31.7) points and a lower risk of treatment failure than no cartilage treatment, microfracture or mosaicplasty.

## Conclusion

After a mean 20-years follow-up patients with FCL, without subsequent KA, had significantly higher PROM-score than preoperatively. Non-surgically treated FCLs had equal result compared to surgically-treated FCLs except ACI-treatment which was associated with better KOOS and lower risk of treatment failure. Full-thickness lesions, >1 FCL, lower level of education, increased BMI were the main risk factors predicting poorer results.

## Background

Focal cartilage lesions (FCL) are frequently found in patients undergoing knee arthroscopies.[1, 2] They may impair quality of life equivalent to end-stage osteoarthritis scheduled for knee arthroplasty (KA)[3, 4]. Due to avascularity, the joint hyaline cartilage, is unable to heal naturally [5]. Several treatment options are available, but the optimal treatment is still unknown[6, 7]. In the 90's and the first decade of 2000, several new cartilage treatment options became available[8-10]. Most patients with surgically treated lesions can now expect acceptable results, but few regain normal knee function[6, 7, 11]. Several clinical studies in cartilage treatment, have shown good/excellent short-term results, but there are concerns regarding the results in the long-term [7]. Newer generations of cell-based treatments have had increasing popularity despite lack of evidence of their superiority[12]. Randomized control trials fail to represent the heterogenous group of patients with a FCL in an orthopaedic practice[13]. Cartilage registries might contribute to our knowledge, but currently only short-term results are available[14]. The long-term natural history of a non-operative treated FCL is largely unknown[15-18].

The aim of the present study was to:

- Evaluate the long-term patient reported outcome of arthroscopically verified FCL in the knee with Knee injury and Osteoarthritis Outcome Score(KOOS) Quality of Life(QoL) subscore.
- Examine the need of subsequent cartilage surgery.
- Identify risk factors for treatment failure after an FCL.
- Compare long-term patient reported outcome and risk of treatment failure after different treatment options including non-operative treatment of FCL.

## Methods

Patients with arthroscopically verified FCLs were identified in six major Norwegian Hospitals between 1999-2012(fig 1). These hospitals had a high volume of cartilage surgery and participated in several prospective cartilage studies during this period[1, 19-21].

The inclusion criteria in this study were: any arthroscopically verified and classified FCL in the knee and patient ≥18 years at the time of surgery. At least one preoperative patient reported outcome measure(PROM) had to be available. Exclusion criteria were cartilage

lesions assessed as gonarthrosis or “kissing-lesions” at the time of operation. Each patient (n=553,Figure 1) received a questionnaire regarding their current height, weight, level of education, current knee function and additional knee surgery. In addition, the participants were asked to complete the PROM used at the time of surgery as well as KOOS[22]. The PROM used preoperatively were KOOS[22], Lysholm[23] and International Cartilage Regeneration & Joint Preservation Society(ICRS) knee pain visual analogue scale (VAS)[24].

See Figure 1 Flowchart for inclusion details.

Patients identified as eligible for participation in the present study were contacted by mail. Patients registered in the Norwegian Population Register as deceased or emigrated, were excluded. After informed consent were obtained, the participants’ trial data and/or surgical report were made available for the main investigator (TB). The following variables were retrieved: The characteristics (localisation, size (measured by a standard 4-mm probe) and ICRS classification[25]) of the FCL, type of surgical treatment, any additional procedures and preoperatively PROM. Nine knees in 8 patients meeting the exclusion criteria at index surgery were then identified and excluded. The final follow-up was performed between 6$^{th}$ of March and 31$^{st}$ of December 2020.

Failure was defined as subsequent KA or osteotomy or KOOS-QoL <50 at final follow-up. KOOS QoL <50 is considered to be the Patients Acceptable Symptom State (PASS) after cartilage surgery[26]. The details of the arthroplasty group have been published previously[27].

Patients with KA or osteotomy were excluded in the analysis of PROM but included in the analysis of treatment failure.

### Statistics

Multiple logistic regression models were used to identify risk factors for failure at final follow-up while multiple linear regression models were used to evaluate the factors influencing the KOOS-QoL score at final follow-up. A Graphical Causal Model (www.dagitty.net/dags.html) was used to identify variables to adjust for in the regression models as suggested by Westreich[28]. A subgroup, excluding patients with patellofemoral lesions was analysed with the same model. Time since cartilage surgery was calculated as the time between index cartilage surgery and the questionnaire follow-up in the KOOS analysis and the end of the study on December 31,2020 for the failure analysis. Lysholm-score

preoperatively and ICRS VAS-pain preoperatively were only registered in 185 and 114 patients respectively and there were no patients with more than one preoperative PROM, however all patients had KOOS score at follow-up.

A paired sample t-test was used to evaluate the difference in PROM-score preoperative and at final follow-up. The data was analysed using SPSS Statistics 26(SPSS, Chicago, Illinois) and STATA 17(StataCorp,Texas).

### Power analysis:

A pre-inclusion power analysis suggested that 64 patient in each group were needed to a detect a difference of 10±20 points of KOOS with a α-level of 0.05 and power-level of 0.8.

### Ethics

The study was approved by the Reginal Ethics Committee reference number 2017/1387.


### Funding

The present study was funded by the Norwegian Research Council (2015107) through the Norwegian Cartilage Project.


## Results

Out of the 553 patients identified, 516 were eligible and of those 322 patients (328 knees) consented to participate (65.1%)(Figure 1). The characteristics of these patients(responders) and their knees are summarized in table 1 and supplementary table 1. At baseline, there were no significant differences between the responders and non-responders apart from the responders being a mean of 3.0 years older(p=0.002). Most of the lesions were ICRS 3/4 (84.1%) and the mean size was 2.0 (CI 1.8-2.2) $cm^2$. The mean follow-up time was 19.1(CI 18.8-19.5) years and the mean age at time of index surgery was 36.8 years. Fifty-nine patients(18%) had had KA surgery at follow-up. Four patients (1.2%) had undergone later femoral- or tibia-osteotomy. There were no patients with more than one category of preoperative PROM registered, 8.8% had KOOS-scores, 56.4% Lysholm-score and 34.8% ICRS Pain-VAS registered preoperatively. Most patients had a pre-enrolment weight-bearing x-ray which did not have any joint-space narrowing.

### Long-term PROM and factors of significant influence

Mean PROM-values preoperative and at final follow-up for the 254 patients (260 knees) without subsequent KA or osteotomy are presented in Table 2 and Figure 2 and there was statistically significant improvement in all PROM-scores. Nine patients did not provide

PROM at final follow-up. The mean KOOS sub-scores for all patients (n=256, 262 knees) with intact native knee at final follow-up is presented in Table1. The unadjusted KOOS-sport/rec and QoL sub-scores at final follow-up by treatment group is presented in Figure 3 and 4. In a multiple linear regression model(Table 3), higher level of education, Autologous-Cartilage-Implantation(ACI) treatment, higher preoperative Lysholm score, longer follow-up time and lesions of the lateral compartment were associated with increased KOOS-QoL, while >1 lesion and ICRS 3-4 lesions were associated with inferior results .

### Subsequent cartilage surgeries

Forty-seven (17.7%) knees had undergone subsequent cartilage surgery after the index surgery as reported by the patients. The incidence of ≥1 subsequent cartilage surgery in the treatment groups were: No operative treatment 10.1%, debridement/microfracture 21.7%, ACI 18.2%, mosaicplasty 26.2% and other treatment 17.9%. The differences between the treatment groups were not statistically significant as assessed by chi-square test (p=0.21, not shown in tables). Most of the patients did not provide sufficient details of the subsequent surgery to classify the treatment.

### Risk factors for treatment failure

At final follow-up 162 knees (49.4%) were classified as failures (59 KA, 4 osteotomies and 99 observations of KOOS QoL<50). The crude and adjusted multiple logistic regression model of failure is summarized in Table 4. Body Mass Index(BMI) 25-29 and BMI≥30 increased the odds of failure at follow-up with an odds ratio of 2.0(Cl 1.1-3.6, p=0.016) and 3.1(Cl 1.6-5.9, p=0.001) respectively. Lower level of education had an odds ratio of 1.8(Cl 1.1-2.8, p=0.011) compared to patients with a bachelor/master-degree. More than one cartilage lesion increased the odds 1.9 times (Cl 1.1-3.3, p=0.035). The ICRS 3-4 lesions had 2.5 times (Cl 1.3-5.0, p=0.009) higher odds of failure compared to ICRS 1-2 lesions. However, lesion size did not influence the odds of subsequent failure, nor did gender, age at time of cartilage surgery, duration of follow-up, Anterior-Cruciate-Ligament(ACL) reconstruction or meniscal resection or the preoperative PROM.

### PROM results and risk of treatment failure by cartilage treatment

There was no significant difference in odds of treatment failure between the no surgical treatment group and the surgically treated FCLs except ACI treatment which were associated with decreased odds of treatment failure (OR 0.3) (Table 4). Moreover, ACI was associated with significantly (p=0.017) higher mean KOOS-QoL than no surgical cartilage treatment (Table 3), but had an increased risk of KA[27]. Crude KOOS-QoL is presented in figure 4.

## Discussion

### Principal findings

Patients with FCL in the knee, without subsequent KA or osteotomy, had significantly better PROM at a mean of 19.8 years follow-up than preoperatively. At final follow-up, 162 knees(49.4%) were classified as treatment failures, with BMI 25-29 and BMI≥30, more than one cartilage lesion, ICRS 3-4 lesions and lower level of education as the main risk factors. There were no difference in KOOS-QoL subscore or odds of treatment failure between the non-surgically treated FCLs and the surgically treated lesions, except that ACI treatment was associated with significantly higher KOOS-QoL and decreased odds of treatment failure.

### Strength and limitations

The main strength of the present study is the high number FCLs in the knee evaluated arthroscopically in detail. Any concurrent knee injury as meniscal or ligamentous lesions were registered. Even though the exact alignment of the patients' leg remains unknown, due to the lack of a standardized preoperative radiographic protocol, the included patients had <5° malalignment due to inclusion criteria in the previous clinical trials[19-21]. To our knowledge, this is the first study outside an ACL-cohort, comparing the PROM results in arthroscopically verified FCL treated with no operative cartilage treatment as well as surgically treated lesions.

There are several limitations. One hundred and fifty of the patients had participated in studies with previously published long-term results [29-31]. They thus might not represent the average patient with FCL[13]. The respond rate of 65% might introduce bias to the interpretation of the results. This is not an RCT and the differences in final PROM results should be interpreted with caution. The number of participants suggested by the power-analysis were not met in all sub-groups, increasing the risk of type-2 error. Several of the patients did not provide sufficient details of any subsequent cartilage treatment after the index surgery. Three different PROMs were used preoperatively, and no patient had >1 preoperative PROM. Due to list-wise deletion this limited the adjustment of the regression models based on PROM data. Standardized preoperative x-rays were not available, nor were an activity scale.

### Long-term PROM results

In the present study we found a mean KOOS-QoL of 58.1 at final follow-up. In a series of 44 patients, Ossendorf et al[32] found a KOOS-QoL of 49 in patients with 1st generation ACI

treatment vs 64 in patients with microfracture. Furthermore, Kreuz et al[33] and Niemeyer et al [34] found KOOS-QoL of 58.0 and 54.3 respectively in their studies. Even though the present study has considerably longer follow-up, the PROM results are likely comparable as several previous studies has suggested stable results from mid- to long-term follow-up[30, 31, 33, 35]. In contrast, Gobbi et al[36] presented 15 years follow-up of 67 athletes with full-thickness lesions treated with microfracture, with a final KOOS-QoL of 82.2. The higher KOOS-score might be due to a more active study population as physical training has been shown to increase the KOOS-score in patients with FCL[37]. Multiple lesions were associated with inferior KOOS-QoL. A possible explanation could be that multiple lesions might alter the knee homeostasis more[38].

Lower level of education was associated with inferior KOOS. Higher risk of heavy manual labour and lower level of physical training might contribute to this. Furthermore, lower socioeconomic status is known for decreasing the self-reported general health[39].

Medial and lateral FCLs were associated with significant better KOOS-QoL score compared to retropatellar lesions. The inferior result in patellar lesions is consistent with previous studies[40-42]. Using the same regression model a subgroup without PF-lesions were analysed, with the same overall results, indicating that the original model was able to adjust for FCL location(Supplementary Table 2).

### Subsequent cartilage surgery

At final follow-up 47(17.7%) of the knees had undergone subsequent cartilage surgery. Niemeyer et al[34] reported in a study of ACI patients that 28,6% required additional cartilage surgery. This is consistent with the findings of Ossendorf et al[32] with 34% reoperations. In the present study there was no significantly different rate of subsequent cartilage surgery, even though there was substantial variation. This could suggest that our analysis was underpowered. We didn't have detailed data on the nature of subsequent cartilage surgery and the variations in the type of surgery between the groups could be substantial.

### Risk factors for treatment failure

The failure rate, defined as TKA, osteotomy or KOOS-QoL<50), was nearly 50%. Several other studies have defined any subsequent cartilage surgery as failure[29, 34-36]. In a 20-year perspective any subsequent surgery might not be the best failure measure. KA is the final outcome of end-stage osteoarthritis and must be considered a failure in cartilage surgery. However, the risk of undergoing a knee replacement might vary considerable between

countries as well as regions of a country[43, 44]. To compensate for this, we also classified patients scoring <50 in KOOS-QoL sub-score a treatment failure, as Chahal et al[26] demonstrated this to be the Patient Acceptable Symptom State (PASS) in patients with FCL. The failure rate of 50% seems high. Nonetheless, as previously discussed the mean KOOS-QoL in the present study is comparable to other long-term studies.

More than one FCL was associated with increased odds of failure, consistent with the results of Gobbi et al[36]. Increased BMI is a known risk factor for both KA and lower KOOS-score even in the general population[11, 43].

### Long-term PROM and risk of failure in different Cartilage treatment strategies

We found an increased KOOS-QoL score in the ACI patients compared to the other treatment strategies including no surgical treatment. In contrast Ossendorf et al[32] found that microfracture patients had significantly higher scores than ACI patients. However, their analysis was not fully adjusted for significantly larger defects in the ACI patients, and this might introduce bias.

In a previously published study of the same cartilage cohort, we found ACI treatment to increase the risk of KA[27]. Considering this, it was notably that ACI had the lowest risk of failure overall. Even though the higher risk of KA is concerning, the number of patients scoring themselves below PASS was considerable higher in the other treatment groups. Possibly the ACI patients have been more prone to receive a KA than the other patients. Cartilage allograft is not available in Norway and revision options in case of a large failed ACI treatment may be limited. This could partly explain the higher rate of KA.

The present study includes a heterogeneous patient cohort. Our findings do, however, highlight the need of long-term follow-up of RCTs**,** as also suggested in a review by Orth et al[18], as well as cartilage-registry studies. Furthermore, including a sham-surgery arm in future RCTs should be considered.

## Conclusion

After a mean 20-years follow-up patients with FCL without subsequent KA had significantly better PROM-score than preoperatively, although nearly 50% of the knees could be classified as treatment failures. Non-surgically treated FCLs had equal result compared to surgically treated FCLs except ACI-treatment which was associated with better KOOS and lower risk of

treatment failure, despite greater risk of KA. More than one FCL, full-thickness lesions, lower level of education, retropatellar lesions and increased BMI were the main risk factors predicting poorer results.

## References


1. Aroen A, Loken S, Heir S, et al. Articular cartilage lesions in 993 consecutive knee arthroscopies. *Am J Sports Med* 2004; 32: 211-215.
2. Hjelle K, Solheim E, Strand T, et al. Articular cartilage defects in 1,000 knee arthroscopies. *Arthroscopy: The Journal of Arthroscopic & Related Surgery* 2002; 18: 730-734. DOI: http://dx.doi.org/10.1053/jars.2002.32839.
3. Heir S, Nerhus TK, Rotterud JH, et al. Focal cartilage defects in the knee impair quality of life as much as severe osteoarthritis: a comparison of knee injury and osteoarthritis outcome score in 4 patient categories scheduled for knee surgery. *Am J Sports Med* 2010; 38: 231-237. 2010/01/01. DOI: 10.1177/0363546509352157.
4. Randsborg PH, Årøen A and Owesen C. The Effect of Lesion Size on Pain and Function in Patients Scheduled for Cartilage Surgery of the Knee. *Cartilage* 2022; 13: 43-49. DOI: 10.1177/19476035221109242.
5. Hunziker EB, Lippuner K, Keel MJ, et al. An educational review of cartilage repair: precepts & practice--myths & misconceptions--progress & prospects. *Osteoarthritis Cartilage* 2015; 23: 334-350. 2014/12/24. DOI: 10.1016/j.joca.2014.12.011.
6. Bekkers JE, Inklaar M and Saris DB. Treatment selection in articular cartilage lesions of the knee: a systematic review. *Am J Sports Med* 2009; 37 Suppl 1: 148s-155s. 2009/12/16. DOI: 10.1177/0363546509351143.
7. Devitt BM, Bell SW, Webster KE, et al. Surgical treatments of cartilage defects of the knee: Systematic review of randomised controlled trials. *The Knee* 2017; 24: 508-517. DOI: https://doi.org/10.1016/j.knee.2016.12.002.
8. Brittberg M, Lindahl A, Nilsson A, et al. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N Engl J Med* 1994; 331: 889-895. 1994/10/06. DOI: 10.1056/nejm199410063311401.
9. Brittberg M. Cell Carriers as the Next Generation of Cell Therapy for Cartilage Repair:A Review of the Matrix-Induced Autologous Chondrocyte Implantation Procedure. *The American Journal of Sports Medicine* 2010; 38: 1259-1271. DOI: 10.1177/0363546509346395.
10. Hangody L, Kish G, Kárpáti Z, et al. Arthroscopic autogenous osteochondral mosaicplasty for the treatment of femoral condylar articular defects. A preliminary report. *Knee Surg Sports Traumatol Arthrosc* 1997; 5: 262-267. 1997/01/01. DOI: 10.1007/s001670050061.
11. Marot V, Murgier J, Carrozzo A, et al. Determination of normal KOOS and WOMAC values in a healthy population. *Knee Surg Sports Traumatol Arthrosc* 2019; 27: 541-548. 2018/09/27. DOI: 10.1007/s00167-018-5153-6.

12. Aae TF, Randsborg PH, Lurås H, et al. Microfracture is more cost-effective than autologous chondrocyte implantation: a review of level 1 and level 2 studies with 5 year follow-up. *Knee Surg Sports Traumatol Arthrosc* 2018; 26: 1044-1052. 2017/11/13. DOI: 10.1007/s00167-017-4802-5.
13. Engen CN, Engebretsen L and Årøen A. Knee Cartilage Defect Patients Enrolled in Randomized Controlled Trials Are Not Representative of Patients in Orthopedic Practice. *Cartilage* 2010; 1: 312-319. DOI: 10.1177/1947603510373917.
14. Maurer J, Grotejohann B, Jenkner C, et al. A Registry for Evaluation of Efficiency and Safety of Surgical Treatment of Cartilage Defects: The German Cartilage Registry (KnorpelRegister DGOU). *JMIR Res Protoc* 2016; 5: e122. 20160629. DOI: 10.2196/resprot.5895.
15. Widuchowski W, Widuchowski J, Faltus R, et al. Long-term clinical and radiological assessment of untreated severe cartilage damage in the knee: a natural history study. *Scand J Med Sci Sports* 2011; 21: 106-110. 2010/02/09. DOI: 10.1111/j.1600-0838.2009.01062.x.
16. Shelbourne KD, Jari S and Gray T. Outcome of untreated traumatic articular cartilage defects of the knee: a natural history study. *J Bone Joint Surg Am* 2003; 85-A Suppl 2: 8-16.
17. Messner K and Maletius W. The long-term prognosis for severe damage to weight-bearing cartilage in the knee: a 14-year clinical and radiographic follow-up in 28 young athletes. *Acta Orthop Scand* 1996; 67: 165-168. 1996/04/01. DOI: 10.3109/17453679608994664.
18. Orth P, Gao L and Madry H. Microfracture for cartilage repair in the knee: a systematic review of the contemporary literature. *Knee Surg Sports Traumatol Arthrosc* 2020; 28: 670-706. DOI: 10.1007/s00167-019-05359-9.
19. Solheim E, Hegna J, Oyen J, et al. Osteochondral autografting (mosaicplasty) in articular cartilage defects in the knee: results at 5 to 9 years. *Knee* 2010; 17: 84-87. DOI: 10.1016/j.knee.2009.07.007.
20. Solheim E, Oyen J, Hegna J, et al. Microfracture treatment of single or multiple articular cartilage defects of the knee: a 5-year median follow-up of 110 patients. *Knee Surg Sports Traumatol Arthrosc* 2010; 18: 504-508. DOI: 10.1007/s00167-009-0974-y.
21. Knutsen G, Engebretsen L, Ludvigsen TC, et al. Autologous chondrocyte implantation compared with microfracture in the knee. A randomized trial. *J Bone Joint Surg Am* 2004; 86-A: 455-464.
22. Roos EM and Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes* 2003; 1: 64. DOI: 10.1186/1477-7525-1-64.
23. Lysholm J and Gillquist J. Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. *Am J Sports Med* 1982; 10: 150-154.
24. International Cartilage Repair Society The cartilage standard evaluation form/knee.ICRS Newsletter, spring 1998. 1998.
25. Brittberg M and Winalski CS. Evaluation of cartilage injuries and repair. *J Bone Joint Surg Am* 2003; 85-A Suppl 2: 58-69.

26. Chahal J, Lansdown DA, Davey A, et al. The Clinically Important Difference and Patient Acceptable Symptomatic State for Commonly Used Patient-Reported Outcomes After Knee Cartilage Repair. *Am J Sports Med* 2021; 49: 193-199. 2020/11/24. DOI: 10.1177/0363546520969883.
27. Birkenes T, Furnes O, Laastad Lygre SH, et al. The Long-Term Risk of Knee Arthroplasty in Patients with Arthroscopically Verified Focal Cartilage Lesions: A Linkage Study with the Norwegian Arthroplasty Register, 1999 to 2020. *J Bone Joint Surg Am* 2023; 105: 951-961. 20230427. DOI: 10.2106/JBJS.22.01174.
28. Westreich D and Greenland S. The Table 2 Fallacy: Presenting and Interpreting Confounder and Modifier Coefficients. *Am J Epidemiol* 2013; 177: 292-298. DOI: 10.1093/aje/kws412.
29. Knutsen G, Drogset JO, Engebretsen L, et al. A Randomized Multicenter Trial Comparing Autologous Chondrocyte Implantation with Microfracture: Long-Term Follow-up at 14 to 15 Years. *J Bone Joint Surg Am* 2016; 98: 1332-1339. 2016/08/19. DOI: 10.2106/jbjs.15.01208.
30. Solheim E, Hegna J, Inderhaug E, et al. Results at 10-14 years after microfracture treatment of articular cartilage defects in the knee. *Knee Surg Sports Traumatol Arthrosc* 2016; 24: 1587-1593. DOI: 10.1007/s00167-014-3443-1.
31. Solheim E, Hegna J, Oyen J, et al. Results at 10 to 14 years after osteochondral autografting (mosaicplasty) in articular cartilage defects in the knee. *Knee* 2013; 20: 287-290. DOI: 10.1016/j.knee.2013.01.001.
32. Ossendorff R, Franke K, Erdle B, et al. Clinical and radiographical ten years long-term outcome of microfracture vs. autologous chondrocyte implantation: a matched-pair analysis. *Int Orthop* 2019; 43: 553-559. 2018/06/18. DOI: 10.1007/s00264-018-4025-5.
33. Kreuz PC, Kalkreuth RH, Niemeyer P, et al. Long-Term Clinical and MRI Results of Matrix-Assisted Autologous Chondrocyte Implantation for Articular Cartilage Defects of the Knee. *Cartilage* 2019; 10: 305-313. 2018/02/13. DOI: 10.1177/1947603518756463.
34. Niemeyer P, Porichis S, Steinwachs M, et al. Long-term Outcomes After First-Generation Autologous Chondrocyte Implantation for Cartilage Defects of the Knee. *The American Journal of Sports Medicine* 2013; 42: 150-157. DOI: 10.1177/0363546513506593.
35. Ogura T, Mosier BA, Bryant T, et al. A 20-Year Follow-up After First-Generation Autologous Chondrocyte Implantation. *The American Journal of Sports Medicine* 2017; 45: 2751-2761. DOI: 10.1177/0363546517716631.
36. Gobbi A, Karnatzikos G and Kumar A. Long-term results after microfracture treatment for full-thickness knee chondral lesions in athletes. *Knee Surg Sports Traumatol Arthrosc* 2014; 22: 1986-1996. 2013/09/21. DOI: 10.1007/s00167-013-2676-8.
37. Wondrasch B, Aroen A, Rotterud JH, et al. The feasibility of a 3-month active rehabilitation program for patients with knee full-thickness articular cartilage lesions: the Oslo Cartilage Active Rehabilitation and Education Study. *J Orthop Sports Phys Ther* 2013; 43: 310-324. DOI: 10.2519/jospt.2013.4354.

38. Saris DB, Dhert WJ and Verbout AJ. Joint homeostasis. The discrepancy between old and fresh defects in cartilage repair. *J Bone Joint Surg Br* 2003; 85: 1067-1076. DOI: 10.1302/0301-620x.85b7.13745.
39. Lindström C, Rosvall M and Lindström M. Socioeconomic status, social capital and self-reported unmet health care needs: A population-based study. *Scand J Public Health* 2017; 45: 212-221. 20170308. DOI: 10.1177/1403494816689345.
40. Pánics G, Hangody LR, Baló E, et al. Osteochondral Autograft and Mosaicplasty in the Football (Soccer) Athlete. *CARTILAGE* 2012; 3: 25S-30S. DOI: 10.1177/1947603511408286.
41. Familiari F, Cinque ME, Chahla J, et al. Clinical Outcomes and Failure Rates of Osteochondral Allograft Transplantation in the Knee: A Systematic Review. *Am J Sports Med* 2018; 46: 3541-3549. 20171017. DOI: 10.1177/0363546517732531.
42. Peterson L, Vasiliadis HS, Brittberg M, et al. Autologous Chondrocyte Implantation: A Long-term Follow-up. *The American Journal of Sports Medicine* 2010; 38: 1117-1124. DOI: 10.1177/0363546509357915.
43. Ackerman IN, Bohensky MA, de Steiger R, et al. Substantial rise in the lifetime risk of primary total knee replacement surgery for osteoarthritis from 2003 to 2013: an international, population-level analysis. *Osteoarthritis Cartilage* 2016. DOI: 10.1016/j.joca.2016.11.005.
44. Norwegian. The Norwegian Arthroplasty Register Annual Report. National Advisory Unit on Arthroplasty and Hip Fractures., 2020.
45. Crawford DC, DeBerardino TM and Williams RJ, 3rd. NeoCart, an autologous cartilage tissue implant, compared with microfracture for treatment of distal femoral cartilage lesions: an FDA phase-II prospective, randomized clinical trial after two years. *J Bone Joint Surg Am* 2012; 94: 979-989. DOI: 10.2106/jbjs.K.00533.
46. Saris D, Price A, Widuchowski W, et al. Matrix-Applied Characterized Autologous Cultured Chondrocytes Versus Microfracture: Two-Year Follow-up of a Prospective Randomized Trial. *Am J Sports Med* 2014; 42: 1384-1394. 2014/04/10. DOI: 10.1177/0363546514528093.
47. Brittberg M, Recker D, Ilgenfritz J, et al. Matrix-Applied Characterized Autologous Cultured Chondrocytes Versus Microfracture: Five-Year Follow-up of a Prospective Randomized Trial. *Am J Sports Med* 2018; 46: 1343-1351. 2018/03/23. DOI: 10.1177/0363546518756976.

Figure 1. Flowchart illustrating the inclusion of patients in the cartilage cohort.

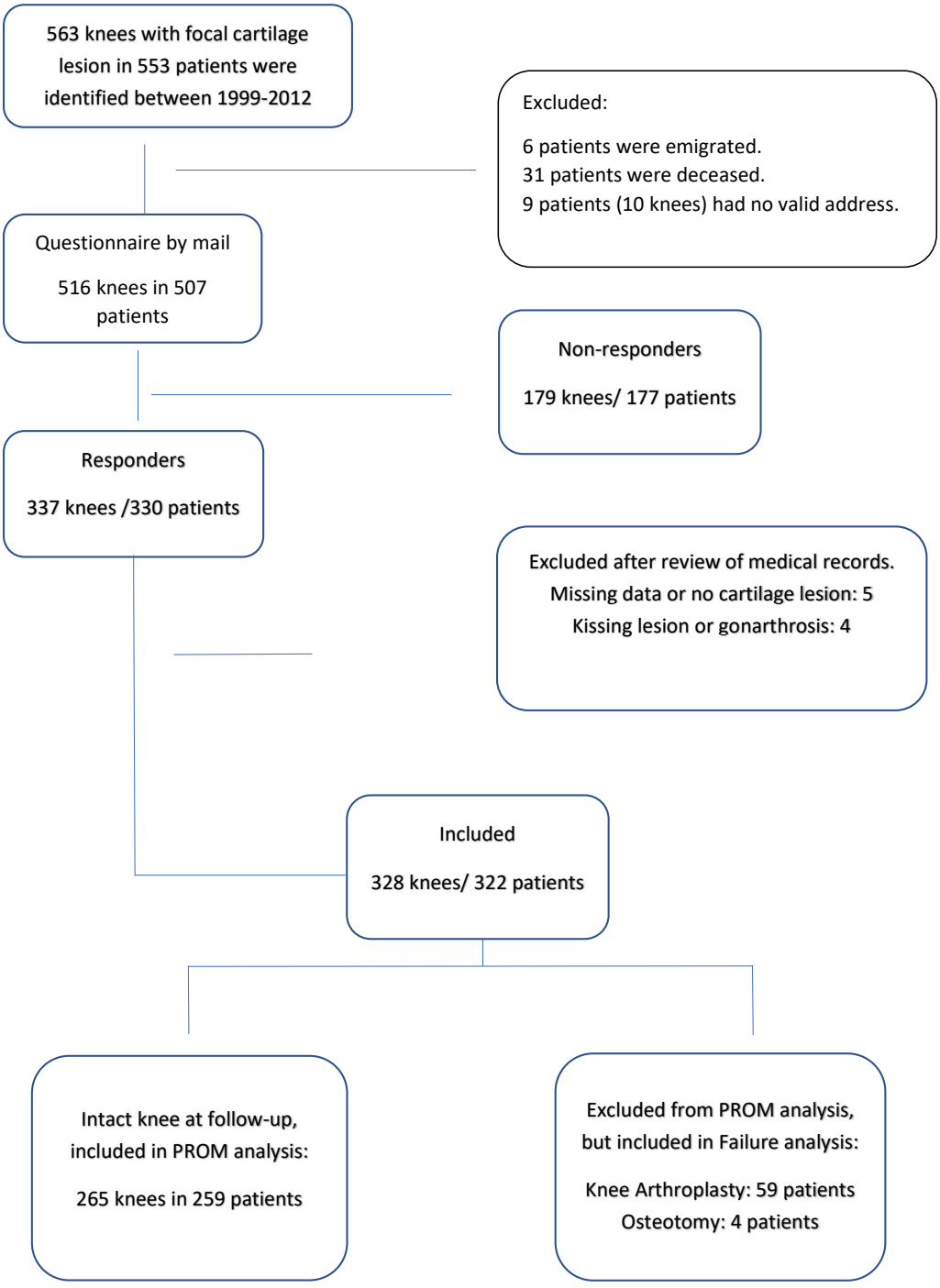
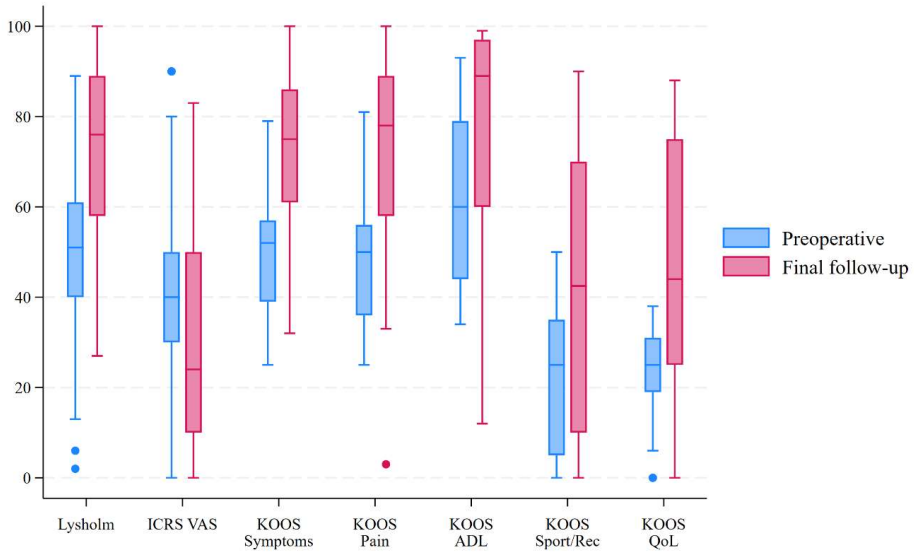
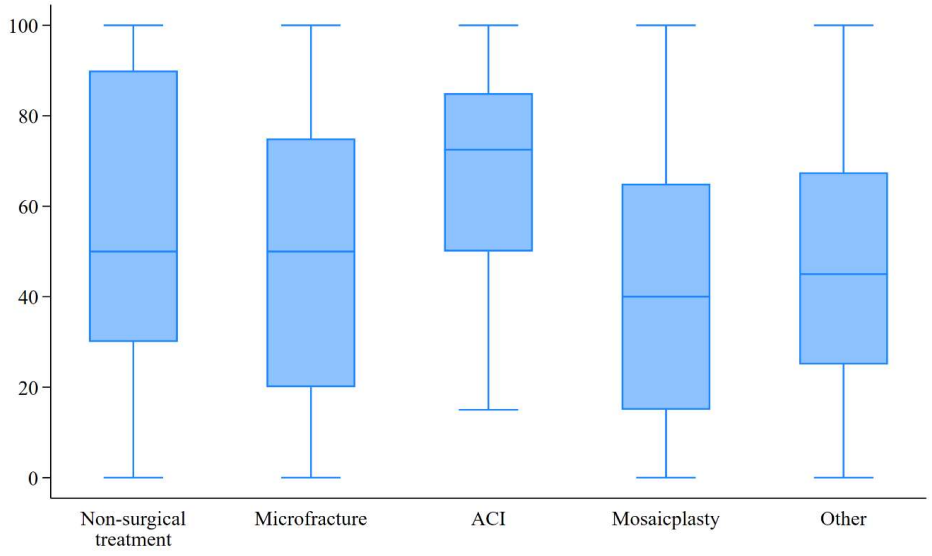


Figure 2 Patient Reported Outcome Measures (PROM) preoperative at the time of index surgery and at final follow-up.



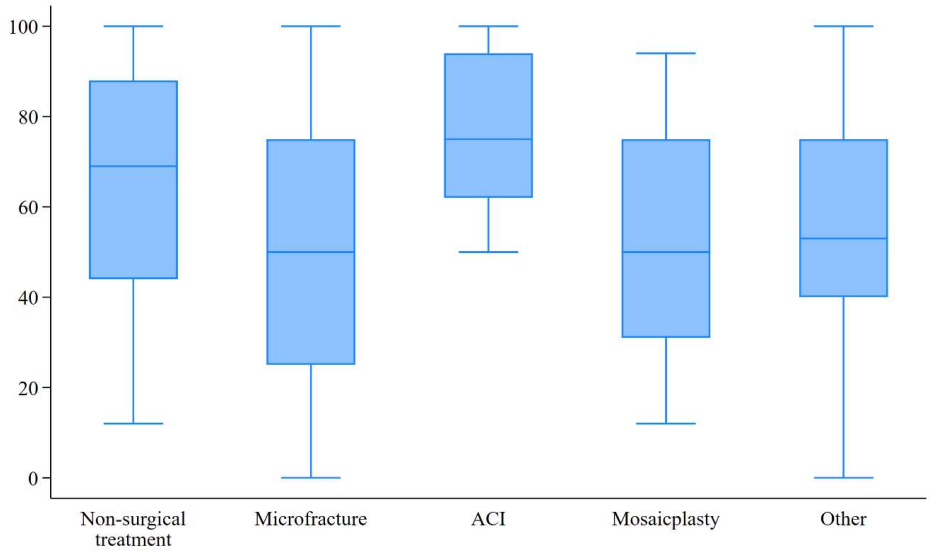

*Boxplot with median and 25th-75th percentile. Whiskers represent the adjacent value within the 1.5 interquartile range. ICRS VAS (Visual analogue scale) 100-no pain, 0-worst pain imaginable.*

Figure 3. Crude KOOS Sport/Rec sub scores at final follow-up by treatment group excluding patient with knee arthroplasty or osteotomy.




*Boxplot with median and 25th-75th percentile. Whiskers represent the adjacent value within the 1.5 interquartile range. Differences between ACI and mosaicplasty as well as mfx were statistically significant($p<0.003$). As were the difference between no treatment and mosaicplasty ($p<0,05$). Mfx- Microfracture, ACI-Autologous Chondrocyte Injection. Other – Debridement, Trufit, Caritpatch or MaioRegen.*

Figure 4. Crude KOOS Quality of Life (QoL) sub scores at final follow-up by treatment group excluding patient with knee arthroplasty or osteotomy.




*Boxplot with median and 25th-75th percentile. Whiskers represent the adjacent value within the 1.5 interquartile range. Only differences between ACI and mosaicplasty as well as mfx were statistically significant($p<0.001$). Mfx- Microfracture, ACI-Autologous Chondrocyte Implantation. Other – Debridement, Trufit, Caritpatch or MaioRegen.*

Table 1 Demographics and descriptive statistics of 328 knees in 322 patients with focal cartilage lesions in 6 Norwegian Hospitals between 1999-2012

| | Frequency or mean[1] |
|---|---|
| Knees | 328 |
| Male/Female | 188(57%)/140(43%) |
| Right/left knee | 173(53%)/154(47%) |
| Age at the time of surgery | 36.8 years (35.6, 38.0) |
| Time from index surgery to PROM follow-up | 19.1 years (18.8, 19.5) |
| Cartilage lesion ICRS 1-2/ 3-4 | 52(16%)/276(84%) |
| Size of cartilage lesion ($mm^2$) | 201.3 $mm^2$(178.9, 223.7) |
| Location of cartilage lesion[2]: | |
| – Patellofemoral | 73 (22.3%) |
| – Medial | 204 (62.2%) |
| – Lateral | 51 (15.5%) |
| Type of treatment: | |
| – No cartilage treatment | 93 (28.4%) |
| – Microfracture | 124 (37.8%) |
| – Debridement | 10 (3.0%) |
| – ACI | 30 (9.1%) |
| – Mosaicplasty | 53 (16.2%) |
| – Other | 18 (5.5%) |
| Level of education: | |
| – High school | 155 (47.3%) |
| – Bachelor/Master degree | 164 (50.0%) |
| Body mass index (BMI) at end of study | 27.4 (26.9, 27.9) |
| – <25 | 100(30.5%) |
| – 25-30 | 137(41.8%) |
| – >30 | 75(22.9%) |
| ACL reconstruction in ipsilateral knee | 50 (15.2%) |
| – At index surgery | 15 (4.6%) |
| – Before or after index surgery | 35 (10.7%) |
| – No | 278 (84.8%) |
| Meniscal resection in ipsilateral knee | 100 (30.5%) |
| – At index surgery | 46 (14.0%) |
| – Before or after index surgery | 54 (16.5%) |
| – No | 228 (69.5%) |
| Knee arthroplasty | 59 (18.0%) |
| Osteotomy | 4(1.2%) |
| KOOS at final follow up n=262 | |
| KOOS Symp | 72.7 (70.2-75.3) |
| KOOS Pain | 73.9 (71.1-71.1) |
| KOOS ADL | 81.0 (78.4-83.7) |
| KOOS Sport/Rec | 50.3 (46.5-46.5) |
| KOOS QoL | 58.1 (54.8-61.3) |

*[1]Percentage or 95% Confidence Interval in parenthesis. [2] For detailed information regarding location by treatment group please refer to supplementary table 3. ICRS – International Cartilage Repair and Joint Preservation Society, VAS – Visual Analogue Scale, OCD – Osteochondritis dissecans, ACI – Autologous Cartilage Implantation, MACI- Matrix induced Autologous Cartilage Implantation, ACL- Anterior Cruciate Ligament*

Table 2. Patient Reported Outcome Measures (PROM) preoperatively at the time of index surgery and at final follow-up in the patients without subsequent knee arthroplasty or osteotomy. Means with 95% confidence intervals are in parentheses.

| PROM | Mean preop | Mean at follow-up | Mean Improvement[2] | p |
|---|---|---|---|---|
| ICRS VAS[1] n=94 | 58.0 (53-62,9) | 71.1 (66,4-75,8) | 12.4 (6.2-18.5) | <0.001 |
| Lysholm n=140 | 50.2 (47.4-53.0) | 72.0 (68.6-75.4) | 21.4 (17.7-25.2) | <0.001 |
| KOOS Symp n=26 | 50.0 (45.2-54.9) | 70.1 (62.1-78.1) | 20.0 (12.2-27.9) | <0.001 |
| KOOS Pain n=26 | 48.6 (42.6-54.6) | 70.4 (60.4-80.4) | 20.4 (11.0-29.7) | <0.001 |
| KOOS ADL n=26 | 61.1 (53.4-68.8) | 77.7 (67.8-87.5) | 16.5 (8.2-24.8) | <0.001 |
| KOOS Sport/rec n=26 | 23.5 (17.2-29.7) | 41.7 (29.0-54.4) | 18.3 (9.0-27.5) | <0.001 |
| KOOS QoL n=26 | 23.1 (18.2-28.1) | 48.9 (38.1-59.7) | 25.8 (17.0-34.6) | <0.001 |

[1]ICRS VAS (Visual analogue scale) 0-no pain, 100-worst pain imaginable. [2] 95% Confidence Interval in parentheses.

Table 3. Factors influencing the KOOS QoL at final follow-up after focal cartilage lesions in the knee. Patients with ipsilateral knee arthroplasty or osteotomy were excluded.

| | Crude | | | | Adjusted[1] | | | |
|---|---|---|---|---|---|---|---|---|
| | Mean difference[15] | 95% CI | | p | Mean difference[15] | 95% CI | | p |
| | | Lower | Upper | | | Lower | Upper | |
| Gender[2] | | | | | | | | |
| Male | ref | | | | | | | |
| Female | -2.7 | -9.2 | 3.8 | 0.418 | | | | |
| Number of cartilage lesions[3] | | | | | | | | |
| 1 | ref | | | | ref | | | |
| ≥2 | -6.4 | -14.3 | 1.4 | 0.111 | -11.1 | -19.5 | -2.8 | 0.009 |
| Size of cartilage lesion[4] | | | | | | | | |
| <2cm$^2$ | ref | | | | ref | | | |
| ≥2cm$^2$ | 3.9 | -2.9 | 10.7 | 0.264 | 4.8 | -2.1 | 11.7 | 0.171 |
| Age at time of index surgery[2] | | | | | | | | |
| < 30 years | ref | | | | | | | |
| 30-39 years | -1.7 | -9.7 | 6.2 | 0.622 | | | | |
| >40 years | 4.3 | -4.3 | 13.0 | 0.325 | | | | |
| Body mass index[5] | | | | | | | | |
| <25 | ref | | | | ref | | | |
| 25-29 | -6.0 | -13.4 | 1.3 | 0.111 | -5.4 | -13.2 | 2.4 | 0.178 |
| ≥30 | -8.2 | -17.1 | 0.7 | 0.072 | -7.0 | -16.1 | 2.1 | 0.132 |
| Level of education[6] | | | | | | | | |
| Bachelor/ Master degree | ref | | | | ref | | | |
| High school | -7.9 | -14.4 | -1.4 | 0.018 | 8.7 | 2.2 | 15.2 | 0.009 |
| Ipsilateral ACL reconstruction[7] | | | | | | | | |
| No | ref | | | | ref | | | |
| Yes | 1.1 | -8.1 | 10.2 | 0.815 | 0.51 | -8.7 | 9.7 | 0.913 |

*Continued*

Table 3 Continued

| | Crude | | | | Adjusted[1] | | | |
|---|---|---|---|---|---|---|---|---|
| | **Mean difference[15]** | **95% CI** | | **p** | **Mean difference[15]** | **95% CI** | | **p** |
| | | Lower | Upper | | | Lower | Upper | |
| Ipsilateral meniscal resection[8] | | | | | | | | |
| No | ref | | | | ref | | | |
| Yes | -0.8 | -7.9 | 6.2 | 0.815 | -2.5 | -9.7 | 4.8 | 0.505 |
| ICRS classification[9] | | | | | | | | |
| 1-2 | ref | | | | ref | | | |
| 3-4 | -11.2 | -19.5 | -2.9 | 0.008 | -9.8 | -18.8 | -0.9 | 0.032 |
| Cartilage treatment at index surgery[10] | | | | | | | | |
| No treatment | ref | | | | ref | | | |
| Microfracture | -11.2 | -19.0 | -3.4 | 0.005 | -6.0 | -15.9 | 3.9 | 0.231 |
| ACI | 13.2 | 0.9 | 25.5 | 0.036 | 17.5 | 3.2 | 31.7 | 0.017 |
| Mosaicplasty | -11.0 | -20.8 | -1.2 | 0.028 | -9.4 | -21.6 | 2.8 | 0.129 |
| Other | -10.1 | --21.3 | 1.1 | 0.078 | -3.8 | -17.7 | 10.1 | 0.592 |
| Location of cartilage lesion[11]: | | | | | | | | |
| Patellofemoral | ref | | | | ref | | | |
| Medial compartment | 7.8 | 0.1 | 15.5 | 0.046 | 7.2 | -0.8 | 15.2 | 0.077 |
| Lateral compartment | 17.1 | 6.4 | 27.7 | 0.002 | 17.6 | 6.9 | 28.3 | 0.001 |
| Time since index cartilage surgery[12] | 0.9 | 0.0 | 1.9 | 0.052 | 0.98 | 0.04 | 1.93 | 0.040 |
| Preoperative Lysholmscore[13] | 0.5 | 0.2 | 0.7 | <0.001 | 0.31 | 0.04 | 0.57 | 0.023 |
| Preoperative ICRS VAS[14] | -0.2 | -0.4 | 0.1 | 0.183 | -0.05 | -0.32 | 0.21 | 0.690 |

[1] Mean difference adjusted according to a Graphical Causal Model.[2] Not adjusted. [3] Adjusted for number of cartilage lesions, Age at cartilage surgery, ACL reconstruction, BMI, Gender, level of education, meniscal resection, size of cartilage lesion, and time from cartilage surgery to questionnaire follow-up. [4] Adjusted for Age at cartilage surgery, BMI, meniscal resection, and time from cartilage surgery to questionnaire follow-up . [5] Adjusted for Age at cartilage surgery, Gender, Level of Education, and time from cartilage surgery to questionnaire follow-up [6] Adjusted for Gender.[7] Adjusted for Gender, Level of education, Age at cartilage surgery, BMI, and time from cartilage surgery to questionnaire follow-up . [8]Adjusted for Age at cartilage surgery, BMI, ICRS classification, and time from cartilage surgery to questionnaire follow-up . [9]Adjusted for Age at cartilage surgery, BMI, meniscal resection, and time from cartilage surgery to questionnaire follow-up . [10]Adjusted for Age at cartilage surgery, ICRS classification, Level of Education, Location of cartilage lesion, Number of cartilage lesions, Size of cartilage lesion, and time from cartilage surgery to questionnaire follow-up . [11]Adjusted for ACL reconstruction, Age at cartilage surgery, Gender and meniscal resection. [12]Adjusted for Location of cartilage lesion, ACL reconstruction, Age at cartilage surgery, Gender, Meniscal resection, BMI, Cartilage treatment at index surgery, ICRS classification, Level of education, Number of cartilage lesions and Size of lesion.[13]Adjusted for ACL reconstruction, Age at cartilage surgery, BMI, Gender, ICRS classification, Level of Education, Location of cartilage lesion, Meniscal resection, Number of cartilage lesions, Size of lesion, and time from cartilage surgery to questionnaire follow-up . [14]Adjusted for ACL reconstruction, Age at cartilage surgery, BMI, Gender, ICRS classification, Level of Education, Location of cartilage lesion, Meniscal resection, Number of cartilage lesions, Size of lesion, time from cartilage surgery to questionnaire follow-up and cartilage treatment at index surgery. 15 Mean difference in QoL score from reference. Negative numbers implies lower mean score than reference. CI- Confidence Interval, OR- Odds Ratio, ACL-Anterior Cruciate Ligament, ACI- Autologous Chondrocyte Implantation

Table 4. Risk factors for treatment failure defined as ipsilateral knee arthroplasty, ipsilateral knee osteotomy or KOOS QoL subscore < 50 in the Norwegian cartilage lesion cohort.

| | | Crude | | | | Adjusted[1] | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Failures, n(%)** | **OR** | **95% CI** | | **p** | **OR** | **95% CI** | | **p** |
| | | | Lower | Upper | | | Lower | Upper | |
| Total | 162(49.4%) | | | | | | | | |
| Gender[2] | | | | | | | | | |
| Male | 87(47.3%) | 1 | | | | | | | |
| Female | 75(53.6%) | 1.3 | 0.8 | 2.0 | 0.262 | | | | |
| Number of cartilage lesions[3] | | | | | | | | | |
| 1 | 101(45.5%) | 1 | | | | | | | |
| ≥2 | 50(60.2%) | 1.9 | 1.2 | 3.2 | 0.010 | 1.9 | 1.1 | 3.3 | 0.035 |
| Size of cartilage lesion[4] | | | | | | | | | |
| <2cm$^2$ | 110(51.9%) | | | | | 1 | | | |
| ≥2cm$^2$ | 52(46.4%) | 0.67 | 0.4 | 1.1 | 0.119 | 0.8 | 0.5 | 1.3 | 0.319 |
| Age at time of index surgery[2] | | | | | | | | | |
| < 30 years | 36(43.9%) | 1 | | | | | | | |
| 30-39 years | 62(49.2%) | 1.2 | 0.7 | 2.2 | 0.454 | | | | |
| >40 years | 64(55.2%) | 1.6 | 0.9 | 2.8 | 0.119 | | | | |
| Body mass index[5] | | | | | | | | | |
| <25 | 37(37.4%) | 1 | | | | 1 | | | |
| 25-29 | 70(51.1%) | 2.5 | 1.4 | 4.4 | 0.001 | 2.0 | 1.1 | 3.6 | 0.016 |
| ≥30 | 45(60.8%) | 2.6 | 1.4 | 5.0 | 0.003 | 3.1 | 1.6 | 5.9 | 0.001 |
| Level of education[6] | | | | | | | | | |
| Bachelor/ Master degree | 70(43.3%) | 1 | | | | 1 | | | |
| High school | 87(56.1%) | 0.5 | 0.3 | 0.8 | 0.003 | 1.8 | 1.1 | 2.8 | 0.011 |
| Ipsilateral ACL reconstruction[7] | | | | | | | | | |
| No | 139(50.4%) | 1 | | | | 1 | | | |
| Yes | 23(47.9%) | 1.0 | 0.5 | 1.8 | 0.916 | 1.1 | 0.6 | 2.1 | 0.785 |
| Ipsilateral meniscal resection[8] | | | | | | | | | |
| No | 110(48.9%) | 1 | | | | 1 | | | |
| Yes | 52(52.5%) | 1.1 | 0.7 | 1.8 | 0.574 | 1.3 | 0.8 | 2.2 | 0.337 |
| ICRS classification[9] | | | | | | | | | |
| 1-2 | 17(32.7%) | 1 | | | | 1 | | | |
| 3-4 | 145(53.3%) | 1.8 | 1.0 | 3.5 | 0.061 | 2.5 | 1.3 | 5.0 | 0.009 |
| Cartilage treatment at index surgery[10] | | | | | | | | | |
| No treatment | 40(44%) | 1 | | | | 1 | | | |
| Microfracture | 71(57.2%) | 1.8 | 1.0 | 3.1 | 0.038 | 1.2 | 0.6 | 2.5 | 0.638 |
| ACI | 8(26.7%) | 0.5 | 0.2 | 1.2 | 0.115 | 0.3 | 0.1 | 1.0 | 0.040 |
| Mosaicplasty | 30(57.7%) | 1.7 | 0.9 | 3.4 | 0.115 | 1.5 | 0.6 | 3.9 | 0.369 |
| Other | 13(46.6%) | 0.8 | 0.5 | 2.7 | 0.749 | 0.8 | 0.3 | 2.7 | 0.752 |

*Continued*

Table 4. Continued

| | Failures, n(%) | Crude | | | | Adjusted[1] | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | OR | 95% CI | | p | OR | 95% CI | | p |
| | | | Lower | Upper | | | Lower | Upper | |
| Location of cartilage lesion[11]: | | | | | | | | | |
| Patellofemoral | 42(57.5%) | 1 | | | | 1 | | | 0.303 |
| Medial compartment | 98(48.8%) | 0.8 | 0.5 | 1.4 | 0.513 | 0.7 | 0.4 | 1.2 | 0.167 |
| Lateral compartment | 22(44.0%) | 0.7 | 0.4 | 1.5 | 0.417 | 0.5 | 0.2 | 1.1 | 0.82 |
| Time since index cartilage surgery[12] | | 1.0 | 0.9 | 1.0 | 0.442 | 1.0 | 0.9 | 1.1 | 0.588 |
| Preoperative Lysholmscore[13] | | 0.98 | 0.96 | 1.0 | 0.013 | 0.98 | 0.96 | 1.00 | 0.107 |
| Preoperative ICRS VAS[14] | | 1.03 | 1.01 | 1.05 | 0.004 | 1.01 | 0.99 | 1.04 | 0.190 |

[1] OR adjusted according to a Graphical Causal Model.[2] Not adjusted. [3] Adjusted for number of cartilage lesions, Age at cartilage surgery, ACL reconstruction, BMI, Gender, level of education, meniscal resection, size of cartilage lesion, and time from cartilage surgery to end of study. [4] Adjusted for Age at cartilage surgery, BMI, meniscal resection, and time from cartilage surgery to end of study. [5] Adjusted for Age at cartilage surgery, Gender, Level of Education, and time from cartilage surgery to end of study. [6] Adjusted for Gender.[7] Adjusted for Gender, Level of education, Age at cartilage surgery, BMI, and time from cartilage surgery to end of study. [8]Adjusted for Age at cartilage surgery, BMI, ICRS classification, and time from cartilage surgery to end of study. [9]Adjusted for Age at cartilage surgery, BMI, meniscal resection, and time from cartilage surgery to end of study. [10]Adjusted for Age at cartilage surgery, ICRS classification, Level of Education, Location of cartilage lesion, Number of cartilage lesions, Size of cartilage lesion, and time from cartilage surgery to end of study. [11]Adjusted for ACL reconstruction, Age at cartilage surgery, Gender and meniscal resection. [12]Adjusted for Location of cartilage lesion, ACL reconstruction, Age at cartilage surgery, Gender, Meniscal resection, BMI, Cartilage treatment at index surgery, ICRS classification, Level of education, Number of cartilage lesions and Size of lesion.[13]Adjusted for ACL reconstruction, Age at cartilage surgery, BMI, Gender, ICRS classification, Level of Education, Location of cartilage lesion, Meniscal resection, Number of cartilage lesions, Size of lesion, and time from cartilage surgery to end of study. [14]Adjusted for ACL reconstruction, Age at cartilage surgery, BMI, Gender, ICRS classification, Level of Education, Location of cartilage lesion, Meniscal resection, Number of cartilage lesions, Size of lesion, time from cartilage surgery to end of study and cartilage treatment at index surgery. CI- Confidence interval OR- Odds Ratio, ACL-Anterior Cruciate Ligament, ACI- Autologous Chondrocyte Implantation

Supplementary Table 1. Cartilage treatment group by location of the cartilage lesion.

| | n(%) | No treatment | Mfx | ACI | Mosaicplasty | Other |
|---|---|---|---|---|---|---|
| Patella | 44(13.4%) | 20(21.5%) | 10(8.1%) | 0 | 13(24.5%) | 1(3.5% |
| Trochlea | 29(8.8%) | 1(1.1%) | 17(13.7%) | 2(6.7%) | 5(9.4%) | 4(14.2%) |
| Medial Femur | 195(59.5%) | 45(48.4%) | 78(62.9%) | 26(86.7%) | 30(56.6%) | 16(57.1%) |
| Lateral Femur | 35(10.7%) | 12(12.9%) | 12(9.7%) | 2(6.7%) | 5(9.4%) | 4(14.3%) |
| Medial Tibia | 9(2.7%) | 7(7.5%) | 0 | 0 | 0 | 2(7.1%) |
| Lateral Tibia | 16(4.9%) | 8(8.6%) | 7(5.6%) | 0 | 0 | 1(3.6%) |

Mfx-Microfracture, ACI- Autologous Cartilage Implantation, Other = Debridement, MaioRegen (Finceramica, Italy), Cartipatch (Xizia, Hong Kong), or TruFit (Smith and Nephew, USA).

Supplementary Table 2. Factors influencing the KOOS QoL at final follow-up after focal cartilage lesions in the knee. Patients with patellofemoral lesions or with ipsilateral knee arthroplasty or osteotomy were excluded.

| | Adjusted[1] | | | |
|---|---|---|---|---|
| | **Mean difference[15]** | **95% CI** | | **p** |
| | | Lower | Upper | |
| Gender[2] | | | | |
| Male | ref | | | |
| Female | -1.5 | -8.9 | 6.0 | 0.700 |
| Number of cartilage lesions[3] | | | | |
| 1 | ref | | | |
| ≥2 | -12.3 | -21.7 | -3.0 | 0.010 |
| Size of cartilage lesion[4] | | | | |
| <2cm$^2$ | ref | | | |
| ≥2cm$^2$ | 0.76 | -6.8 | 8.4 | 0.843 |
| Age at time of index surgery[2] | | | | |
| < 30 years | ref | | | |
| 30-39 years | 2.0 | -6.9 | 10.9 | 0.659 |
| >40 years | 11.2 | 1.6 | 20.8 | 0.022 |
| Body mass index[5] | | | | |
| <25 | ref | | | |
| 25-29 | -2.2 | -11.0 | 6.6 | 0.624 |
| ≥30 | -6.7 | -17.1 | 3.7 | 0.205 |
| Level of education[6] | | | | |
| Bachelor/Master degree | ref | | | |
| High school | 9.0 | 1.7 | 16.4 | 0.017 |
| Ipsilateral ACL reconstruction[7] | | | | |
| No | ref | | | |
| Yes | -0.84 | -10.3 | 8.6 | 0.860 |
| Ipsilateral meniscal resection[8] | | | | |
| No | ref | | | |
| Yes | -6.7 | -14.9 | 1.4 | 0.105 |
| ICRS classification[9] | | | | |
| 1-2 | ref | | | |
| 3-4 | -8.3 | -18.2 | 1.7 | 0.104 |
| Cartilage treatment at index surgery[10] | | | | |
| No treatment | ref | | | |
| Debridement or Microfracture | -3.1 | -15.1 | 8.8 | 0.605 |
| ACI | 17.9 | 1.8 | 33.9 | 0.029 |
| Mosaicplasty | -3.5 | -18.9 | 11.9 | 0.655 |
| Other | -5.8 | -21.0 | 9.35 | 0.447 |
| Location of cartilage lesion[11]: | | | | |
| Medial compartment | ref | | | |
| Lateral compartment | 12.0 | 2.5 | 21.3 | 0.012 |
| Time since index cartilage surgery[12] | 1.3 | 0.25 | 2.32 | 0.015 |
| Preoperative Lysholmscore[13] | 0.27 | -0.05 | 0.59 | 0.101 |
| Preoperative ICRS VAS[14] | -0.03 | -0.32 | 0.26 | 0.835 |

[1] Mean difference adjusted according to a Graphical Causal Model.[2] Not adjusted. [3] Adjusted for number of cartilage lesions, Age at cartilage surgery, ACL reconstruction, BMI, Gender, level of education, meniscal resection, size of cartilage lesion, and time from cartilage surgery to questionnaire follow-up. [4] Adjusted for Age at cartilage surgery, BMI, meniscal resection, and time from cartilage surgery to questionnaire follow-up. [5] Adjusted for Age at cartilage surgery, Gender, Level of Education, and time from cartilage surgery to questionnaire follow-up. [6] Adjusted for Gender.[7] Adjusted for Gender, Level of education, Age at cartilage surgery, BMI, and time from cartilage surgery to questionnaire follow-up. [8]Adjusted for Age at cartilage surgery, BMI, ICRS classification, and time from cartilage surgery to questionnaire follow-up. [9]Adjusted for Age at cartilage surgery, BMI, meniscal resection, and time from cartilage surgery to questionnaire follow-up. [10]Adjusted for Age at cartilage surgery, ICRS classification, Level of Education, Location of cartilage lesion, Number of cartilage lesions, Size of cartilage lesion, and time from cartilage surgery to questionnaire follow-up[11]Adjusted for ACL reconstruction, Age at cartilage surgery, Gender and meniscal resection. [12]Adjusted for Location of cartilage lesion, ACL reconstruction, Age at cartilage surgery, Gender, Meniscal resection, BMI, Cartilage treatment at index surgery, ICRS classification, Level of education, Number of cartilage lesions and Size of lesion.[13]Adjusted for ACL reconstruction, Age at cartilage surgery, BMI, Gender, ICRS classification, Level of Education, Location of cartilage lesion, Meniscal resection, Number of cartilage lesions, Size of lesion, and time from cartilage surgery to questionnaire follow-up[14]Adjusted for ACL reconstruction, Age at cartilage surgery, BMI, Gender, ICRS classification, Level of Education, Location of cartilage lesion, Meniscal resection, Number of cartilage lesions, Size of lesion, time from cartilage surgery to questionnaire follow-upand cartilage treatment at index surgery. 15 Mean difference in QoL score from reference. Negative numbers implies lower mean score than reference. CI- Confidence Interval, OR- Odds Ratio, ACL-Anterior Cruciate Ligament, ACI- Autologous Chondrocyte Implantation

# Paper III

Received: 23 October 2023 | Accepted: 24 December 2023

DOI: 10.1002/ksa.12050



Knee Surgery, Sports Traumatology, Arthroscopy WILEY

# Previous cartilage surgery is associated with inferior patient-reported outcomes after knee arthroplasty

**Thomas Birkenes**[1,2,3] | **Ove Furnes**[1,2,4] | **Stein Håkon Låstad Lygre**[4,5] | **Eirik Solheim**[1] | **Asbjørn Årøen**[6,7,8] | **Gunnar Knutsen**[9] | **Jon Olav Drogset**[10,11,12] | **Stig Heir**[13] | **Lars Engebretsen**[6,8,14] | **Sverre Løken**[14] | **Håvard Visnes**[8,12,15]

**Correspondence**
Thomas Birkenes, Department of Clinical Medicine, University of Bergen, Bergen, Norway.
Email: thbirkenes@hotmail.com

**Funding information**
Norwegian Research Council, Grant/Award Number: 2015107

**Abstract**

**Purpose:** The hypothesis of the present study assumed that a history of focal cartilage lesions would not affect Knee Injury and Osteoarthritis Outcome scores (KOOSs) following knee arthroplasty compared to a matched national cohort of knee arthroplasty patients.

**Methods:** Fifty-eight knee arthroplasty patients with previous surgery for focal cartilage lesions (cartilage cohort) were compared to a matched cohort of 116 knee arthroplasty patients from the Norwegian Arthroplasty Register (control group). Age, sex, primary or revision arthroplasty, type of arthroplasty (total, unicondylar or patellofemoral), year of arthroplasty surgery and arthroplasty brand were used as matching criteria. Demographic data and KOOS were obtained through questionnaires. Regression models were employed to adjust for confounding factors.

**Results:** Mean follow-up post knee arthroplasty surgery was 7.6 years (range 1.2–20.3) in the cartilage cohort and 8.1 (range 1.0–20.9) in the control group. The responding patients were at the time of surgery 54.3 versus 59.0 years in the cartilage and control group, respectively. At follow-up the control group demonstrated higher adjusted Knee Injury and Osteoarthritis Outcome subscores than the previous focal cartilage patients with a mean adjusted difference (95% confidence interval in parentheses): Symptoms 8.4 (0.3, 16.4), Pain 11.8 (2.2, 21.4), Activities of daily living (ADL) 9.3 (−1.2, 18.6), Sport and recreation 8.9 (−1.6, 19.4) and Quality of Life (QoL) 10.6 (0.2, 21.1). The control group also demonstrated higher odds of reaching the patient-acceptable symptom state threshold for the Knee Injury and Osteoarthritis Outcome subscores with odds ratio: Symptoms 2.7 (1.2, 6.4), Pain 3.0 (1.3, 7.0), ADL 2.1 (0.9, 4.6) and QoL 2.4 (1.0, 5.5).

**Conclusion:** Previous cartilage surgery was associated with inferior patient-reported outcomes after knee arthroplasty. These patients also exhibited

For author affiliations, please refer to page 368.

**Abbreviations:** ADL, Activities of daily living; FCL, focal cartilage lesion; KOOS, Knee Injury and Osteoarthritis Outcome Score; NAR, Norwegian Arthroplasty Register; PASS, patient-acceptable symptom state; PROM, Patient-Reported Outcome Measure; QoL, Quality of Life; TKA, total knee arthroplasty.

significantly lower odds of reaching the patient-acceptable symptom state threshold for the Knee Injury and Osteoarthritis Outcome subscores.

**Level of Evidence:** Level III.

**KEYWORDS**
cartilage, focal cartilage lesions, knee arthroplasty, PASS, PROM

## INTRODUCTION

Focal cartilage lesions (FCLs) in the knee exhibit poor natural healing capabilities [1] and may significantly reduce quality of life (QoL) [2, 3]. Even in surgically treated FCLs, normal knee function is often not achieved [4]. The risk of knee arthroplasty in the younger FCL patient is greater, regardless of cartilage treatment strategy [5]. In Norway, more than 95% of knee arthroplasties have been reported to the Norwegian Arthroplasty Register (NAR) since 1994 [6]. Previous knee injury, such as FCL, significantly increases the risk of later osteoarthrosis [7, 8].

While knee arthroplasty generally leads to improvements in function and satisfaction, irrespective of the type of implant used [9], a recent meta-analysis [10] found that previous knee surgery is associated with lower patient satisfaction after knee arthroplasty. None of the patients included in that analysis had been treated for FCL. Only a few studies [11, 12], involving a limited number of patients, have reported patient-reported outcomes after knee arthroplasty in individuals with previous FCL. These studies have several limitations such as only including patients treated with microfracture or the inclusion of patients with concomitant meniscal allografts and thus have limited external validity. Consequently, the patient-reported results of knee arthroplasty in patients with previous FCL remain largely unknown. The aim of the present study was thus to examine the patient-reported results of knee arthroplasty following an FCL and compare these results to a matched national cohort of knee arthroplasty patients. The hypothesis posited that prior FCL did not influence patient-reported outcomes after knee arthroplasty.

## METHODS

### Cartilage cohort

In a previously published long-term follow-up of 322 patients operated between 1999 and 2012 in six Norwegian hospitals with an arthroscopically verified FCL in the knee, 59 patients with subsequent knee arthroplasty were identified [5]. FCL surgeries were performed by experienced cartilage surgeons. The mean duration from FCL surgery to knee arthroplasty was 12.7 years. In one of the patients, insufficient details on the arthroplasty procedure were available, and the patient was excluded from the present study. Consequently, 58 patients with knee arthroplasty following previous FCLs were included.

### Control cohort

A matched control group (1:3) from the NAR operated between 1994 and 2020, was recruited, with 174 eligible participants identified. Patients in the NAR registered as deceased, having rheumatoid arthritis, having had a previous FCL or any type of cartilage surgery, or a previous multi-ligamentous injury were excluded prior to matching. The FCL group and the control group were then matched on the following variables: Year of birth (+/−10 years), sex, primary or revision arthroplasty (and cause of revision), type of arthroplasty (total, unicondylar or patellofemoral), year of arthroplasty surgery and brand of the arthroplasty. The inclusion procedure is illustrated in Figure 1. Of the 174 patients found eligible for the control group, 116 (66.7%) consented to participate in the present study. The characteristics of the exposure groups are summarized in Table 1.

### Data collection

Each patient in the control group received a questionnaire by post, along with the Knee Injury and Osteoarthritis Outcome Score (KOOS) [13], as this has been validated for both knee arthroplasty and FCL patients [14–16]. The cartilage cohort had previously completed the same questionnaire regarding body height, weight, level of education, knee function, level of activity and any previous knee surgery. The knee arthroplasty patients of both groups had completed their KOOS scores at minimum 1-year postsurgery. The NAR does not contain information on the treating surgeon.

### Statistics

Demographic differences between the previous cartilage patients and the control group were assessed using the Student $T$ test and the $\chi^2$ test.

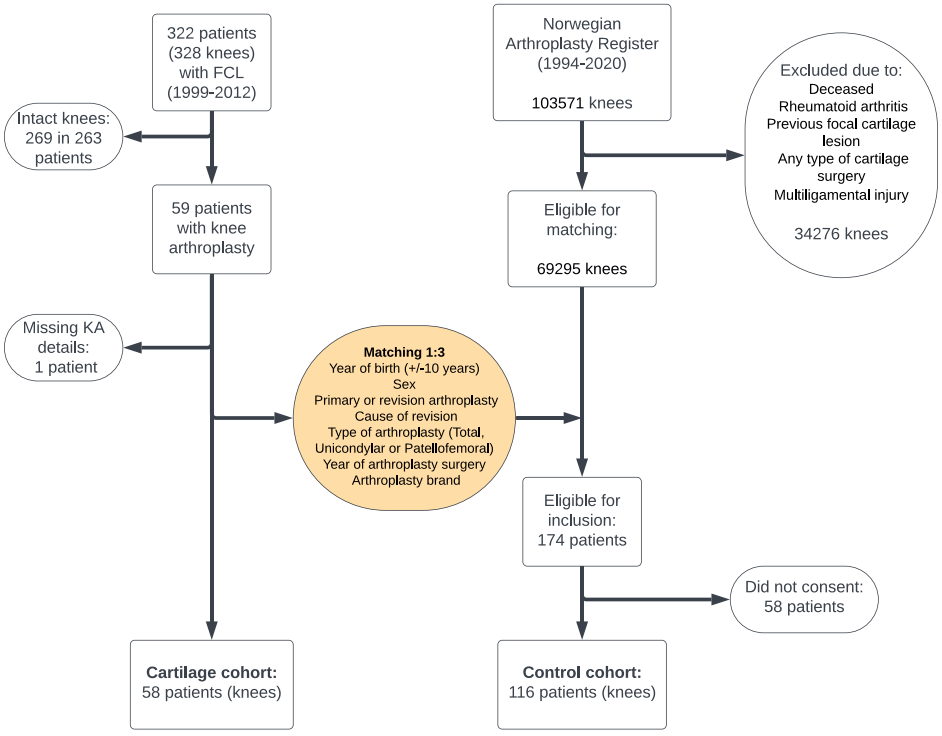



**FIGURE 1** Flowchart illustrating the inclusion of participants. FCL, focal cartilage lesion; KA, knee arthroplasty.

Multiple linear regression models were employed to analyse the differences in KOOS subscores between the previous cartilage patients and the patients from the control group. The models were adjusted for the following variables: sex, age at the time of arthroplasty surgery, level of education, primary or revision arthroplasty, type of arthroplasty, body mass index (BMI) group and any additional knee surgery before arthroplasty surgery, except cartilage surgery or purely diagnostic arthroscopy. The continuous variables in the model were evaluated and linear correlations were found.

Logistic regression models were utilized to estimate the odds of not reaching the patient acceptable symptom state (PASS) for each KOOS subscore. These models were adjusted with the same variables as the multiple regression models. The PASS score for KOOS subscores at 3 years follow-up after knee arthroplasty reported by Connelly et al. [17], with a threshold of a KOOS Symptoms score of 84.0, KOOS Pain 87.5, KOOS activities of daily living (ADL) 87.5, and KOOS QoL 66.0 was used. A $p < 0.05$ was regarded as statistically significant. The data were analysed using STATA 17 (StataCorp).

## Power analysis

Prior to enrolment, a power analysis was performed. To achieve an 80% chance of detecting a significant difference of 10 points in KOOS subscales between the exposure groups with an assumed standard deviation of 20, 64 patients in each group were required. A 10-point difference was selected as the minimal clinically important difference, as suggested by the developers of the KOOS score [13].

# RESULTS

The mean follow-up from the knee arthroplasty to the reporting of KOOS scores by the participants was 7.6 years (range 1.2–20.3) in the cartilage cohort and 8.1 (range 1.0–20.9) in the control group. Osteoarthritis was reported as the indication for the knee arthroplasty surgeries in all participants in the study population. All 11 patients (knees) with patellofemoral or unicompartmental knee arthroplasty had received knee arthroplasty in the same compartment where the previous FCL were located. None of the patients had

**TABLE 1** Demographics and descriptive statistics.

| | Frequency or mean[a] | | |
|---|---|---|---|
| | KA after focal cartilage lesion | Control group | *p* |
| Knees | 58 | 116 | |
| Male/female | 29 (50.0%)/29 (50.0%) | 62 (53.5%)/54 (46.6%) | 0.7 |
| Right/left knee | 32 (55.2%)/26 (44.8%) | 110 (94.8%)/6 (5.2%) | <0.001 |
| Age at the time of KA surgery | 54.3 (51.6–57.0) | 59.0 (57.3–60.7) | 0.003 |
| Age at follow-up | 61.9 (59.2–64.5) | 67.1 (65.4–68.8) | <0.001 |
| Years from arthroplasty surgery to end of study | 7.6 (6.1–9.1) | 8.1 (7.1–9.0) | 0.6 |
| Level of education | | | |
| High school | 32 (59.3%) | 87 (75.7%) | 0.03 |
| Bachelor's/Master's degree | 22 (40.7%) | 28 (24.3%) | 0.5 |
| Body mass index (BMI) at follow-up | 29.5 (28.3–30.7) | 30.0 (29.1–30.9) | |
| <25 | 7 (13.4%) | 12 (11.0%) | |
| 25–29 | 26 (50.0%) | 55 (50.5%) | 0.9 |
| ≥30 | 19 (36.5%) | 42 (38.5%) | |
| Previous ACL reconstruction in ipsilateral knee | | | |
| Yes | 8 (13.8%) | 1 (0.9%) | |
| No | 50 (86.2%) | 115 (99.1%) | <0.001 |
| Previous meniscal resection in ipsilateral knee | | | |
| Yes | 17 (29.3%) | 20 (17.2%) | |
| No | 41 (70.7%) | 96 (82.8%) | 0.04 |
| Previous ipsilateral osteotomy | 1 (1.7%) | 1 (0.9%) | 0.6 |
| Any previous knee surgery except cartilage surgery | | | |
| Yes | 33 (56.9%) | 29 (25.0%) | <0.001 |
| No | 25 (43.1%) | 87 (75.0%) | |
| Type of knee arthroplasty | | | |
| Unicompartmental | 8 (13.8%) | 22 (19.1%) | |
| Patellofemoral | 3 (5.2%) | 4 (3.5%) | |
| Total KA | 42 (72.4%) | 76 (66.1%) | 0.7 |
| Total KA with patella | 5 (8.6%) | 13 (11.3%) | |
| Primary knee arthroplasty | 45 (77.6%) | 109 (94%) | 0.001 |
| Revision knee arthroplasty | 13 (22.4%) | 7 (6%) | |

Abbreviations: ACL, anterior cruciate ligament; KA, knee arthroplasty.

[a]Percentage or 95% confidence interval in parenthesis.

received focal inlay implants. Patients in the FCL group were significantly younger at the questionnaire follow-up and at the time of knee arthroplasty (Table 1). The FCL cohort had significantly more knees with revision arthroplasties ($p = 0.001$), more previous knee surgeries in addition to the previous cartilage surgery ($p < 0.001$) and a higher level of education ($p = 0.03$). No significant differences between the groups in the distribution of sex, BMI, follow-up time, or type of arthroplasty were observed.

The KOOS subscores for the arthroplasty patients from the cartilage cohort and the control group are presented in

Figure 2. The adjusted results, as presented in Table 2, demonstrated significantly lower scores for KOOS Symptoms (8.4 points, $p = 0.042$), Pain (11.8 points, $p = 0.016$) and QoL (10.4 points, $p = 0.045$) subscores in the cartilage cohort. A sensitivity analysis was performed without adjusting for previous additional surgeries, but otherwise using the same regression models (Supporting Information S1: Table 1). KOOS Symptoms and Pain subscore for the cartilage cohort remained significantly inferior to those of the control group, but QoL was not significantly lower. Given the high number of revision arthroplasties in the cartilage cohort, a sensitivity analysis using the same regression models was performed, but only including the primary knee arthroplasty (Supporting Information S1: Table 2). In addition, a sensitivity analysis only including total knee arthroplasty (TKA) was performed. The results were consistent with the original analysis.

Approximately 65% of the arthroplasty patients with previous FCL failed to reach the PASS thresholds for the KOOS subscores versus 46% in the control group (Table 3). There were significantly higher odds of reaching the PASS threshold in the subscores for KOOS Symptoms Pain and QoL in the control group (Table 3).

## DISCUSSION

The principal findings of the present study were that at an average of 8 years following knee arthroplasty, patients with a history of previous cartilage surgery demonstrated significantly lower scores for KOOS Symptoms, Pain and QoL compared to a matched cohort from the NAR. Additionally, there were significantly lower odds of reaching the PASS threshold for the same KOOS subscores in the previous cartilage patients.

Failed FCL surgery with residual symptoms remains a clinical challenge [18]. In the absence of osteoarthritis, resurfacing with mini-implants has gained popularity and is advocated in a recent consensus paper [18]. In the present study, all previous FCL patients were reported to have osteoarthritis by the treating surgeon at the time of knee arthroplasty. Preoperative X-rays were not available to the research group, but the surgeon probably no longer considered the condition to be an FCL, but rather osteoarthritis in one or more compartments of the knee.

In a study of 972 patients from the NAR Lygre et al. [19] reported similar or slightly better KOOS subscores than in the control group in the present study. The tendency towards better KOOS score in their study might be explained by an older patient population (76 years vs. 67 years in the control group in the present study) as younger age has been shown to predict poorer Patient Reported Outcome Measures (PROMs) in knee arthroplasty patients [20]. Furthermore, Lygre et al. only included primary TKAs. Nevertheless, this might suggest that the KOOS subscores in the control group were representative of the average knee arthroplasty patient in Norway.

Several studies have reported no correlation between previous knee surgery and PROM scores in knee

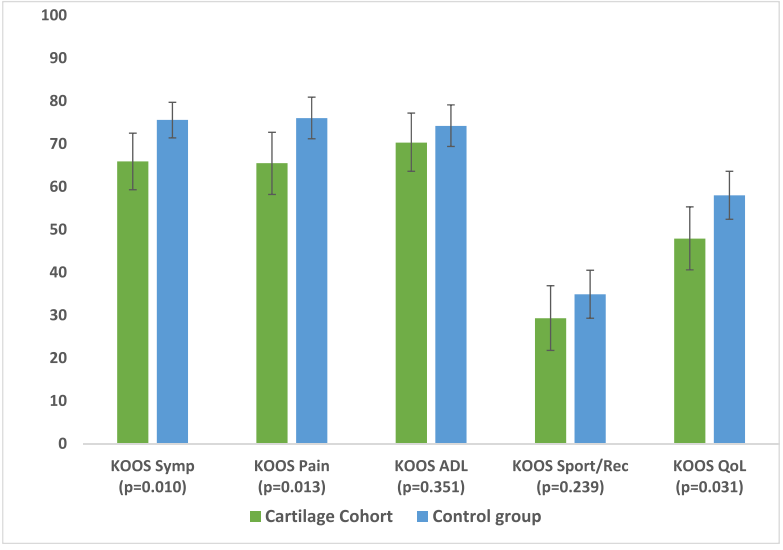



**FIGURE 2** KOOS score at final follow-up for the arthroplasty patients from the cartilage cohort and the control group. Mean score with 95% confidence intervals. ADL, activities of daily living; KOOS, Knee Injury and Osteoarthritis Outcome Score; QoL, Quality of Life.

**TABLE 2** Difference in KOOS score between the knee arthroplasty patients with previous focal cartilage lesion and the knee arthroplasty patients in the control group.

| | Crude | | Adjusted[a] | |
|---|---|---|---|---|
| | Mean difference[b] | *p* | Mean difference[b] | *p* |
| KOOS Symptoms | | | | |
| Cartilage cohort | Ref | | Ref | |
| Control group | 9.6 (2.3, 16.9) | 0.01 | 8.4 (0.3, 16.4) | 0.04 |
| KOOS Pain | | | | |
| Cartilage cohort | Ref | | Ref | |
| Control group | 10.9 (2.5, 19.4) | 0.01 | 11.8 (2.2, 21.4) | 0.02 |
| KOOS ADL | | | | |
| Cartilage cohort | Ref | | Ref | |
| Control group | 4.3 (−3.9, 12.6) | 0.3 | 9.3 (−1.2, 18.6) | 0.053 |
| KOOS Sport/rec | | | | |
| Cartilage cohort | Ref | | Ref | |
| Control group | 5.5 (−3.7, 14.8) | 0.2 | 8.9 (−1.6, 19.4) | 0.1 |
| KOOS QoL | | | | |
| Cartilage cohort | Ref | | Ref | |
| Control group | 10.4 (1.2, 19.6) | 0.03 | 10.6 (0.2, 21.1) | 0.045 |

Abbreviations: ADL, activities of daily living; KOOS, Knee Injury and Osteoarthritis Outcome Score; QoL, Quality of Life.

[a]Adjusted for age at arthroplasty surgery, level of education, primary or revision arthroplasty, sex, type of arthroplasty and previous ipsilateral knee surgery in addition to cartilage surgery.

[b]Mean difference in KOOS score from reference with 95% confidence intervals in parentheses. Negative numbers imply lower mean score than reference.

**TABLE 3** The odds of failing to achieve the patient-acceptable symptom state for the KOOS subscores.

| | | Crude | | Adjusted[a] | |
|---|---|---|---|---|---|
| | Failures,*n* (%) | OR[b] | *p* | OR[b] | *p* |
| KOOS Symptoms | | | | | |
| Control group | 52 (44.8%) | 1 | | 1 | |
| Cartilage cohort | 40 (69.0%) | 2.7 (1.4, 5.3) | 0.003 | 2.7 (1.2, 6.4) | 0.020 |
| KOOS Pain | | | | | |
| Control group | 51 (44.0% | 1 | | 1 | |
| Cartilage cohort | 39 (67.2%) | 2.6 (1.4, 5.1) | 0.004 | 3.0 (1.3, 7.0) | 0.010 |
| KOOS activities of daily living | | | | | |
| Control group | 57 (49.1%) | 1 | | 1 | |
| Cartilage cohort | 34 (58.6%) | 1.5 (0.8, 2.8) | 0.239 | 2.1 (0.9, 4.6) | 0.076 |
| KOOS Quality of Life | | | | | |
| Control group | 53 (45.7%) | 1 | | 1 | |
| Cartilage cohort | 38 (65.5%) | 2.3 (1.2, 4.3) | 0.014 | 2.4 (1.0, 5.5) | 0.041 |

Abbreviation: KOOS, Knee Injury and Osteoarthritis Outcome Score.

[a]Adjusted for age at arthroplasty surgery, level of education, primary or revision arthroplasty, sex, type of arthroplasty and previous ipsilateral knee surgery in addition to cartilage surgery.

[b]Odds ratio from the regression model with 95% confidence intervals in parentheses.

arthroplasty patients [21–23]. However, a recent meta-analysis by Zhang et al. [24] found that previous knee surgery had a negative effect on postoperative PROMs in knee arthroplasty patients. In the present study, the patients in the cartilage cohort had significantly more surgical procedures in addition to their cartilage surgery than those in the control group. To reduce the risk of these additional procedures confounding the analysis of the KOOS score, the regression models were adjusted for any additional surgical procedures apart from cartilage surgery and purely diagnostic arthroscopy. The sensitivity analysis (Supporting Information S1: Table 1) without this adjustment, also demonstrated inferior results in the cartilage cohort for KOOS Symptoms and Pain, but not for QoL. This supports the findings of Zhang et al. [24].

There were also significantly more revision arthroplasties in the cartilage cohort. Although this variable was part of the matching procedure, a complete match was not achieved due to variations in response rates. The regression models were thus adjusted for primary versus revision arthroplasty. The sensitivity analysis including only primary knee arthroplasty (Supporting Information S1: Table 2) showed equivalent results to the original analysis, indicating that the models adequately adjusted for revision knee arthroplasty.

Significantly lower KOOS Symptoms, Pain, and QoL subscores after knee arthroplasty were demonstrated in the previous cartilage cohort. This concurs with the findings of Ansari et al. [11] in a cohort of 21 previous microfracture patients with a mean 7.8 points lower improvement in the Knee Society Score (KSS) in the cartilage cohort than in a matched group of knee arthroplasty patients. The difference in KSS is, however, below the clinically important difference demonstrated by Lizaur-Utrilla et al. [25]. Ansari et al. [11] did not report any power analysis prior to analysing the KSS results and the power analysis of the present study suggests that the Ansari study was underpowered.

Frank et al. [12] presented 13 knee arthroplasty patients with previous chondral auto/allograft matched 1:1 to a cohort of knee arthroplasty patients with osteoarthritis, finding a mean KSS improvement of 16 points lower in the cartilage cohort. However, they included patients with concomitant meniscal allograft in the cartilage cohort, which could have substantially confounded their results.

This represents the first study of patient-reported results in knee arthroplasty patients with previous cartilage lesions where PASS is reported. Reporting the percentage of patients having reached the PASS threshold offers several advantages, as outlined in a recent review by Mabrouk et al. [26]. It ensures that identified differences are not only statistically significant but also clinically relevant. Significantly better odds of reaching PASS threshold in the control group than in the cartilage cohort for the KOOS Symptoms, Pain and QoL subscores were found, and PASS was not reached by two-thirds of the cartilage cohort. This supports the findings of lower KOOS subscores in the cartilage cohort.

The reason for inferior results in the cartilage cohort remains elusive. However, several explanations for why previous FCLs still seem to result in inferior patient satisfaction after knee arthroplasty surgery could be considered. There is likely to be substantial selection bias in which cartilage patients need a knee arthroplasty. Psychological factors have been shown to influence PROMs [27] and knee arthroplasty patients with failed cartilage surgery might have more psychological issues than the average knee arthroplasty patients. In a recent review by Olsen et al. [28], preoperative pain catastrophizing was associated with worse pain in knee arthroplasty patients. Furthermore, Sellevold et al. [29] found preoperative duration of pain and psychological stress to be associated with less improvement after knee arthroplasty surgery. The cartilage cohort might have experienced a longer duration of knee pain prior to the knee arthroplasty than the control group. One or more FCLs have been shown to alter the knee homeostasis [30], potentially reducing knee function even after a knee arthroplasty.

The main strength of the present study was the high number of included patients with knee arthroplasty after a previous arthroscopically verified and symptomatic FCL in the ipsilateral knee. The follow-up period after knee arthroplasty was mid- to long-term, and several studies have shown stable PROMs from 1 year postoperative in knee arthroplasty patients [31–33]. The previous FCL patients with patellofemoral or unicompartmental knee arthroplasty had received knee arthroplasty in the compartment where the previous FCL was located, suggesting a correlation between the FCL and the subsequent knee arthroplasty. Any additional ipsilateral knee surgery was reported by the participants in the questionnaire, reducing the risk of overlooking any surgery performed at another hospital.

There were several limitations to this study. The necessary number of FCL knees required by the preinclusion power analysis was not met, with a shortfall of six knees. To reduce the risk of an underpowered analysis, an analysis of whether patients' self-reported KOOS subscores were above the PASS threshold was performed.

Only 67% of eligible patients agreed to participate in the present study, potentially introducing bias to the results. Furthermore, radiographs before the knee arthroplasty were not available and there could have been a discrepancy in the degree of osteoarthritis in the FCL group and the control group. However, Dowsey et al. [34] found no association between Kellgren–Lawrence scores and preoperative PROMs in knee arthroplasty patients. Preoperative PROMs were not available, and these are known to be a key factor in determining the postoperative PROM scores [10, 35, 36]. There could have been a discrepancy in the preoperative KOOS scores between the groups. However, several studies have demonstrated

that cartilage patients have similar KOOS QoL subscores to patients awaiting knee arthroplasty [2, 3], indicating that the preoperative PROM in the cartilage cohort might be comparable to those in the control group.

Although the control group was matched, differences in the distribution of age, education level and revision TKA due to uneven response rates were observed. This resulted in unbalanced groups, necessitating adjustment with regression models.

Improvement in function and satisfaction is provided by knee arthroplasty regardless of the type of implant in patients with osteoarthrosis [9]. This seems to be true also in the context of a previous FCL [12]. However, the present study suggests that both surgeons and patients should be aware of lower improvement in PROMs after knee arthroplasty in cases with a history of previous FCL as part of the shared decision making.

## CONCLUSION

Previous cartilage surgery was associated with inferior patient-reported outcome after knee arthroplasty at mean 8 years following knee arthroplasty. Patients with previous focal cartilage lesions demonstrated significantly lower KOOS Symptoms, Pain and QoL subscores compared to a matched cohort. The cartilage cohort also had significantly lower odds of reaching the PASS threshold for the same KOOS subscores.

### AUTHOR CONTRIBUTIONS

**Thomas Birkenes:** Conceptualization; methodology; formal analysis; writing—original draft. **Håvard Visnes:** Conceptualization; writing—editing; supervision. **Ove Furnes:** Conceptualization; methodology; writing—editing. **Asbjørn Årøen:** Conceptualization; resources; writing—editing; funding acquisition. **Stein Håkon Låstad Lygre:** Methodology; formal analysis; writing—editing. **Eirik Solheim:** Resources; writing—editing. **Gunnar Knutsen:** Resources; writing—editing. **Jon Olav Drogset:** Resources; writing—editing. **Stig Heir:** Resources; writing—editing. **Lars Engebretsen:** Resources; writing—editing. **Sverre Løken:** Resources; writing—editing. All authors have read and approved the final manuscript.


### AFFILIATIONS

[1]Department of Clinical Medicine, University of Bergen, Bergen, Norway

[2]Department of Orthopaedic Surgery, Haukeland University Hospital, Bergen, Norway

[3]Sports Traumatology and Arthroscopy Research Group, Bergen, Norway

[4]Norwegian Arthroplasty Register, Department of Orthopaedic Surgery, Haukeland University Hospital, Bergen, Norway

[5]Department of Occupational Medicine, Haukeland University Hospital, Bergen, Norway

[6]Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[7]Akershus University Hospital, Lorenskog, Norway

[8]Oslo Sports Trauma Research Center, Oslo, Norway

[9]University Hospital of North Norway, Tromsoe, Norway

[10]Trondheim University Hospital, Trondheim, Norway

[11]Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway

[12]Norwegian Knee Ligament Register, Department of Orthopaedic Surgery, Haukeland University Hospital, Bergen, Norway

[13]Martina Hansen Hospital, Baerum, Norway

[14]Oslo University Hospital, Oslo, Norway

[15]Hospital of Southern Norway, Kristiansand, Norway



### ACKNOWLEDGEMENTS

The present study was funded by the Norwegian Research Council (ref nr 2015107) through the Norwegian Cartilage Project.


### CONFLICT OF INTEREST STATEMENT

Gunnar Knutsen, Lars Engebretsen and Jon Olav Drogset are editorial board members of KSSTA. The remaining authors declare no conflict of interest.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions. Any request would, however, need to be approved by the Data Protection officer at Haukeland University Hospital.

### ETHICS STATEMENT

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Regional Ethics Committee (2017/1387). All participants have provided informed consent prior to inclusion.


### ORCID

*Thomas Birkenes* http://orcid.org/0000-0003-1583-5740
*Ove Furnes* http://orcid.org/0000-0001-8223-2515
*Stein Håkon Låstad Lygre* http://orcid.org/0000-0001-9146-4510
*Eirik Solheim* http://orcid.org/0000-0001-6799-1636
*Asbjørn Årøen* http://orcid.org/0000-0002-2337-0755
*Gunnar Knutsen* http://orcid.org/0000-0003-2591-7977
*Jon Olav Drogset* http://orcid.org/0000-0001-9481-2453
*Stig Heir* http://orcid.org/0000-0001-6493-074X
*Lars Engebretsen* http://orcid.org/0000-0003-2294-921X
*Sverre Løken* http://orcid.org/0000-0002-5258-1535
*Håvard Visnes* http://orcid.org/0000-0001-8209-2129

## REFERENCES


1. Hunziker, E.B., Lippuner, K., Keel, M.J. & Shintani, N. (2015) An educational review of cartilage repair: precepts & practice—myths & misconceptions—progress & prospects. *Osteoarthritis and Cartilage*, 23, 334–350.
2. Heir, S., Nerhus, T.K., Røtterud, J.H., Løken, S., Ekeland, A., Engebretsen, L. et al. (2010) Focal cartilage defects in the knee impair quality of life as much as severe osteoarthritis: a comparison of knee injury and osteoarthritis outcome Score in 4 patient categories scheduled for knee surgery. *The American Journal of Sports Medicine*, 38, 231–237.
3. Randsborg, P.H., Årøen, A. & Owesen, C. (2022) The effect of lesion size on pain and function in patients scheduled for cartilage surgery of the knee. *Cartilage*, 13, 43–49.
4. Devitt, B.M., Bell, S.W., Webster, K.E., Feller, J.A. & Whitehead, T.S. (2017) Surgical treatments of cartilage defects of the knee: systematic review of randomised controlled trials. *The Knee*, 24, 508–517.
5. Birkenes, T., Furnes, O., Laastad Lygre, S.H., Solheim, E., Aaroen, A., Knutsen, G. et al. (2023) The long-term risk of knee arthroplasty in patients with arthroscopically verified focal cartilage lesions: a linkage study with the Norwegian Arthroplasty Register, 1999 to 2020. *Journal of Bone and Joint Surgery*, 105, 951–961.
6. Norwegian National Advisory Unit on Arthroplasty and Hip Fractures. (2020) The Norwegian Arthroplasty Register Annual Report. Available from: https://www.helse-bergen.no/49e0eb/siteassets/seksjon/nasjonal_kompetansetjeneste_leddproteser_hoftebrudd/share-point-documents/rapport/report-2020_english.pdf [Accessed 1st June 2020].
7. Ogura, T., Mosier, B.A., Bryant, T. & Minas, T. (2017) A 20-year follow-up after first-generation autologous chondrocyte implantation. *The American Journal of Sports Medicine*, 45, 2751–2761.
8. Poulsen, E., Goncalves, G.H., Bricca, A., Roos, E.M., Thorlund, J.B. & Juhl, C.B. (2019) Knee osteoarthritis risk is increased 4-6 fold after knee injury—a systematic review and meta-analysis. *British Journal of Sports Medicine*, 53, 1454–1463.
9. Kahlenberg, C.A., Lyman, S., Joseph, A.D., Chiu, Y.F. & Padgett, D.E. (2019) Comparison of patient-reported outcomes based on implant brand in total knee arthroplasty: a prospective cohort study. *The Bone & Joint Journal*, 101-B, 48–54.
10. Scott, C.E., Oliver, W.M., Macdonald, D., Wade, F.A., Moran, M. & Breusch, S.J. (2016) Predicting dissatisfaction following total knee arthroplasty in patients under 55 years of age. *The Bone & Joint Journal*, 98-B, 1625–1634.
11. Ansari, M.H., Pareek, A., Johnson, N.R., Abdel, M.P., Stuart, M.J. & Krych, A.J. (2017) Clinical outcome of total knee arthroplasty after prior microfracture: a matched cohort study. *Orthopedics*, 40, e473–e478.
12. Frank, R.M., Della Valle, C.J., Plummer, D.R., Chalmers, P.N. & Cole, B.J. (2017) Does prior cartilage restoration impact outcomes following knee arthroplasty? *Orthopedic Clinics of North America*, 48, 265–273.
13. Roos, E.M. & Lohmander, L.S. (2003) The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health and Quality of Life Outcomes*, 1, 64.
14. Engelhart, L., Nelson, L., Lewis, S., Mordin, M., Demuro-Mercon, C., Uddin, S. et al. (2012) Validation of the Knee Injury and Osteoarthritis Outcome Score subscales for patients with articular cartilage lesions of the knee. *The American Journal of Sports Medicine*, 40, 2264–2272.
15. Roos, E.M., Engelhart, L., Ranstam, J., Anderson, A.F., Irrgang, J.J., Marx, R.G. et al. (2011) ICRS recommendation document: patient-reported outcome instruments for use in patients with articular cartilage defects. *Cartilage*, 2, 122–136.
16. Roos, E.M. & Toksvig-Larsen, S. (2003) Knee injury and Osteoarthritis Outcome Score (KOOS)—validation and comparison to the WOMAC in total knee replacement. *Health and Quality of Life Outcomes*, 1, 17.
17. Connelly, J.W., Galea, V.P., Rojanasopondist, P., Matuszak, S.J., Ingelsrud, L.H., Nielsen, C.S. et al. (2019) Patient acceptable symptom state at 1 and 3 years after total knee arthroplasty: thresholds for the Knee Injury and Osteoarthritis Outcome Score (KOOS). *Journal of Bone and Joint Surgery*, 101, 995–1003.
18. Becher, C., Megaloikonomos, P.D., Lind, M., Eriksson, K., Brittberg, M., Beckmann, J. et al. (2023) High degree of consensus amongst an expert panel regarding focal resurfacing of chondral and osteochondral lesions of the femur with mini-implants. *Knee Surgery, Sports Traumatology, Arthroscopy*, 31, 4027–4034.
19. Lygre, S.H.L., Espehaug, B., Havelin, L.I., Vollset, S.E. & Furnes, O. (2010) Does patella resurfacing really matter? Pain and function in 972 patients after primary total knee arthroplasty: an observational study from the Norwegian Arthroplasty Register. *Acta Orthopaedica*, 81, 99–107.
20. Jiang, Y., Sanchez-Santos, M.T., Judge, A.D., Murray, D.W. & Arden, N.K. (2017) Predictors of patient-reported pain and functional outcomes over 10 years after primary total knee arthroplasty: a prospective cohort study. *The Journal of Arthroplasty*, 32, 92–100.e2.
21. Issa, K., Naziri, Q., Johnson, A., Pivec, R., Bonutti, P. & Mont, M. (2012) TKA results are not compromised by previous arthroscopic procedures. *Journal of Knee Surgery*, 25, 161–164.
22. Rothermich, M., Nam, D., Brophy, R., Li, K., Barrack, R. & Nunley, R. (2017) The impact of prior surgery after total knee arthroplasty. *The Journal of Knee Surgery*, 30, 57–62.
23. Viste, A., Abdel, M.P., Ollivier, M., Mara, K.C., Krych, A.J. & Berry, D.J. (2017) Prior knee arthroscopy does not influence long-term total knee arthroplasty outcomes and survivorship. *The Journal of Arthroplasty*, 32, 3626–3631.
24. Zhang, L.Y., Cui, C.M., Min, J.K., Cao, Y.Q. & Cai, J.Y. (2021) Does prior arthroscopic procedure impact outcomes of knee arthroplasty? A systematic review and meta-analysis. *European Review for Medical and Pharmacological Sciences*, 25, 4459–4469.
25. Lizaur-Utrilla, A., Gonzalez-Parreño, S., Martinez-Mendez, D., Miralles-Muñoz, F.A. & Lopez-Prats, F.A. (2020) Minimal clinically important differences and substantial clinical benefits for Knee Society Scores. *Knee Surgery, Sports Traumatology, Arthroscopy*, 28, 1473–1478.
26. Mabrouk, A., Nwachukwu, B., Pareek, A., Karlsson, J., Mouton, C., Ollivier, M. et al. (2023) MCID and PASS in knee surgeries. Theoretical aspects and clinical relevance references. *Knee Surgery, Sports Traumatology, Arthroscopy*, 31, 2060–2067.
27. Mawarikado, Y., Inagaki, Y., Fujii, T., Imagita, H., Fukumoto, T., Kubo, T. et al. (2022) Preoperative factors affecting patient-reported outcome measures for total knee arthroplasty. *Progress in Rehabilitation Medicine*, 7. Available from: https://doi.org/10.2490/prm.20220049
28. Olsen, U., Lindberg, M.F., Rose, C., Denison, E., Gay, C., Aamodt, A. et al. (2023) Factors correlated with pain after total knee arthroplasty: a systematic review and meta-analysis. *PLoS One*, 18(3), e0283446. Available from: https://doi.org/10.1371/journal.pone.0283446
29. Sellevold, V.B., Olsen, U., Lindberg, M.F., Steindal, S.A., Aamodt, A., Lerdal, A. et al. (2023) "I am accustomed to something in my body causing pain": a qualitative study of knee replacement non-improvers' stories of previous painful and stressful experiences. *BMC Musculoskeletal Disorders*, 24, 305.
30. Saris, D.B.F., Dhert, W.J.A. & Verbout, A.J. (2003) Joint homeostasis. The discrepancy between old and fresh defects in cartilage repair. *The Journal of Bone and Joint Surgery. British Volume*, 85, 1067–1076.

31. Nerhus, T.K., Heir, S., Thornes, E., Madsen, J.E. & Ekeland, A. (2010) Time-dependent improvement in functional outcome following LCS rotating platform knee replacement. *Acta Orthopaedica*, 81, 727–732.
32. Sayah, S.M., Karunaratne, S., Beckenkamp, P.R., Horsley, M., Hancock, M.J. & Hunter, D.J. et al. (2021) Clinical course of pain and function following total knee arthroplasty: a systematic review and meta-regression. *The Journal of Arthroplasty*, 36, 3993–4002.e37.
33. Sebastia-Forcada, E., Ruiz-Lozano, M., Perez-Aznar, A., Miralles-Muñoz, F.A., Gonzalez-Navarro, B. & Lizaur-Utrilla, A. (2024) Functional outcome change over 10 years after primary total knee arthroplasty. A Prospective Longitudinal Cohort Study. *The Journal of Arthroplasty*, 39(2), 374–378. https://doi.org/10.1016/j.arth.2023.08.042
34. Dowsey, M.M., Dieppe, P., Lohmander, S., Castle, D., Liew, D. & Choong, P.F.M. (2012) The association between radiographic severity and pre-operative function in patients undergoing primary knee replacement for osteoarthritis. *The Knee*, 19, 860–865.
35. Martin, R.K., Wastvedt, S., Pareek, A., Persson, A., Visnes, H., Fenstad, A.M. et al. (2022) Predicting subjective failure of ACL reconstruction: a machine learning analysis of the Norwegian Knee Ligament Register and patient reported outcomes. *Journal of ISAKOS*, 7, 1–9.
36. Olsen, U., Lindberg, M.F., Rose, C., Denison, E., Gay, C., Aamodt, A. et al. (2022) Factors correlated with physical function 1 year after total knee arthroplasty in patients with knee osteoarthritis: a systematic review and meta-analysis. *JAMA Network Open*, 5(7), e2219636. Available from: https://doi.org/10.1001/jamanetworkopen.2022.19636

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Birkenes, T., Furnes, O., Lygre, S.H.L., Solheim, E., Årøen, A., Knutsen, G. et al. (2024) Previous cartilage surgery is associated with inferior patient-reported outcomes after knee arthroplasty. *Knee Surgery, Sports Traumatology, Arthroscopy*, 32, 361–370. https://doi.org/10.1002/ksa.12050

**Supplementary Table** 1 Difference in KOOS score between the knee arthroplasty patients with previous focal cartilage lesion and the knee arthroplasty patents in the control group (not adjusted for previous knee surgery)

| | Crude | | Adjusted[a] | |
|---|---|---|---|---|
| | **Mean difference[b]** | **p** | **Mean difference[b]** | **p** |
| KOOS Symptoms | | | | |
| – Cartilage cohort | ref | | ref | |
| – Control group | 9.6 (2.3,16.9) | 0.01 | 8.3 (0.5,16.1) | 0.04 |
| KOOS Pain | | | | |
| – Cartilage cohort | ref | | ref | |
| – Control group | 10.9 (2.5,19.4) | 0.01 | 10.8 (1.5,20.1) | 0.02 |
| KOOS ADL | | | | |
| – Cartilage cohort | ref | | Ref | |
| – Control group | 4.3 (-3.9,12.6) | 0.3 | 7.7 (-1.4,16.9) | 0.1 |
| KOOS Sport/rec | | | | |
| – Cartilage cohort | ref | | Ref | |
| – Control group | 5.5 (-3.7,14.8) | 0.2 | 8.6 (-1.6,18.7) | 0.1 |
| KOOS QoL | | | | |
| – Cartilage cohort | ref | | Ref | |
| – Control group | 10.4 (1.2,19.6) | 0.03 | 8.9 (-1.2,19.1) | 0.08 |

[a]Adjusted for age at arthroplasty surgery, level of education, primary or revision arthroplasty, sex, and type of arthroplasty. [b]Mean difference in KOOS score from reference with 95% confidence intervals in parentheses. Negative numbers imply lower mean score than reference.

**Supplementary Table 2** Difference in KOOS score between only the primary knee arthroplasty patients with previous focal cartilage lesion and the primary knee arthroplasty patients in the control group.

| | Ajusted[a] Mean difference[a] | p |
|---|---|---|
| KOOS Symptoms | | |
| – Cartilage cohort | ref | |
| – Control group | 8.7 (-0.0,17.5) | 0.05 |
| KOOS Pain | | |
| – Cartilage cohort | ref | |
| – Control group | 12.4 (1.9,22.9) | 0.02 |
| KOOS ADL | | |
| – Cartilage cohort | ref | |
| – Control group | 10.2 (0.3,20.1) | 0.04 |
| KOOS Sport/rec | | |
| – Cartilage cohort | ref | |
| – Control group | 10.3 (-1.1,21.6) | 0.08 |
| KOOS QoL | | |
| – Cartilage cohort | ref | |
| – Control group | 11.4 (-0.3,23.2) | 0.06 |

[a]Adjusted for age at arthroplasty surgery, level of education, primary or revision arthroplasty, sex, type of arthroplasty and previous ipsilateral knee surgery in addition to cartilage surgery.
[b]Mean difference in KOOS score from reference with 95% confidence intervals in parentheses. Negative numbers imply lower mean score than reference

# Questionnaires

«FORNAVN» «ETTERNAVN» «Side» kne «Pasientnr»

**1.Høyde**:……. **Vekt**: …….

**2.Høyeste fullførte utdannelse:**

☐ Grunnskole ☐ Videregående ☐ Høgskole ☐ Universitet

**3.Hvordan er det andre kneet?** ☐ Normalt ☐ Besvær Hvilket besvær?.....

**4.Er det andre årsaker til at du har problemer med å gå?** ( F eks smerter fra andre ledd, ryggsmerter, hjerte-karsykdommer eller andre sykdommer) ☐ Ja ☐ Nei

**5.Er du operert flere ganger i (flettefelt side) kneet?** ☐ Ja ☐ Nei

Hvis ja, spesifiser:

Årstall:…… Hva slags operasjon……..

Årstall:…… Hva slags operasjon……..

Årstall:…… Hva slags operasjon……..

**6.Hvor godt fungerer kneet ditt i forhold til et friskt kne?**

☐ 100% | ☐ 90% | ☐ 80% | ☐ 70% | ☐ 60% | ☐ 50% | ☐ 40% | ☐ 30% | ☐ 20% | ☐ 10%

**7.Hvor ofte driver du mosjon/trening:**

☐ Aldri ☐ <1 gang pr uke ☐ 1 gang pr uke ☐ 2-3 ganger pr uke ☐ Hver dag

**8.Dersom du driver slik mosjon, så ofte som en eller flere ganger i uka; hvor hardt mosjonerer du?**

☐ Blir ikke andpusten/svett ☐ Blir andpusten/svett ☐ Tar meg nesten helt ut

**9.Hvor lenge holder du på hver gang?** (i gjennomsnitt)

☐ <15 min ☐ 15-29 min ☐ 30 min – 1time ☐ Mer enn 1 time

**10.Hva slags mosjon/trening driver du med?……**

**11.Har du vanligvis minst 30 min fysisk aktivitet daglig på arbeid eller fritid?** ☐ **Ja** ☐ **Nei**

**12.Omtrent hvor mange timer sitter du i ro på en vanlig dag? ……**

**13. Sett kryss ved det alternativet som passer din aktivitet best:**

**Nivå 1** (deltar 4-7 dager pr uke)

☐ Hopp, brå vridninger og vendinger (håndball, fotball, basketball, volleyball, turn, squash)

☐ Løp, vridning, vending (tennis, alpinski, ishockey, friidrett)

☐ Ingen løping, hopping eller vridning (sykling, svømming)

**Nivå 2** (deltar 1-3 dager pr uke)

☐ Hopp, brå vridninger og vendinger (håndball, fotball, basketball, volleyball, turn, squash)

☐ Løp, vridning, vending (tennis, alpinski, ishockey, friidrett)

☐ Ingen løping, hopping eller vridning (sykling, svømming)

**Nivå 3** (deltar 1-3 ganger i mnd)

☐ Hopp, brå vridninger og vendinger (håndball, fotball, basketball, volleyball, turn, squash)

☐ Løp, vridning, vending (tennis, alpinski, ishockey, friidrett)

☐ Ingen løping, hopping eller vridning (sykling, svømming)

**Nivå 4** (ingen idrett)

☐ Jeg utfører daglige gjøremål uten problem

☐ Jeg har moderate problemer med daglige gjøremål

☐ Jeg har store problemer med daglige gjøremål (krykker, full uførhet)

# KOOS – SPØRRESKJEMA FOR KNEPASIENTER

«FORNAVN» «ETTERNAVN» «Side» kne
«Pasientnr»

**Veiledning:** Dette spørreskjemaet inneholder spørsmål om hvordan du opplever kneet ditt. Informasjonen vil hjelpe oss til å følge med i hvordan du har det og fungerer i ditt daglige liv. Besvar spørsmålene ved å krysse av for det alternativ du synes passer best for deg (kun ett kryss ved hvert spørsmål). Hvis du er usikker, kryss likevel av for det alternativet som føles mest riktig.

## Symptom

Tenk på de **symptomene** du har hatt fra kneet ditt den **siste uken** når du besvarer disse spørsmålene**.**

S1. Har kneet vært hovent?

| Aldri | Sjelden | I blant | Ofte | Alltid |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

S2. Har du følt knirking, hørt klikking eller andre lyder fra kneet?

| Aldri | Sjelden | I blant | Ofte | Alltid |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

S3. Har kneet haket seg opp eller låst seg?

| Aldri | Sjelden | I blant | Ofte | Alltid |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

S4. Har du kunnet rette kneet helt ut?

| Alltid | Ofte | Iblant | Sjelden | Aldri |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

S5. Har du kunnet bøye kneet helt?

| Alltid | Ofte | I blant | Sjelden | Aldri |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

## Stivhet

De neste spørsmålene handler om **leddstivhet**. Leddstivhet innebærer vanskeligheter med å komme i gang eller økt motstand når du bøyer eller strekker kneet. Marker graden av leddstivhet du har opplevd i kneet ditt den **siste uken**.

S6. Hvor stivt er kneet ditt når du nettopp har våknet om morgenen?

| Ikke noe | Litt | Moderat | Betydelig | Ekstremt |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

S7. Hvor stivt er kneet ditt **senere på dagen** etter å ha sittet, ligget eller hvilt?

| Ikke noe | Litt | Moderat | Betydelig | Ekstremt |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

## Smerte

P1. Hvor ofte har du vondt i kneet?

| Aldri | Månedlig | Ukentlig | Daglig | Hele tiden |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

Hvilken grad av smerte har du hatt i kneet ditt den **siste uken** ved følgende aktiviteter?

P2. Snu/vende på belastet kne

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

P3. Rette kneet helt ut

| Ingen | Lett | Moderate | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

P4. Bøye kneet helt

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

P5. Gå på flatt underlag

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

P6. Gå opp eller ned trapper

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

P7. Om natten i sengen (smerter som forstyrrer søvnen)

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

P8. Sittende eller liggende

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

P9. Stående

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

## Funksjon I hverdagen

De neste spørsmål handler om din fysiske funksjon. **Angi graden av vanskeligheter du har opplevd den siste uken ved følgende aktiviteter på grunn av dine kneproblemer**.

A1. Gå ned trapper

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

A2. Gå opp trapper

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

Angi graden av **vanskeligheter** du har opplevd ved hver aktivitet den **siste uken**.

A3. Reise deg fra sittende stilling

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

A4. Stå stille

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

A5. Bøye deg, f.eks. for å plukke opp en gjenstand fra gulvet

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

A6. Gå på flatt underlag

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

A7. Gå inn/ut av bil

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

A8. Handle/gjøre innkjøp

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

A9. Ta på sokker/strømper

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

A10. Stå opp fra sengen

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

A11. Ta av sokker/strømper

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

A12. Ligge i sengen (snu deg, holde kneet i samme stilling i lengre tid)

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

A13. Gå inn og ut av badekar/dusj

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

A14. Sitte

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

A15. Sette deg og reise deg fra toalettet

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

Angi graden av **vanskeligheter** du har opplevd ved hver aktivitet den **siste uken**.

A16. Gjøre tungt husarbeid (måke snø, vaske gulv, støvsuge osv.)

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

A17. Gjøre lett husarbeid (lage mat, tørke støv osv.)

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

**Funksjon, sport og fritid**

De neste spørsmålene handler om din fysiske funksjon. Angi graden av vanskeligheter du har opplevd **den siste uken** ved følgende aktiviteter på grunn av dine kneproblemer.

SP1. Sitte på huk

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

SP2. Løpe

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

SP3. Hoppe

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

SP4. Snu/vende på belastet kne

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

SP5. Stå på kne

| Ingen | Lett | Moderat | Betydelig | Svært stor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

**Livskvalitet**

Q1. Hvor ofte gjør ditt kneproblem seg bemerket?

| Aldri | Månedlig | Ukentlig | Daglig | Alltid |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

Q2. Har du forandret levesett for å unngå å overbelaste kneet?

| Ingenting | Noe | Moderat | Betydelig | Fullstendig |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

Q3. I hvor stor grad kan du stole på kneet ditt?

| Fullstendigl | I stor grad | Moderat | Til en viss grad | Ikke i det hele tatt |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

Q4. Generelt sett, hvor store problemer har du med kneet ditt?

| Ingen | Lette | Moderate | Betydelige | Svært store |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

**Takk for at du tok deg tid og besvarte samtlige spørsmål!**

# Orginalskjema
# Lysholmscore for kne

Sett kryss ved de utsagn som best beskriver dine kneplager

**Halting (5 poeng):**

____ Ingen (5)

____ Lett halting (3)

____ Mye og konstant (0)

**Støtte (5 poeng):**

____ Ingen (5)

____ Stokk eller krykke (2)

____ Vektbæring umulig (0)

**Låsninger (15 poeng)**

___ Aldri låsninger eller følelse av at kneet hekter seg opp (15)

___ Følelse av hekting, men aldri låsninger (10)

___ Låsning av og til (6)

___ Ofte låsning (2)

___ Låst kne ved utfylling (0)

**Instabilitet (25 poeng)**

(kneet gir etter/ikke til å stole på)

___ Gir aldri etter (25)

___ Av og til ved idrett eller hard anstrengelse (20)

___ Ofte ved idrett eller hard anstrengelse. Evt ikke i stand til å delta (15)

___ Av og til ved dagligdagse aktiviteter (10)

___ Ofte ved dagligdagse aktiviteter (5)

___ For hvert skritt (0)

**Smerte (25 poeng)**

___ Ingen smerte(25)

___ Bare av og til og litt ved hard anstrengelse (20)

___ Betydelig ved hard anstrengelse (15)

___ Betydelig under eller etter mer enn 2 km gange (10)

___ Betydelig under eller etter mindre enn 2 km gange (5)

___ Konstant smerte (0)

**Hevelse (10 poeng)**

___ Ingen hevelse (10)

___ Ved hard anstrengelse (6)

___ Ved vanlig anstrengelse (2)

___ Konstant hevelse (0)

**Trappegang (10 poeng)**

___ Ingen problemer (10)

___ Lett hemmet (6)

___ Ett trinn av gangen (2)

___ Umulig (0)

**Dype knebøy (5 poeng)**

___ Ingen problem (5)

___ Lett hemmet (4)

___ Ikke mer enn 90 grader (2)

___ Umulig (0)

Orginalskjema

# ICRS EVALUERINGSSKJEMA / KNE

## 1. I forhold til det andre (friske) kneet fungerer det skadede kneet:

| I | II | III | IV |
|---|---|---|---|
| 90–100% | 70-90% | 40-70% | 0-40% |
| ☐ | ☐ | ☐ | ☐ |

## 2. Angi hvor store smertene i kneet er på denne skalaen:

Ingen smerter |----------|----------|----------|----------| Verst tenkelige smerter

## 3. Symptomer (Høyeste aktivitetsnivå uten symptomer):

Hvilke aktiviteter (velg høyeste aktivitetsnivå av de under) kan du gjøre, eller kan du tenke deg at du kunne gjøre, uten å få følgende plager med kneet:

| | Aktivitetsnivå | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| a) | Smerter i kneet under aktivitet | ☐ | ☐ | ☐ | ☐ |
| b) | Hevelse i kneet pga. aktiviteter | ☐ | ☐ | ☐ | ☐ |
| c) | Kneet gir etter, henger seg opp, låser seg ved aktivitet | ☐ | ☐ | ☐ | ☐ |
| d) | Startsmerter | ☐ | ☐ | ☐ | ☐ |

**Aktivitetsnivå:**

1 Hopping, raske vridninger/vendinger, fotball, håndball

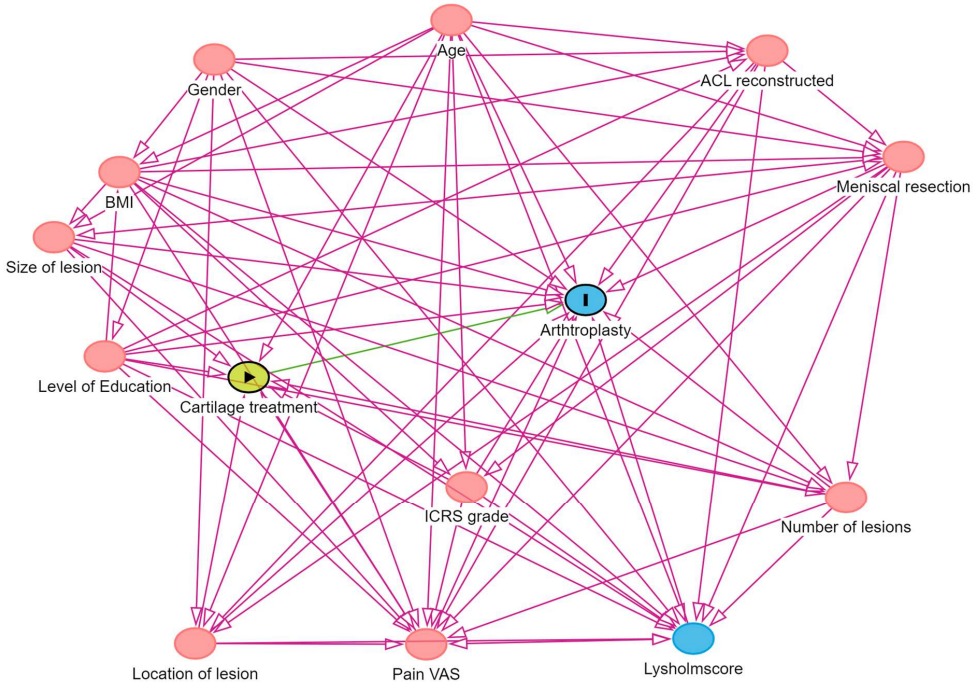
2 Tungt manuelt arbeid, alpint, tennis

3 Lett manuelt arbeid, løping/jogging

4 Stillesittende arbeid, daglige gjøremål

# DAG example

Example of DAG analysis



Graphic design: Communication Division, UiB / Print: Skipnes Kommunikasjon AS


uib.no

ISBN: 9788230852668 (print)
9788230867686 (PDF)