**Title:** The impact of loading and physical activity measures on outcomes in patients with knee osteoarthritis, and implant survivorship in patients following knee arthroplasty

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# List of Abbreviations

3D: three-dimensional

ACL: anterior cruciate ligament

ANOVA: analysis of variance

BMI: body mass index

CI: confidence interval

CIBPA : Canadian-Italian Business & Professional Association

FRQS: Fonds de recherche du Québec – Santé

ICOAP : Intermittent and Constant Osteoarthritis Pain score

FoV: field of view

FCS: fully conditional specification

Hz: hertz

KAM : knee adduction moment

KEM : knee extension moment

KFM: knee flexion moment

KL: Kellgren-Lawrence

KOOS: Knee injury and Osteoarthritis Outcome Score

MRI: magnetic resonance imaging

NIH: National Institutes of Health

NRS: numeric rating scale

OA: osteoarthritis

OR: odds ratio

PA: physical activity

PCS : Pain Catastrophizing Scale

PMM: predictive mean matching

PRISMA-ScR: Preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews

Px: pixel

RA: rheumatoid arthritis

REPAR: Quebec Rehabilitation Research Network

SD: standard deviation

SPA: sensitivity to physical activity

TE: echo time

THA: total hip arthroplasty

TKA: total knee arthroplasty

TR: repetition time

TSK: Tampa Scale of Kinesiophobia

UKA: unicompartmental knee arthroplasty

UCLA: University of California at Los Angeles

VM: vastus medialis

# Abstract

Obesity, quadriceps muscle weakness and joint injury play a role in knee osteoarthritis (OA) pathogenesis through the creation of an abnormal loading environment at the knee. Better understanding these relationships can fill knowledge gaps and inform treatment strategies. Moreover, physical activity (PA) and sports participation recommendations following unicompartmental (UKA) and total knee arthroplasty (TKA) are mainly based on expert consensus. An overview of the literature on the topic is needed. Lastly, sensitivity to physical activity (SPA) is an approach to assess pain in response to PA. A better understanding of the merits and limitations of SPA measures in patients with knee OA is needed. Therefore, the goals of this thesis were: 1) to better understand how joint loading during walking relates to knee OA severity, 2), to better understand how measures of adiposity relate to knee OA severity, 3) to describe the literature examining the impact of PA level and sports participation on implant integrity and failure in patients post UKA and TKA, and 4) to evaluate the merits and limitations of SPA measures and their prognostic value in patients with knee OA. This was achieved via four manuscripts.

First, a cross-sectional study examined relationships between knee joint moments during gait and tibiofemoral cartilage thickness in patients with non-traumatic (n = 22) and post-traumatic knee OA (n = 19) (Chapter 3). Regression analyses revealed that a higher knee adduction moment impulse was associated with a lower medial-to-lateral cartilage thickness ratio. A higher late stance knee extension moment was associated with greater medial femoral condyle cartilage thickness and medial-to-lateral cartilage thickness. These relationships differed between groups, suggesting that the influence of knee loading on articular cartilage may differ between these OA subtypes.

Next, a cross-sectional study examined whether vastus medialis (VM) intramuscular fat relates to OA severity and quadriceps muscle strength in patients with non-traumatic (n = 22) and post-

traumatic knee OA (n = 19) (Chapter 4). Regression analyses revealed that VM intramuscular fat was positively associated with body mass index, but not OA severity or group. Higher VM intramuscular fat was also associated with reduced knee extensor muscle torque. It is unclear whether this is due to VM intramuscular fat or other factors, such as diet and physical inactivity.

Then, a scoping review summarized the literature examining the impact of PA level and sports participation on implant integrity and failure in patients following UKA and TKA (Chapter 5). Five databases were searched, articles were screened by two reviewers, and extracted data were summarized using descriptive analysis. Eighteen studies met inclusion criteria. Following UKA (n = 5), no studies reported a deleterious effect of PA level or sports participation on implant integrity or failure. Following TKA (n = 13), four studies reported an association between greater PA levels, but not sports participation, with greater implant wear or failure.

Lastly, a longitudinal observational study (n = 81) compared evoked pain responses across five physical tasks and evaluated the prognostic value of SPA indices in patients with knee OA for pain and physical function after an 8-week activity-based rehabilitation program. The 6-Minute Walk Test and Stair Climb Test were the most evocative tasks in patients with knee OA. However, regression analyses did not support the prognostic value of task-specific SPA indices with respect to recovery trajectories following an 8-week rehabilitation program in patients with knee OA.

Altogether, this work has identified: 1) potential differences in how knee joint loading may impact articular cartilage between patients with non-traumatic and post-traumatic knee OA, 2) the potential role of VM intramuscular fat in impairing quadriceps muscle function in patients with knee OA, 3) the state of the scientific literature regarding the impact of PA level and sports participation on implant integrity and failure following knee arthroplasty, and 4) the potential merits and limitations of different SPA measurement strategies in patients with knee OA.

# Abrégé

L'obésité, la faiblesse musculaire des quadriceps et les lésions articulaires jouent un rôle dans la pathogenèse de l'arthrose du genou en créant un environnement de charge anormal au niveau du genou. Une meilleure compréhension de ces relations peut combler les lacunes dans les connaissances et éclairer les stratégies de traitement. De plus, les recommandations en matière d'activité physique (AP) et de pratique sportive après une arthroplastie unicompartimentale (AUG) et une arthroplastie totale du genou (ATG) sont principalement basées sur un consensus d'experts. Un large aperçu de la littérature sur le sujet est nécessaire. Enfin, la sensibilité à l'activité physique (SAP) est une approche pour évaluer la douleur provoquée en réponse à l'activité physique. Une meilleure compréhension des mérites et des limites des mesures de la SAP chez les patients atteints d'arthrose du genou est nécessaire. Par conséquent, les objectifs principaux de cette thèse étaient: 1) mieux comprendre comment la charge articulaire pendant la marche est liée à la gravité de l'arthrose du genou, 2) mieux comprendre comment les mesures de l'adiposité sont liées à la gravité de l'arthrose du genou, 3) décrire la littérature examinant l'impact du niveau d'AP et de la participation sportive sur l'intégrité matérielle et l'échec des prothèses chez les patients ayant subi une AUG et une ATG, et 4) évaluer les mérites et les limites des mesures de la SAP et leur valeur pronostique chez les patients atteints d'arthrose du genou. Quatre manuscrits ont été rédigés à cette fin.

Premièrement, une étude transversale a examiné les relations entre les moments de forces externe subi au genou pendant la marche et l'épaisseur du cartilage tibiofémoral chez des patients souffrant d'arthrose du genou non traumatique (n = 22) et post-traumatique (n = 19) (chapitre 3). Les analyses de régression ont révélé qu'une impulsion de moment d'adducteur du genou plus élevée était négativement associée au rapport d'épaisseur du cartilage médial-latéral. Un moment

d'extension du genou plus élevé était associé à une plus grande épaisseur du cartilage du condyle fémoral médial, et à un plus grand rapport d'épaisseur du cartilage médial-latéral. Ces relations différaient entre les groupes, ce qui suggère que l'influence de la charge articulaire au genou sur le cartilage articulaire peut différer entre ces sous-types d'arthrose.

Ensuite, nous avons mené une étude transversale pour déterminer si la graisse intramusculaire du vaste interne (VI) est liée à la gravité de l'arthrose et à la force musculaire des quadriceps chez les patients atteints d'arthrose du genou non traumatique (n = 22) et post-traumatique (n = 19) (chapitre 4). Les analyses de régression ont révélé que la graisse intramusculaire du VM était positivement associée à l'indice de masse corporelle, mais pas à la gravité de l'arthrose ou au groupe. Un taux de graisse intramusculaire du VI plus élevé était également associé à une réduction de la force musculaire au niveau des quadriceps. Il n'est pas clair si cela est dû à la graisse intramusculaire du VI ou à d'autres facteurs, tels que le régime alimentaire et la sédentarité.

Par la suite, une revue de la portée a résumé la littérature examinant l'impact du niveau d'AP et de la participation sportive sur l'intégrité matérielle et l'échec des prothèses chez les patients après une AUG et une ATG (Chapitre 5). Cinq bases de données ont été consultées, deux examinateurs ont examiné les articles et les données extraites ont été résumées au moyen d'une analyse descriptive. Dix-huit études répondaient aux critères d'inclusion. Après une AUG (n = 5), aucune étude n'a rapporté d'effet délétère du niveau d'AP ou de la participation sportive sur l'intégrité matérielle ou l'échec des prothèses. Après une ATG (n = 13), quatre études ont signalé une association entre des niveaux d'AP plus élevés, mais pas la participation sportive, avec une usure ou une défaillance plus importante des implants.

Enfin, une étude observationnelle longitudinale (n = 81) a comparé la douleur évoquée par cinq tâches et a évalué la valeur pronostique des indices de la SAP pour la douleur et la fonction physique après un programme de réadaptation de huit semaines chez les patients souffrant d'arthrose du genou. Le test de marche de 6 minutes et le test de montée d'escalier étaient les tâches physiques les plus évocatrices chez les patients souffrant d'arthrose du genou. Les analyses de régression n'appuyaient pas la valeur pronostique des mesures de la SAP en ce qui concerne les trajectoires de récupération chez ces patients.

En conclusion, cette thèse a identifié : 1) les différences potentielles dans la manière dont la charge de l'articulation du genou peut avoir un impact sur le cartilage articulaire entre les patients atteints d'arthrose du genou non traumatique et post-traumatique, 2) le rôle potentiel de la graisse intramusculaire VM dans l'altération de la fonction musculaire du quadriceps chez les patients atteints d'arthrose du genou, 3) l'état de la littérature scientifique concernant l'impact du niveau d'AP et de la participation sportive sur l'intégrité et l'échec de l'implant suite à une arthroplastie du genou, et 4) les avantages et les limites potentiels des différentes stratégies de mesure de la SAP chez les patients atteints d'arthrose du genou.

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# Contribution to Original Knowledge

This Ph.D. thesis includes four original manuscripts (Chapters 3 to 6). Chapters 3 and 4 have been published in peer-review journals. Chapter 5 was submitted to a peer-reviewed journal and the revised manuscript is currently under review. Chapter 6 is in preparation for submission to a peer-review journal.

In Chapter 3, the manuscript "*The relationship between knee loading during gait and cartilage thickness in non-traumatic and post-traumatic knee osteoarthritis*" was the first to examine cross-sectional relationships between knee joint moments and measures of disease progression (e.g., cartilage thickness) in patients with non-traumatic and post-traumatic knee OA. The findings of this manuscript helped to fill knowledge gaps by adding to the paucity of research examining the relationship between sagittal plane knee joint moments and tibiofemoral cartilage thickness. The findings also provided new insight into the pathomechanics of knee OA by demonstrating that the potential influence of knee joint loading on articular cartilage may differ between patients with non-traumatic and post-traumatic knee OA. Although our findings must be corroborated by future longitudinal studies, our findings may have important implications with respect to tailoring treatment approaches (e.g., load-modifying interventions such as gait retraining or high tibial osteotomy) for patients with non-traumatic and post-traumatic knee OA.

In Chapter 4, the manuscript "*Vastus medialis intramuscular fat is associated with reduced quadriceps strength, but not knee osteoarthritis severity*" was the first to examine the cross-sectional relationship between VM intramuscular fat with radiographic knee OA severity and quadriceps muscle strength in patients with non-traumatic and post-traumatic knee OA. More specifically, the findings of our study supported the hypothesis that increased VM intramuscular fat is associated with reduced quadriceps muscle strength, although no association was found with

radiographic knee OA severity. Furthermore, this manuscript added to the paucity of research examining whether VM intramuscular fat differs between patients with knee OA and healthy adults, as well as between knee OA subtypes.

In chapter 5, the manuscript "*Understanding the impact of physical activity level and sports participation on implant integrity and failure in patients following unicompartmental and total knee arthroplasty: A scoping review*" provided a broad overview of the scientific literature examining the impact of PA level and sports participation on implant integrity and failure in patients following UKA and TKA for tibiofemoral OA. This scoping review was a first step in establishing guidance on PA and sports participation following knee arthroplasty by 1) summarizing the scientific evidence available to inform recommendations, 2) outlining how studies on the topic were conducted, 3) providing an in-depth discussion on the clinical implications of our findings while considering study limitations, and 4) identifying where further research is needed.

In Chapter 6, the manuscript "*Comparing evoked pain responses and the prospective prognostic value of measures of sensitivity to physical activity among people with knee osteoarthritis*" was the first to examine the potential prognostic value of SPA-Pain indices for pain and physical function following an 8-week rehabilitation program in patients with knee OA. Furthermore, this manuscript extended past work by shedding light on the potential value of different task-specific SPA measurement strategies and their respective merits and limitations in patients with knee OA. More specifically, the magnitude of evoked pain responses, as well as the floor and ceiling effects, were assessed for five standardized physical tasks. Recommendations informed by our findings were then provided regarding which physical tasks may be most appropriate for assessing SPA in patients with knee OA.

# Contribution of Authors

Mr. Anthony Teoli was the first author on all four manuscripts in this Ph.D. thesis because he was principally responsible for data analysis and manuscript writing for all studies. For Chapters 3 and 4, an existing dataset from Dr. Shawn Robbins was used. Mr. Teoli was involved in participant recruitment and data collection prior to commencing his Ph.D. During his Ph.D., he was responsible for study conception (Chapter 4), data processing, statistical analysis, data interpretation and visualization, as well as writing (original draft, reviewing, editing) and publishing the manuscripts. For Chapter 5, Mr. Teoli was responsible for study conception, study methodology, development of the search strategy and execution of searches, study screening and selection, data charting, data synthesis, assessment of study quality, as well as writing (original draft, review, editing) and submitting the manuscript to a peer-review journal. For Chapter 6, an existing dataset belonging to Dr. Timothy Wideman was used. Mr. Teoli was not involved in participant recruitment and data collection. He was responsible for developing the research question, data processing, statistical analysis, data interpretation/visualization, as well as writing the manuscript (original draft, reviewing, editing).

For Chapter 3, Melissa Cloutier-Gendron, Shirley Yin Kay Ho and Susan Gu assisted with data acquisition, data processing, statistical analysis and revising the manuscript. Dr. Jean-Pierre Pelletier and Dr. Johanne Martel-Pelletier provided guidance on study methodology, performed magnetic resonance imaging (MRI) data processing and interpretation, and revised the manuscript. Dr. Shawn Robbins was responsible for obtaining funding, assisted with study conception and design, data acquisition, data processing, statistical analysis, data interpretation, as well as drafting and revising the manuscript.

For Chapter 4, Dr. Johanne Martel-Pelletier, Francois Abram and Dr. Jean-Pierre Pelletier provided guidance on study methodology, performed formal analyses related to MRI data using software they developed, and revised the manuscript. Dr. Shawn Robbins provided guidance on study methodology, and assisted with study conception, data acquisition, data processing, formal analysis, was well as drafting and revising the manuscript.

For Chapter 5, Dr. Patrick Ippersiel was listed as second author in recognition of his contribution to the screening and data extraction process, as well as revising and editing the manuscript. Dr. André Bussières and Dr. John Antoniou provided guidance regarding study methodology and revised the manuscript. Dr. Shawn Robbins assisted with study conception, provided guidance on study methodology, and revised the manuscript.

For Chapter 6, Arthur Woznowski-Vu provided guidance on study methodology. Dr. Timothy Wideman was responsible for obtaining funding, study conception and data collection. Dr. Wideman also provided guidance on study methodology and revised the manuscript. Dr. Shawn Robbins provided guidance on study methodology, and assisted with drafting and revising the manuscript.

# Chapter 1: Introduction

## 1.1 Knee osteoarthritis

### 1.1.1 The burden of osteoarthritis

Osteoarthritis (OA) is a degenerative joint disorder that affects approximately 15% of Canadians (1) and approximately 250 million people worldwide (2). OA is a leading cause of pain and physical disability among older adults, with substantial individual and socioeconomic burden (3). The joints most commonly affected by OA are the knee, hip and hands, with knee OA accounting for approximately 85% of the burden of OA worldwide (4).

### 1.1.2 Pathophysiology of osteoarthritis

OA is a complex, multifactorial disease that affects the entire joint. OA arises initially from maladaptive repair responses due to different mechanical, inflammatory and metabolic factors, which ultimately lead to structural deterioration of the joint (5). Structural OA-related changes include progressive loss of articular cartilage, thickening of subchondral bone, formation of osteophytes, inflammation of the synovium, formation of bone marrow lesions, degeneration of peri-articular structures (i.e., ligaments, menisci, etc.) and hypertrophy of the joint capsule (6). The exposure of an individual to certain OA risk factors increases the susceptibility of the joint to damage and failure of repair (5). Established risk factors for knee OA, for instance, include age (7), genetics (8), female sex, previous joint injury, obesity (9), knee joint loading (10), joint malalignment or deformity (11) and heavy work activities (12). The relative contribution of these risk factors to OA development and progression seems to vary depending on the joint affected.

### 1.1.3 Osteoarthritis pain

Pain is the most disabling symptom for individuals with OA, being the primary reason for consulting a healthcare professional (13). OA pain is usually intermittent and in response to movement or weight-bearing activities. Pain at rest and night pain are also frequently reported. There are two distinct types of joint pain that are commonly reported in individuals with OA: 1) a dull background aching, throbbing pain, and 2) a sharp, stabbing pain that is intermittent but more severe (14, 15). A small subset of individuals with OA also report burning, shooting or electric shock-like pain, which has been suggested to be more indicative of neuropathic pain (16, 17).

## 1.2 Understanding osteoarthritis pain

### 1.2.1 The biopsychosocial model for osteoarthritis pain

Historically, OA pain has been viewed and treated through a biomedical lens, whereby OA pain was assumed to be driven primarily by the activation of nociceptors in response to joint damage (18). However, there is a discordance between structural joint damage and pain in patients with knee OA (19, 20). This discordance has led to further interdisciplinary research shedding light on other, more complex, pain processing mechanisms contributing to the OA pain experience. As a result, OA pain is better conceptualized through a biopsychosocial framework (21, 22).

The biopsychosocial model recognizes that there are different biological (e.g., joint pathology, inflammation, genetics, etc.), psychological (e.g., fear, anxiety, depression, etc.), social (e.g., socioeconomic status, social support, education, etc.) and behavioral factors (e.g., sleep, diet, exercise, etc.) which dynamically interact with one another to modulate the experience of pain (21, 22). This model helps to explain the significant pain variability experienced by patients with OA and provides valuable insight into the potential role of each factor in predisposing, initiating, maintaining, and exacerbating pain in the OA population (21, 22).

### 1.2.2 Peripheral mechanisms of osteoarthritis pain

There are many potential peripheral nociceptive mechanisms that can contribute to OA pain and the subsequent development of peripheral sensitization. Peripheral sensitization is defined as, "increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields" (23). Although articular cartilage is aneural under normal circumstances, there is evidence to suggest that neovascularization of the cartilage and menisci caused by OA-related inflammatory factors can stimulate the formation of new sensory nerves through shared regulatory pathways (24). As a result, articular cartilage is one potential source of nociception in OA. Other joint structures richly innervated by nociceptors include subchondral bone, ligaments, the joint capsule and synovium, the menisci, and periarticular muscles (25). Inflammation within the joint is also characteristic of the OA process and can result in increased mechanosensitivity of joint nociceptors (26, 27). There is also a growing body of research that provides support for a neuropathic component of pain in individuals with OA, believed to be due, in part, to damage to sensory fibers innervating the knee (16, 17). Collectively, these changes can increase the nociceptive input into the dorsal horn of the spinal cord, inducing peripheral sensitization and causing joint movement within normal ranges to become painful (26, 27).

### 1.2.3 Central sensitization and osteoarthritis pain

In patients with OA, changes leading to central sensitization are often initiated by the inflammatory and mechanical processes which accompany peripheral sensitization (26, 27). Central sensitization is characterized by an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity (28), and has been shown to be present in a subgroup (~30%) of individuals with OA (29). Characteristic features of central sensitization

include an increased painful response to threshold stimuli (hyperalgesia) and innocuous stimuli (allodynia). There can also be extra-segmental spreading of referred pain and hyperalgesia past the site of injury (secondary hyperalgesia), as well as enhanced generalized responsiveness to peripheral stimuli such as mechanical pressure, heat and cold (30, 31). Central sensitization in patients with OA is believed to be caused by several neurophysiological mechanisms including spinal cord sensitization, enhanced descending facilitation, and reduced descending inhibition, among others (25, 29). The latter would explain, in part, why certain patients with OA experience severe pain disproportionate to the structural damage at the affected joint (19, 20).

### 1.2.4 Psychological factors

Psychological factors such as pain-related fear and pain catastrophizing are considered risk factors, as they may exacerbate and/or contribute to the maintenance of chronic pain in patients with knee OA (21). Pain catastrophizing is defined as, "an exaggerated negative response to actual or anticipated pain" and is characterized by helplessness, magnification and rumination (32). Catastrophizing is common in patients with OA and is a risk factor for adverse long-term outcomes such as physical disability, increased pain severity and enhanced pain sensitivity (33). Pain-related fear is an umbrella term used to describe fear that arises when stimuli that are associated with pain are perceived as threatening bodily integrity (34). Greater levels of fear-avoidance beliefs are significantly associated with higher levels of pain intensity and disability in patients with OA (35).

### 1.2.5 Social, lifestyle and other factors

Social factors (e.g., income, education, employment, etc.) can also interact with pathophysiological processes and individual-level variables to influence outcomes in patients with

OA (36). Lifestyle factors such as obesity (37), and increased comorbidity count (38) have been shown to be predictive of worsening symptoms over time in patients with knee OA. Poor sleep is also associated with increased pain and pain sensitivity in individuals with OA (39).

## 1.3 Challenges and general research gaps regarding knee joint loading in patients with knee osteoarthritis and following knee arthroplasty

Knee joint loading during functional activities (e.g., gait) has been theorized to be a key risk factor for knee OA onset and progression (40). For instance, a recent systematic review and meta-analysis demonstrated that an increased peak knee adduction moment (KAM, proxy for medial knee joint loading) was associated with greater odds of medial tibiofemoral OA progression (10). Other risk factors for knee OA development and progression, such as obesity (41, 42) or quadriceps muscle weakness (43, 44), can also contribute to increased or abnormal knee joint loading. Regular exercise and PA are recommended for the management of knee OA to improve pain and physical function (45, 46), among other health benefits (i.e., weight loss, increase in muscle strength, etc.). However, there is uncertainty with regards to how different types of PA and exercise (and the associated knee joint loads) affect the structural integrity of their patients' knees, especially in the presence of other knee OA risk factors (i.e., obesity, previous knee joint injury, etc.) (47). Therefore, further research is needed to better understand how joint loading and measures of adiposity influence knee joint cartilage health in patients with knee OA.

In addition, regular exercise and PA also play a fundamental role in the post-operative rehabilitation of patients following UKA and TKA (48, 49). However, high-intensity PA and high-impact sports following knee arthroplasty are typically discouraged to reduce the potential negative impact on implant survivorship due to a greater number of loading cycles and greater

knee joint forces (50, 51). Recommendations regarding PA and sports limitations following knee arthroplasty are mainly based on expert consensus (52), with insight from studies that assessed knee forces in vivo (50, 53), and using estimates from joint models (54-56). Therefore, a broad overview of the scientific literature examining the impact of PA and sports participation on implant integrity and failure following UKA and TKA is needed to better inform current recommendations.

Lastly, increased pain during exercise has been identified as a major barrier to engaging in activity-based interventions for individuals with knee OA (57), and is associated with poor treatment adherence in physiotherapy clinics (58). Recent work has examined an approach to quantifying the pain response (i.e., how pain changes) to standardized physical activities in patients with knee OA, also known as sensitivity to physical activity (SPA) (59, 60). SPA indices are generated by subtracting the pain score before a PA from the pain score immediately after the same PA, making them broadly aligned with the pain experienced while performing daily activities (59-62). A better understanding of the potential merits and limitations of SPA measures in patients with knee OA is needed and is an essential step in developing SPA as a potential clinical assessment tool and integrating sensitized responses to PA within clinical management. Moreover, the prospective value of SPA measures in patients with knee OA remains largely unexplored (60).

Therefore, the overarching goals of this thesis are: 1) to better understand how joint loading during walking relate to knee OA severity, 2) to better understand how measures of adiposity relate to knee OA severity, 3) to describe the available scientific literature examining the impact of PA and sports participation on implant integrity and failure in patients following a UKA and TKA for tibiofemoral knee OA, and 4) to evaluate the potential merits and limitations of SPA measures and their respective potential prospective value in patients with knee OA.

## 1.4 Chapter 1 References


1. Badley EM, Wilfong JM, Zahid S, Perruccio AV. Special Report: The Burden of Osteoarthritis in Canada. Arthritis Society; 2021.
2. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2012;380(9859):2163-96.
3. Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. Nature Reviews Rheumatology. 2014;10(7):437-41.
4. Vos T, Allen C, Arora M, Barber RM, Bhutta ZA, Brown A, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet. 2016;388(10053):1545-602.
5. Roos EM, Arden NK. Strategies for the prevention of knee osteoarthritis. Nature Reviews Rheumatology. 2016;12(2):92-101.
6. Chen D, Shen J, Zhao W, Wang T, Han L, Hamilton JL, et al. Osteoarthritis: toward a comprehensive understanding of pathological mechanism. Bone Research. 2017;5(1):1-13.
7. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Rheumatic Disease Clinics of North America. 2008;34(3):515-29.
8. Van Meurs J. Osteoarthritis year in review 2016: genetics, genomics and epigenetics. Osteoarthritis and Cartilage. 2017;25(2):181-9.
9. Silverwood V, Blagojevic-Bucknall M, Jinks C, Jordan J, Protheroe J, Jordan K. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. Osteoarthritis and Cartilage. 2015;23(4):507-15.
10. D'Souza N, Charlton J, Grayson J, Kobayashi S, Hutchison L, Hunt M, et al. Are biomechanics during gait associated with the structural disease onset and progression of lower limb osteoarthritis? A systematic review and meta-analysis. Osteoarthritis and Cartilage. 2021.
11. Tanamas S, Hanna FS, Cicuttini FM, Wluka AE, Berry P, Urquhart DM. Does knee malalignment increase the risk of development and progression of knee osteoarthritis? A systematic review. Arthritis Care & Research. 2009;61(4):459-67.
12. McWilliams D, Leeb B, Muthuri S, Doherty M, Zhang W. Occupational risk factors for osteoarthritis of the knee: a meta-analysis. Osteoarthritis and Cartilage. 2011;19(7):829-39.
13. Neogi T. The epidemiology and impact of pain in osteoarthritis. Osteoarthritis and Cartilage. 2013;21(9):1145-53.
14. Hawker GA. Experiencing painful osteoarthritis: what have we learned from listening? Current Opinion in Rheumatology. 2009;21(5):507-12.
15. Hawker G, Stewart L, French M, Cibere J, Jordan J, March L, et al. Understanding the pain experience in hip and knee osteoarthritis–an OARSI/OMERACT initiative. Osteoarthritis and Cartilage. 2008;16(4):415-22.
16. Dimitroulas T, Duarte RV, Behura A, Kitas GD, Raphael JH. Neuropathic pain in osteoarthritis: a review of pathophysiological mechanisms and implications for treatment. Seminars in Arthritis and Rheumatism. 2014;44(2):145-54.
17. French HP, Smart KM, Doyle F. Prevalence of neuropathic pain in knee or hip osteoarthritis: a systematic review and meta-analysis. Seminars in Arthritis and Rheumatism. 2017;47(1):1-8.

18. Zimmerman M. Pain mechanisms and mediators in osteoarthritis. Seminars in Arthritis and Rheumatism. 1989;18(4):22-9.
19. Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. BMC Musculoskeletal Disorders. 2008;9(1):1-11.
20. Finan PH, Buenaver LF, Bounds SC, Hussain S, Park RJ, Haque UJ, et al. Discordance between pain and radiographic severity in knee osteoarthritis: findings from quantitative sensory testing of central sensitization. Arthritis & Rheumatism. 2013;65(2):363-72.
21. Clauw DJ, Essex MN, Pitman V, Jones KD. Reframing chronic pain as a disease, not a symptom: rationale and implications for pain management. Postgraduate Medicine. 2019;131(3):185-98.
22. Engel GL. The need for a new medical model: a challenge for biomedicine. Science. 1977;196(4286):129-36.
23. International Association for the Study of Pain (IASP). Pain Terms and Definitions. 2021. Available from: https://www.iasp-pain.org/resources/terminology/.
24. Mapp PI, Walsh DA. Mechanisms and targets of angiogenesis and nerve growth in osteoarthritis. Nature Reviews Rheumatology. 2012;8(7):390-8.
25. Eitner A, Hofmann GO, Schaible H-G. Mechanisms of osteoarthritic pain. Studies in humans and experimental models. Frontiers in Molecular Neuroscience. 2017;10:349.
26. Malfait A-M, Schnitzer TJ. Towards a mechanism-based approach to pain management in osteoarthritis. Nature Reviews Rheumatology. 2013;9(11):654-64.
27. Schaible H-G. Mechanisms of chronic pain in osteoarthritis. Current Rheumatology Reports. 2012;14(6):549-56.
28. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3):S2-S15.
29. Lluch E, Torres R, Nijs J, Van Oosterwijck J. Evidence for central sensitization in patients with osteoarthritis pain: a systematic literature review. European Journal of Pain. 2014;18(10):1367-75.
30. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. The Journal of Pain. 2009;10(9):895-926.
31. Nijs J, Van Houdenhove B, Oostendorp RA. Recognition of central sensitization in patients with musculoskeletal pain: application of pain neurophysiology in manual therapy practice. Manual Therapy. 2010;15(2):135-41.
32. Sullivan MJ, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. Psychological Assessment. 1995;7(4):524.
33. Edwards RR, Cahalan C, Mensing G, Smith M, Haythornthwaite JA. Pain, catastrophizing, and depression in the rheumatic diseases. Nature Reviews Rheumatology. 2011;7(4):216-24.
34. Leeuw M, Goossens ME, Linton SJ, Crombez G, Boersma K, Vlaeyen JW. The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. Journal of Behavioral Medicine. 2007;30(1):77-94.
35. Martinez-Calderon J, Flores-Cortes M, Morales-Asencio JM, Luque-Suarez A. Pain-related fear, pain intensity and function in individuals with chronic musculoskeletal pain: a systematic review and meta-analysis. The Journal of Pain. 2019;20(12):1394-415.
36. Luong M-LN, Cleveland RJ, Nyrop KA, Callahan LF. Social determinants and osteoarthritis outcomes. Aging Health. 2012;8(4):413-37.

37. Bastick AN, Wesseling J, Damen J, Verkleij SP, Emans PJ, Bindels PJ, et al. Defining knee pain trajectories in early symptomatic knee osteoarthritis in primary care: 5-year results from a nationwide prospective cohort study (CHECK). British Journal of General Practice. 2016;66(642):e32-e9.
38. Calders P, Van Ginckel A. Presence of comorbidities and prognosis of clinical symptoms in knee and/or hip osteoarthritis: a systematic review and meta-analysis. Seminars in Arthritis and Rheumatism. 2018;47(6):805-13.
39. Parmelee PA, Tighe CA, Dautovich ND. Sleep disturbance in osteoarthritis: linkages with pain, disability, and depressive symptoms. Arthritis Care & Research. 2015;67(3):358-65.
40. Andriacchi TP, Mündermann A, Smith RL, Alexander EJ, Dyrby CO, Koo S. A framework for the in vivo pathomechanics of osteoarthritis at the knee. Annals of Biomedical Engineering. 2004;32(3):447-57.
41. Chapple CM, Nicholson H, Baxter GD, Abbott JH. Patient characteristics that predict progression of knee osteoarthritis: a systematic review of prognostic studies. Arthritis Care & Research. 2011;63(8):1115-25.
42. Zheng H, Chen C. Body mass index and risk of knee osteoarthritis: systematic review and meta-analysis of prospective studies. BMJ Open. 2015;5(12):e007568.
43. Culvenor AG, Ruhdorfer A, Juhl C, Eckstein F, Øiestad BE. Knee extensor strength and risk of structural, symptomatic, and functional decline in knee osteoarthritis: a systematic review and meta-analysis. Arthritis Care & Research. 2017;69(5):649-58.
44. Øiestad BE, Juhl CB, Culvenor AG, Berg B, Thorlund JB. Knee extensor muscle weakness is a risk factor for the development of knee osteoarthritis: an updated systematic review and meta-analysis including 46 819 men and women. British Journal of Sports Medicine. 2022;56(6):349-55.
45. Bannuru RR, Osani M, Vaysbrot E, Arden N, Bennell K, Bierma-Zeinstra S, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis and Cartilage. 2019;27(11):1578-89.
46. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis & Rheumatology. 2020;72(2):220-33.
47. Nissen N, Holm PM, Bricca A, Dideriksen M, Tang LH, Skou ST. Clinicians' beliefs and attitudes to physical activity and exercise therapy as treatment for knee and/or hip osteoarthritis: a scoping review. Osteoarthritis and Cartilage. 2021.
48. Mistry JB, Elmallah RD, Bhave A, Chughtai M, Cherian JJ, McGinn T, et al. Rehabilitative guidelines after total knee arthroplasty: a review. The Journal of Knee Surgery. 2016;29(03):201-17.
49. Papalia R, Campi S, Vorini F, Zampogna B, Vasta S, Papalia G, et al. The role of physical activity and rehabilitation following hip and knee arthroplasty in the elderly. Journal of Clinical Medicine. 2020;9(5):1401.
50. D'Lima DD, Steklov N, Patil S, Colwell CW. The Mark Coventry Award: in vivo knee forces during recreation and exercise after knee arthroplasty. Clinical Orthopaedics and Related Research. 2008;466(11):2605-11.
51. Kuster MS, Stachowiak GW. Factors affecting polyethylene wear in total knee arthroplasty. Orthopedics. 2002;25(2):S235-S42.
52. Healy WL, Sharma S, Schwartz B, Iorio R. Athletic activity after total joint arthroplasty. Journal of Bone and Joint Surgery. 2008;90(10):2245-52.

53. D'Lima DD, Patil S, Steklov N, Slamin JE, Colwell Jr CW. Tibial forces measured in vivo after total knee arthroplasty. The Journal of Arthroplasty. 2006;21(2):255-62.
54. Dahlkvist N, Mayo P, Seedhom B. Forces during squatting and rising from a deep squat. Engineering in Medicine. 1982;11(2):69-76.
55. Ericson MO, Bratt A, Nisell R, Nemeth G, Ekholm J. Load moments about the hip and knee joints during ergometer cycling. Scandinavian Journal of Rehabilitation Medicine. 1986;18(4):165-72.
56. Winter DA. Moments of force and mechanical power in jogging. Journal of Biomechanics. 1983;16(1):91-7.
57. Kanavaki AM, Rushton A, Efstathiou N, Alrushud A, Klocke R, Abhishek A, et al. Barriers and facilitators of physical activity in knee and hip osteoarthritis: a systematic review of qualitative evidence. BMJ Open. 2017;7(12):e017042.
58. Jack K, McLean SM, Moffett JK, Gardiner E. Barriers to treatment adherence in physiotherapy outpatient clinics: a systematic review. Manual Therapy. 2010;15(3):220-8.
59. Wideman TH, Edwards RR, Finan PH, Haythornthwaite JA, Smith MT. Comparing the predictive value of task performance and task-specific sensitivity during physical function testing among people with knee osteoarthritis. Journal of Orthopaedic & Sports Physical Therapy. 2016;46(5):346-56.
60. Wideman TH, Finan PH, Edwards RR, Quartana PJ, Buenaver LF, Haythornthwaite JA, et al. Increased sensitivity to physical activity among individuals with knee osteoarthritis: relation to pain outcomes, psychological factors, and responses to quantitative sensory testing. Pain. 2014;155(4):703-11.
61. Woznowski-Vu A, Aternali A, Gervais A, Pavilanis AD, Nijs J, Sullivan MJ, et al. The prospective prognostic value of biopsychosocial indices of sensitivity to physical activity among people with back pain. The Clinical Journal of Pain. 2021;37(10):719-29.
62. Woznowski-Vu A, Uddin Z, Flegg D, Aternali A, Wickens R, Sullivan MJ, et al. Comparing novel and existing measures of sensitivity to physical activity among people with chronic musculoskeletal pain. The Clinical Journal of Pain. 2019;35(8):656-67.

# Chapter 2: Background

## 2.1 Is regular physical activity and exercise safe for patients with knee osteoarthritis?

Regular exercise and PA are crucial for the management of knee OA (1), and have been shown to be effective in the treatment of 26 chronic diseases and primary prevention of at least 35 chronic diseases (2). This is especially important, given that many patients with OA have one or more comorbidities (3). However, increasing pain during exercise has been identified as a major barrier to engaging in activity-based interventions for individuals with knee OA (4, 5), and is associated with poor treatment adherence in outpatient physiotherapy clinics (6). Furthermore, it is unclear whether the mechanical joint loading generated from different PAs (e.g., walking, running, etc.) and sports may negatively impact the articular cartilage, especially when considering inflammatory factors and the presence of other knee OA risk factors (i.e., joint injury, obesity). This uncertainty has been echoed by both healthcare professionals (7) and patients with knee OA (8), and can present as a barrier to engaging in regular exercise and PA.

Recent research has begun to address these uncertainties. For instance, two systematic reviews concluded that knee joint loading from therapeutic exercise interventions does not appear to be harmful for articular cartilage, nor does it increase the concentration of molecular biomarkers related to cartilage turnover and inflammation in people at risk of, or with knee OA (9, 10). However, other systematic reviews have demonstrated conflicting findings with regards to sports participation (11, 12). For instance, Driban et al. demonstrated that individuals who participated in higher-impact sports (soccer [OR = 3.5], competitive weight lifting [OR= 6.9]) had a significantly higher prevalence of knee OA when compared to non-exposed participants (11). Similarly, Tran et al. demonstrated an increased risk of developing knee OA after sports exposure, regardless of the type of sport (RR = 1.37; 95% CI 1.14 to 1.64; 21 studies) (12). It is unclear

whether these findings are due to knee joint loading itself, specific sport demands, a sport-related injury, or another unknown factor. Lastly, a systematic umbrella review by Kraus et al. has highlighted the paucity of research examining the impact of specific types of PA on structural outcomes in patients with knee OA (13). Taken together with the conflicting findings presented above, it can be difficult for healthcare providers to confidently provide tailored recommendations to patients with knee OA regarding specific PAs. Furthermore, previous research has emphasized the need for studies examining the impact of PA on structural OA outcomes, while also considering the presence of knee OA risk factors (i.e., obesity, knee joint injury), which may alter the knee joints' response to PA (14). Therefore, more research is required before specific forms of PA can be deemed safe for knee joint structures and confidently recommended in patients with knee OA.

## 2.2 The relationship between knee joint load and measures of cartilage health

### 2.2.1 Measures of knee joint loading during gait and their association with knee osteoarthritis severity and progression

Walking is the most common form of PA among adults, being both practical and accessible (15). However, knee joint loading during functional activities, such as walking, has been theorized to be a key risk factor for knee OA onset and progression (16). For instance, greater knee joint loading in individuals with altered gait kinematics (e.g., individuals with knee OA or following a knee injury) can cause a shift to occur in the contact location to cartilage regions not normally conditioned to increased loading. The inability of these cartilage regions to adapt to changes in load bearing could lead to degenerative changes in the medial tibiofemoral compartment (16). Joint loads are estimated non-invasively via three-dimensional (3D) gait analysis. The following

sections will discuss different estimates of knee joint loading and their respective associations with knee OA severity and progression.

*2.2.1.1 Knee adduction moment (KAM)*

The KAM is a proxy for medial/lateral load distribution within the knee (16). The KAM waveform is characterized by two peaks during stance phase with the first occurring in early stance and the second occurring in late stance. Different methods have been used to analyze the KAM waveform, such as examining the peak value on the curve (peak KAM) (17) and calculating the area under the curve during stance (KAM impulse) (18). The peak KAM represents the maximum magnitude of the curve, whereas the KAM impulse represents both the magnitude and duration of the curve (17, 18).

In patients with knee OA, a higher peak KAM is associated with greater disease severity (16, 19, 20) and increased odds of medial tibiofemoral OA progression (Odds ratio [OR]: 1.88, 95% CI: 1.08, 3.29) (21). A higher KAM impulse was also associated with greater loss of medial tibial cartilage volume over 12 months ($\beta$ = 29.9, 95% CI: 6.3 to 53.5, $P = 0.01$) (22), as well as 2-year medial cartilage thickness loss in patients with knee OA (23). Another study found a KAM impulse-by-BMI ($P = 0.034$) interaction, revealing that larger joint loads in those with knee OA with higher BMIs were associated with greater loss of medial tibial cartilage volume over 2.5 years (24). These findings suggest that mechanical factors, such as increased medial knee joint load, may play an important role in the development and progression of knee OA.

*2.2.1.2 Knee flexion moment (KFM) and knee extension moment (KEM)*

Biomechanical studies examining the association between knee joint loading (estimated via external knee joint moments) and knee OA status have typically focused on the KAM (21). As a result, much less is known about the potential influence of sagittal plane knee joint moments, such as the KFM and the KEM, on knee OA status (21). The KFM and KEM represent the net muscular contribution to the knee and have also been shown to play an important role in knee joint loading in patients with knee OA (25). For instance, the KFM has been shown to influence medial knee joint contact forces (26, 27), and baseline peak KFM values were shown to predict changes in 5-year tibial medial-to-lateral cartilage thickness (B = -0.064, $P = 0.009$) in patients with medial tibiofemoral OA (28). However, another study found no association between baseline peak KFM on any medial knee OA progression outcome measures after 2 years (23). Patients with severe knee OA also exhibit smaller knee extension angles and a reduced KEM in late stance when compared with asymptomatic individuals and older individuals with moderate knee OA (29). This has been hypothesized to be a compensatory strategy to increase knee joint stiffness and reduce the external load on the knee joint in individuals with knee OA (30).

### 2.2.2 Summary and gaps in knowledge

In summary, further investigation is required to better understand the relationship between knee joint moments and knee OA-related cartilage changes. Much less is known about the effect of joint loading during walking on knee joint structural integrity in the presence of other knee OA risk factors, such as a previous knee joint injury (14). Previous research has highlighted two main mechanisms linking knee joint injury to the future development of post-traumatic knee OA (31). The first mechanism is acute cartilage injury resulting in chondrocyte apoptosis and necrosis, which can progress to chronic inflammation and cartilage loss (31). The second mechanism

involves chronic changes in the mechanical environment of the knee joint that persist following an injury (e.g., anterior cruciate ligament [ACL] tear), resulting in changes in knee joint congruity, alignment, and stability, and subsequent OA-related structural changes (31). As a result, having sustained a previous knee joint injury could alter the knee joints' response to joint loading (14), potentially influencing the susceptibility of the knee joint to damage and failure of repair (32). Further research is needed to better understand how the presence of these risk factors may influence the relationship between knee joint loading and measures of cartilage health.

Knee OA can be categorized as non-traumatic (patients with no history of a previous knee injury or trauma) or post-traumatic (OA diagnosed secondary to trauma, injury, surgery) (33). Differences in knee kinetics during gait (34) and the relationship between knee alignment and cartilage thickness have been shown to differ between patients with non-traumatic and post-traumatic medial compartment knee OA (35). Furthermore, previous research would also suggest that the relative importance of different knee joint moments may also differ between these knee OA subtypes. For instance, the KAM would appear to have greater relevance in patients with non-traumatic knee OA, whereas sagittal knee moments (e.g., KEM, KFM) appear to be more relevant in patients following ACL reconstruction, with important implications for the potential future development of post-traumatic knee OA (22, 36, 37). Therefore, differences in structural OA-related changes and knee mechanics exist between patients with non-traumatic and post-traumatic knee OA. By extension, the relationship between measures of disease progression (e.g., cartilage thickness) and knee joint moments might also differ between these knee OA subtypes. This has not been previously examined. A greater understanding of this relationship would provide valuable insight into the potential difference in mechanisms affecting disease progression between these OA subtypes.

## 2.3 The relationship between obesity and measures of cartilage health

### 2.3.1 Obesity - an important risk factor for knee osteoarthritis development and progression

Obesity is a modifiable risk factor for knee OA development and progression (38, 39). One potential mechanism linking obesity with knee OA pathogenesis is the abnormal loading environment created by different mechanical and systemic factors (40). For instance, mechanical factors such as excess body weight can increase the loading and mechanical stress at the knee joint (40). Furthermore, systematic factors, such as the production and release of cytokines and adipokines by adipose tissue which promote low-grade systemic inflammation have been shown to play a role in disrupting cartilage and bone homeostasis, as well as in altering muscle function and force production (40-42). In addition, low-grade systematic inflammation can be exacerbated by conditions such as metabolic syndrome, which is defined by a cluster of cardiometabolic factors that commonly accompany obesity (i.e., central adiposity, dyslipidemia, impaired fasting glucose levels and hypertension) (40). Together, these factors can increase the susceptibility of the knee joint to damage and failure of repair. Consequently, there has been extensive research examining how global measures of adiposity (e.g., BMI) relate to knee joint health (43-45). There has also been growing interest in local measures of adiposity, such as intermuscular fat (between muscles and beneath fascia) and intramuscular fat (stored within the muscle) (46), and how they may influence OA status and clinical outcomes in patients with knee OA (47-49).

#### *2.3.1.1 Thigh intermuscular and intramuscular fat in patients with knee osteoarthritis*

A recent systematic review and meta-analysis demonstrated that patients with knee OA had greater thigh intermuscular (n = 6 studies) and intramuscular (n = 1 study) fat content

compared to individuals without knee OA (46). Sarcopenia is thought to be accelerated in individuals with knee OA and quadriceps muscle atrophy is hypothesized to be followed by an increase in fat infiltration, in part due to physical inactivity and disuse secondary to joint pain (50). This is consistent with previous research demonstrating an association between higher quadriceps intramuscular fat with worse pain and physical function in patients with knee OA (47). Similarly, women with advanced knee OA demonstrated greater ectopic adipogenesis in the VM muscle following disuse atrophy when compared to women without knee OA (51).

*2.3.1.2 The influence of quadriceps intramuscular fat on osteoarthritis status and clinical outcomes in patients with knee osteoarthritis*

There is also evidence to suggest that quadriceps intramuscular fat (particularly VM intramuscular fat) relates to OA status and cartilage measures. For instance, higher quadriceps intramuscular fat fractions were associated with greater radiographic knee OA severity ($r = 0.25$, $P = 0.002$) (47). Greater VM intramuscular fat was also associated with global knee cartilage volume loss ($\beta = -0.13$, $P = 0.015$) and the progression of bone marrow lesions ($\beta = 0.10$, $P < 0.001$) over a 2-year period in patients with knee OA (49). Similarly, greater VM intramuscular fat was associated with an increase in cartilage, meniscus, or bone marrow lesion MRI scores (OR 2.05 [95% CI 1.25–3.36]) over 3 years in patients with knee OA, after accounting for age, sex and BMI (48). Furthermore, reducing VM intramuscular fat via lifestyle interventions, such as exercise and weight loss, has been shown to have a beneficial effect on knee cartilage preservation in healthy adults (52). For instance, in a community-based longitudinal study of healthy adults without any diagnosed arthropathy (n=197), a reduction in VM fat infiltration was associated with

a reduced annual loss of medial tibial (β = -10 $mm^3$; 95% CI: -19 to 0 $mm^3$; *P* = 0.04) and patella (β = -18 $mm^3$; 95% CI: -36 to 0 $mm^3$; *P* = 0.04) cartilage volume at 2-year follow-up (52).

*2.3.1.3 Mechanisms linking increased intramuscular quadriceps adiposity with knee osteoarthritis pathogenesis*

Although not fully understood, intramuscular quadriceps adiposity has been linked to knee OA pathogenesis via several potential mechanisms. The release of proinflammatory cytokines by intramuscular fat may disrupt knee joint cartilage homeostasis, leading to further OA progression (42). Intramuscular fat can also alter muscle metabolism by causing defects in insulin signaling (i.e., reduced insulin-stimulated muscle glucose transport activity and glycogen synthesis) and reducing the oxidative enzymatic capacity of muscle (41). Furthermore, it is believed that intramuscular fat infiltration may cause normal muscle fibres to rearrange themselves within the framework of the muscle, which can lead to changes in muscle fiber orientation (53). Together, these changes can lead to impaired normal muscle function, reduced knee joint stability and abnormal knee joint loading. This is consistent with previous research demonstrating that greater thigh intramuscular fat is associated with an impairment in neuromuscular activation and decreased quadriceps strength in older adults (54, 55), although studies in patients with knee OA report conflicting findings (51, 52).

**2.3.2 Summary and gaps in knowledge**

The VM muscle has an important role in functional knee stability (56) and reduced quadriceps muscle strength is a risk factor for the development (57) and progression (58) of knee OA. Consequently, VM intramuscular fat may impact knee joint structure and muscle function and

warrants further investigation. Given the paucity of studies conducted on the topic (46), further studies are necessary to assess whether VM intramuscular fat differs between patients with knee OA and healthy adults, and to determine whether VM intramuscular fat is associated with radiographic knee OA severity and quadriceps muscle strength.

There is also minimal research comparing thigh intramuscular fat between different knee OA subtypes, including non-traumatic and post-traumatic knee OA (59). Impairments in muscle strength and activation occur in patients with knee OA (57) or after a knee trauma (60), with the potential to influence knee joint loading. However, it is unclear if impairments in muscle function may be explained by differences in intramuscular fat content between patients with knee OA with or without a history of knee trauma (e.g., ligament rupture). Considering that previous knee trauma is a major risk factor for knee OA initiation and progression (61), the relationship between disease severity and intramuscular fat might also vary between these OA subtypes.

## 2.4 Taking an active approach following knee arthroplasty

### 2.4.1 Unicompartmental and total knee arthroplasty for knee osteoarthritis

Two treatment options for patients with end-stage knee OA who have not seen improvements in pain and physical function with less invasive approaches (i.e., rehabilitation, medication, injections, etc.) are a UKA and TKA (62). A UKA is typically done when the OA is predominantly present in either the medial or lateral knee joint compartment. Therefore, UKAs replace only the arthritic part of the joint, while TKAs replace the entire knee joint (62). UKAs generally consist of less than 10% of all primary knee arthroplasties, with the majority being TKAs (63, 64). When compared to a TKA, a UKA generally provides improved range of motion, knee kinematics and physical function (65, 66). This may allow patients to return to more technically

demanding and higher-level activities or sports. A recent systematic review demonstrated that the 25-year survivorship of TKA and UKA implants is 82% and 70% (67).

### 2.4.2 Physical activity and sports participation following knee arthroplasty

Patients are encouraged to remain active following their knee arthroplasty. Patients also desire an increased functional capacity following their knee arthroplasty, with evolving expectations towards being able to participate in physical activities or sports (68). Most patients return to PA and sports following knee arthroplasty, with a trend towards participation in low-impact activities and sports (69, 70). This trend may be explained by the fact that higher-impact activities and sports are typically discouraged following knee arthroplasty to reduce the potential negative impact on implant component survivorship. Previous research has also suggested that implant wear is a function of use, and not time (71, 72). As a result, physical activities and sports with a greater number of loading cycles, joint loads and/or technical demands may induce important stress at the bone-implant fixation surface and accelerate wear of implant components, leading to premature implant failure and revision (71, 72).

### 2.4.3 Is regular physical activity and exercise safe following knee arthroplasty?

Recommendations regarding PA and sports limitations following knee arthroplasty are mainly based on expert consensus (73), with insight from studies that assessed knee forces in vivo (74, 75), and using estimates from joint models (76-79). However, these recommendations have been put into question in recent years due to evidence suggesting no increased risk of implant wear or failure with greater levels of PA (80-82) and sports participation (83, 84). For instance, in a study by Mont et al. (82), the high-activity group had similar radiographic outcomes (i.e., no

progressive radiolucencies, no evidence of osteolysis) when compared to the low-activity group, with neither group having any revisions at 4 years follow-up. Similarly, there was no evidence of additional wear or loosening and revision rates were similar in patients performing high-impact activity when compared to those performing medium- or low- impact activities at 6 years post TKA (83). However, other studies have reported conflicting findings (85-87).

### 2.4.4 Summary and knowledge gaps

Whether participation in sport and high-impact activities increases the risk of knee arthroplasty implant failure remains unclear, and may explain the often inconsistent and contradictory recommendations provided to patients in clinical practice. The first steps in establishing guidance on PA and sports participation following UKA and TKA are to understand the scientific evidence available to inform recommendations, to understand how studies on the topic are conducted and to identify where further research is needed. Thus, a broad overview of the available scientific literature on patients of all ages following both primary UKA and TKA for knee OA is needed.

## 2.5 Sensitivity to physical activity

### 2.5.1 Movement-evoked pain as a barrier to rehabilitation and regular physical activity

Exercise and PA-based interventions tailored to the individual are strongly recommended and appropriate for individuals with knee OA (1, 88). Furthermore, consensus guidelines highlight that adherence to regular PA is a key determinant of long-term knee OA outcomes (89). However, increased pain during exercise (i.e., exercise-induced hyperalgesia) has been identified as a major barrier to engaging in activity-based interventions for individuals with knee OA (4, 5), and is

associated with poor treatment adherence in outpatient physiotherapy clinics (6). Potential underlying mechanisms of exercise-induced hyperalgesia in patients with OA include changes in peripheral pain processing (e.g., increased responsiveness and reduced thresholds of nociceptive neurons) and central pain processing (e.g., amplification of neural signaling within the central nervous system), eliciting pain hypersensitivity (90-92). This can cause mechanical joint loading or movement within normal ranges, such as during PA or exercise, to become painful (91, 92). Exercise-induced hyperalgesia in patients with knee OA may partially be a result of the current reliance on measures of physical performance to guide exercise prescription (93). Framing activity-based interventions on physical performance alone may overlook potential negative responses patients may have to PA, resulting in a sub-set of patients experiencing symptom flare-ups and ultimately, poor treatment responses. Alternatively, the clinical measurement of activity-related pain may flag elevated risk of treatment failure and prompt the use of alternate approaches (e.g., tailored activity-based interventions) (94).

### 2.5.2 The importance of assessing movement-evoked pain

There has been substantial effort to better understand and identify predominant OA pain mechanisms to help identify highly sensitive groups of individuals who may not respond to standard OA treatments, with the goal of improving pain-related patient outcomes through the provision of a more personalized pain management regime (95). One specific example of a recent advancement on this front is the growing recognition of the importance of distinguishing between pain-at-rest and movement-evoked pain (93, 96). When compared with pain at rest, movement-evoked pain is characterized by distinct underlying mechanisms, tends to be more severe, has a more direct impact on functional recovery and has different responses to treatment (93). However,

current clinical assessment strategies are not specifically designed to measure pain evoked by activity engagement and several methodological problems have been identified in traditional pain assessment (spontaneous pain measures and pain recall questionnaires) (96). For instance, spontaneous pain measures (e.g., pain at rest) do not involve PA or consider movement (97). Additionally, pain recall questionnaires are dependent on recall capacity and are unable to differentiate between the pain experience before, during and after movement (96). This is concerning, given that, "failure to distinguish between pain-at-rest and movement-evoked pain could threaten trial precision and the ability to identify interventions with the most clinically relevant effects on pain" (93). Therefore, movement-evoked pain may be a particularly important measure of musculoskeletal pain above and beyond traditional pain assessments, and standardized approaches to assessing pain during relevant physical activities are needed to better address these barriers and to advance research in this area (93, 96).

### 2.5.3 Sensitivity to physical activity in patients with knee osteoarthritis

Recent work has begun to address these knowledge gaps through the development of novel approaches to assessing the negative responses to engagement in PA, including increased pain intensity, dysfunction in the endogenous pain-inhibitory system and negative pain-related thoughts and feelings (94, 98-100). The term SPA has been used to broadly capture the full range of these negative multidimensional and biopsychosocial responses to engagement in an activity. Past studies have used SPA-Pain indices among individuals with musculoskeletal pain (e.g., knee OA) to evaluate the change in pain intensity in relation to a standardized physical task such as the 6-Minute Walk Test (94, 98). Participants are first required to verbally rate their pain before and after a PA or task using a 0 (no pain) to 100 (most pain imaginable) numeric rating scale (NRS).

SPA-Pain indices are then generated by subtracting the pain score before a physical task from the pain score immediately after the same physical task, making them broadly aligned with the pain experienced while performing daily activities (94, 98, 100).

SPA has been observed among patients with knee OA (94, 101), as well as in other chronic pain conditions, such as back pain (99), whiplash (102) and fibromyalgia (103). For instance, after climbing a flight of stairs, patients with knee OA (n = 37, mean age = 64.8 years, 28 females) experienced a significantly greater increase in pain than the age- and sex-matched healthy controls ($P < 0.001$) (101). Additionally, the mean NRS pain scores (scale range: 0-10) reported by the knee OA group after the stair climb task (NRS: 3.8 ± 2.9) was twice that reported before the stair climb task (NRS: 1.8 ± 2.4) (101). Another study by Wideman et al. sought to determine the degree to which patients with knee OA show heightened SPA in response to a standardized walking task (94). Their sample consisted of 107 patients with chronic knee OA (75 women, mean age: 61 years). Eighty-five percent of the study sample had positive SPA indices (i.e., increased knee discomfort) while performing a 6-Minute Walk Test and the mean NRS knee discomfort scores (scale range: 0-100) increased by approximately 130% from the beginning to the end of the standardized walking task (94). As a result, assessing movement-evoked pain is especially relevant in patients with chronic conditions such as knee OA.

### 2.5.4. The relationship between sensitivity to physical activity, central sensitization, and psychological factors

Although the mechanisms underlying movement-evoked pain are not fully understood, there is evidence to suggest that SPA is influenced by processes related to central sensitization (94). Central sensitization is an amplification of pain via increased excitability and/or reduced

inhibition in certain neural networks and has been hypothesized to be a mechanism contributing to the persistence of pain in patients with knee OA (95). Higher levels of SPA have been shown to be significantly correlated ($r = 0.305$, $P < 0.01$) with elevated scores on clinical indicators of central sensitization, such as temporal summation of mechanical pain at the knee in patients with knee OA (94). Temporal summation has been identified as a potential underlying mechanism of SPA due to the repetitive mechanical demands of physical tasks (i.e., walking, stair climbing), resulting in "wind-up" of nociception at the dorsal horn of the spinal cord (94, 100, 102).

Higher levels of SPA in the knee OA population have also been shown to cross-sectionally predict self-reported pain ($\beta = 0.365$, $P < 0.001$), physical function ($\beta = 0.351$, $P < 0.001$) and performance on the 6-Minute Walk Test ($\beta = -0.257$, $P = 0.03$) after controlling for significant covariates, psychological factors and quantitative sensory testing measures (94). Furthermore, post-6-Minute Walk Test knee discomfort emerged as a unique cross-sectional predictor of self-reported physical function ($\beta = 0.296$, $P < 0.05$) and pain-related interference ($\beta = 0.255$, $P < 0.05$) after controlling for other potential predictors, in patients with knee OA (98).

Previous work would also suggest that psychological factors play a role in the experience of movement-evoked pain in patients with knee OA (94, 98). For instance, Wideman and colleagues reported that elevated levels of pain catastrophizing (attentional biases to pain including vigilance and inability to disengage from pain-related stimuli) were associated with increased SPA ($r = 0.215$, $P < 0.05$) in patients with knee OA, even after controlling for significant covariates (94). Consequently, there is evidence to suggest that higher SPA is associated with elevated scores on clinical indices of pain hypersensitivity and psychological risk factors, and that SPA predicts a range of pain-related outcomes in patients with knee OA.

### 2.5.5 Summary and knowledge gaps

Clinical measures of SPA may be particularly helpful in identifying and managing patients who may be at an elevated risk for treatment failure following best-practice knee OA treatments (e.g., active rehabilitation) due to their sensitized responses to PA. Recent work has begun to shed light on the potential prognostic value of SPA-Pain indices in patients with low back pain (99). However, studies in patients with knee OA have used primarily cross-sectional designs (94, 98). As a result, prospective longitudinal studies are needed to determine the potential prognostic value of SPA-Pain indices with respect to recovery trajectories in patients with knee OA. Furthermore, it is unclear which physical activities or tasks are most appropriate for assessing SPA in patients with knee OA (94). This is especially important for identifying physical tasks that both elicit SPA and can be feasibly performed in typical practice settings, as well as for mitigating potential floor and ceiling effects when assessing SPA in patients with knee OA. Therefore, a better understanding of the potential merits and limitations of SPA measures are needed and is an essential step in developing SPA as a potential clinical assessment tool and integrating sensitized responses to PA within clinical management.

## 2.6 Overall summary, gaps and rationale

The above literature review shed light on knowledge gaps regarding 1) the influence of joint loading on the structural integrity of the knee in patients with knee OA, 2) the influence of local measures of adiposity on quadriceps muscle strength and disease severity in patients with knee OA, 3) the influence of PA level and sports participation on knee arthroplasty implant integrity and failure, and 4) the merits and limitations of SPA measures in patients with knee OA. This Ph.D. thesis will contribute evidence to knowledge gaps in these areas.

First, factors such as obesity, quadriceps muscle weakness and knee joint injury have all been suggested, in part, to influence knee OA pathogenesis through the creation of an abnormal loading environment at the knee (32). Considering that previous knee trauma is a major risk factor for knee OA development and progression (61), the relationship between knee joint loading during gait and local measures of adiposity with measures of OA status (e.g., cartilage thickness, radiographic OA severity) might also differ patients with non-traumatic and post-traumatic knee OA. This has not been previously examined. As such, we must expand our knowledge base by investigating the potential role of joint loading during gait and local measures of adiposity on the structural integrity of the knee joint in patients with non-traumatic and post-traumatic knee OA. A greater understanding of this relationship would provide valuable insight into the potential difference in mechanisms affecting disease progression between these knee OA subtypes.

Second, recommendations regarding PA and sports limitations following knee arthroplasty are mainly based on expert consensus (73) and have been put into question in recent years due to evidence suggesting no increased risk of implant wear or failure with greater levels of PA (80-82) and sports participation (83, 84). A scoping review will be the first step in establishing guidance on PA and sports participation following UKA and TKA by summarizing the scientific evidence available to inform recommendations, shedding light on how studies on the topic are conducted, and identifying where further research is needed.

Lastly, SPA is an approach to assessing the negative responses to engagement in PA. However, it is unclear which physical activities or tasks are most appropriate for assessing SPA in patients with knee OA (94). This is especially important for identifying physical tasks that both elicit SPA and can be feasibly performed in typical practice settings (104), as well as for mitigating potential floor and ceiling effects when assessing SPA in patients with knee OA (94). Furthermore,

studies in patients with knee OA have used primarily cross-sectional designs (94, 98, 101, 105). As a result, longitudinal studies are needed to determine the potential prognostic value of SPA-Pain indices with respect to recovery trajectories in patients with knee OA. Therefore, a better understanding of the potential merits and limitations of SPA measures in patients with knee OA is needed and is an essential step in developing SPA as a potential clinical assessment tool and integrating sensitized responses to PA within clinical management.

## 2.7 Objectives & hypotheses

The overarching goals of this thesis were: 1) to better understand how joint loading during walking relates to disease severity in patients with non-traumatic and post-traumatic knee OA, 2) to better understand how local measures of adiposity relate to disease severity in patients with non-traumatic and post-traumatic knee OA, 3) to describe the scientific literature examining the impact of PA and sports participation on implant integrity and failure in patients following a UKA and TKA for tibiofemoral knee OA, and 4) to evaluate the potential merits and limitations of SPA measures and their respective potential prospective value in patients with knee OA. This was achieved via four specific manuscripts, and the specific objectives are outlined below.

**Chapter 3: The relationship between knee loading during gait and cartilage thickness in non-traumatic and post-traumatic knee osteoarthritis**

A starting point to inform this thesis was to investigate the relationship between knee joint loading during gait and the structural integrity of the knee joint in patients with non-traumatic and post-traumatic knee OA. The specific objective of this study was to examine the relationship between external knee joint moments (KAM, KFM, KEM) during gait and cartilage thickness,

measured using magnetic resonance imaging (MRI), in patients with non-traumatic and post-traumatic knee OA. We hypothesized that the relationship between knee joint moments during gait and cartilage thickness would differ between participants with non-traumatic and post-traumatic knee OA. Our hypothesis is based on previous research demonstrating that medial knee joint loading (e.g., the KAM) plays a role in medial tibiofemoral OA progression in patients with non-traumatic knee OA (22, 37), but appears to be less relevant in patients following ACL reconstruction (36). This may have important implications for the potential future development of post-traumatic knee OA.

**Chapter 4: Vastus medialis intramuscular fat is associated with reduced quadriceps strength, but not knee osteoarthritis severity**

The specific objectives of this study were to: 1) compare vastus medialis (VM) intramuscular fat between patients with non-traumatic and post-traumatic knee OA and healthy adults and 2) estimate the extent to which VM intramuscular fat relates to radiographic OA severity and quadriceps muscle strength in patients with non-traumatic and post-traumatic knee OA. We hypothesized that patients with knee OA would have a greater proportion (%) of VM intramuscular fat compared to healthy adults, and increased VM intramuscular fat would be associated with worse radiographic knee OA severity and reduced quadriceps strength in patients with knee OA.

**Chapter 5: Understanding the impact of physical activity level and sports participation on implant integrity and failure in patients following unicompartmental and total knee arthroplasty: A scoping review**

The primary aim of this scoping review was to describe the available scientific literature examining the impact of PA and sports participation on implant integrity and failure in adult patients of all ages following a UKA and TKA for tibiofemoral knee OA. The secondary aim was to identify knowledge gaps on the topic and provide recommendations for future research.

## Chapter 6: Comparing evoked pain responses and the prospective prognostic value of measures of sensitivity to physical activity among people with knee osteoarthritis

The specific objectives of this study were to 1) compare baseline evoked pain responses across five physical tasks in patients with knee OA and 2) evaluate the relative prognostic value of SPA-Pain indices in patients with knee OA for pain and physical function after an 8-week activity-based rehabilitation program. For objective #1, we hypothesized that the 6-Minute Walk Test and the Stair Climb Test would be the most evocative of the physical tasks, as increased pain is commonly reported by patients with knee OA during weight-bearing activities of longer duration or that are more physically demanding. For objective #2, we hypothesized that the SPA-Pain indices generated from the most evocative tasks would have the greatest prognostic value for pain and physical function after an 8-week activity-based rehabilitation program.

## 2.8 Chapter 2 References


1. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee: a Cochrane systematic review. British Journal of Sports Medicine. 2015;49(24):1554-7.
2. Pedersen BK, Saltin B. Exercise as medicine–evidence for prescribing exercise as therapy in 26 different chronic diseases. Scandinavian Journal of Medicine & Science in Sports. 2015;25:1-72.
3. Swain S, Sarmanova A, Coupland C, Doherty M, Zhang W. Comorbidities in Osteoarthritis: A systematic review and meta-analysis of observational studies. Arthritis Care & Research. 2020;72(7):991-1000.
4. Holden MA, Nicholls EE, Young J, Hay EM, Foster NE. Role of exercise for knee pain: what do older adults in the community think? Arthritis Care & Research. 2012;64(10):1554-64.
5. Kanavaki AM, Rushton A, Efstathiou N, Alrushud A, Klocke R, Abhishek A, et al. Barriers and facilitators of physical activity in knee and hip osteoarthritis: a systematic review of qualitative evidence. BMJ Open. 2017;7(12):e017042.
6. Jack K, McLean SM, Moffett JK, Gardiner E. Barriers to treatment adherence in physiotherapy outpatient clinics: a systematic review. Manual Therapy. 2010;15(3):220-8.
7. Nissen N, Holm PM, Bricca A, Dideriksen M, Tang LH, Skou ST. Clinicians' beliefs and attitudes to physical activity and exercise therapy as treatment for knee and/or hip osteoarthritis: a scoping review. Osteoarthritis and Cartilage. 2021.
8. Bunzli S, BHealthSci POB, Ayton D, Dowsey M, Gunn J, Choong P, et al. Misconceptions and the acceptance of evidence-based nonsurgical interventions for knee osteoarthritis. A qualitative study. Clinical Orthopaedics and Related Research. 2019;477(9):1975.
9. Bricca A, Juhl CB, Steultjens M, Wirth W, Roos EM. Impact of exercise on articular cartilage in people at risk of, or with established, knee osteoarthritis: a systematic review of randomised controlled trials. British Journal of Sports Medicine. 2019;53(15):940-7.
10. Bricca A, Struglics A, Larsson S, Steultjens M, Juhl CB, Roos EM. Impact of exercise therapy on molecular biomarkers related to cartilage and inflammation in individuals at risk of, or with established, knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. Arthritis Care & Research. 2019;71(11):1504-15.
11. Driban JB, Hootman JM, Sitler MR, Harris KP, Cattano NM. Is participation in certain sports associated with knee osteoarthritis? A systematic review. Journal of Athletic Training. 2017;52(6):497-506.
12. Tran G, Smith TO, Grice A, Kingsbury SR, McCrory P, Conaghan PG. Does sports participation (including level of performance and previous injury) increase risk of osteoarthritis? A systematic review and meta-analysis. British Journal of Sports Medicine. 2016;50(23):1459-66.
13. Kraus VB, Sprow K, Powell KE, Buchner D, Bloodgood B, Piercy K, et al. Effects of physical activity in knee and hip osteoarthritis: a systematic umbrella review. Medicine and science in sports and exercise. 2019;51(6):1324.
14. Voinier D, White DK. Walking, running, and recreational sports for knee osteoarthritis: An overview of the evidence. European Journal of Rheumatology. 2022.
15. Hulteen RM, Smith JJ, Morgan PJ, Barnett LM, Hallal PC, Colyvas K, et al. Global participation in sport and leisure-time physical activities: A systematic review and meta-analysis. Preventive medicine. 2017;95:14-25.

16. Andriacchi TP, Mündermann A, Smith RL, Alexander EJ, Dyrby CO, Koo S. A framework for the in vivo pathomechanics of osteoarthritis at the knee. Annals of Biomedical Engineering. 2004;32(3):447-57.
17. Schipplein O, Andriacchi T. Interaction between active and passive knee stabilizers during level walking. Journal of Orthopaedic Research. 1991;9(1):113-9.
18. Kean CO, Hinman RS, Bowles KA, Cicuttini F, Davies-Tuck M, Bennell KL. Comparison of peak knee adduction moment and knee adduction moment impulse in distinguishing between severities of knee osteoarthritis. Clinical Biomechanics. 2012;27(5):520-3.
19. Mündermann A, Dyrby CO, Hurwitz DE, Sharma L, Andriacchi TP. Potential strategies to reduce medial compartment loading in patients with knee osteoarthritis of varying severity: reduced walking speed. Arthritis & Rheumatism. 2004;50(4):1172-8.
20. Sharma L, Hurwitz DE, Thonar EJM, Sum JA, Lenz ME, Dunlop DD, et al. Knee adduction moment, serum hyaluronan level, and disease severity in medial tibiofemoral osteoarthritis. Arthritis & Rheumatism. 1998;41(7):1233-40.
21. D'Souza N, Charlton J, Grayson J, Kobayashi S, Hutchison L, Hunt M, et al. Are biomechanics during gait associated with the structural disease onset and progression of lower limb osteoarthritis? A systematic review and meta-analysis. Osteoarthritis and Cartilage. 2021.
22. Bennell KL, Bowles K-A, Wang Y, Cicuttini F, Davies-Tuck M, Hinman RS. Higher dynamic medial knee load predicts greater cartilage loss over 12 months in medial knee osteoarthritis. Annals of the Rheumatic Diseases. 2011;70(10):1770-4.
23. Chang AH, Moisio KC, Chmiel JS, Eckstein F, Guermazi A, Prasad PV, et al. External knee adduction and flexion moments during gait and medial tibiofemoral disease progression in knee osteoarthritis. Osteoarthritis and Cartilage. 2015;23(7):1099-106.
24. Brisson NM, Wiebenga EG, Stratford PW, Beattie KA, Totterman S, Tamez-Peña JG, et al. Baseline knee adduction moment interacts with body mass index to predict loss of medial tibial cartilage volume over 2.5 years in knee osteoarthritis. Journal of Orthopaedic Research. 2017;35(11):2476-83.
25. Pinto RF, Birmingham TB, Philpott HT, Primeau CA, Leitch KM, Arsenault DA, et al. Changes and associations between gait biomechanics and knee inflammation after aspiration and corticosteroid injection for knee osteoarthritis. Arthritis Care & Research. 2022.
26. Trepczynski A, Kutzner I, Bergmann G, Taylor WR, Heller MO. Modulation of the relationship between external knee adduction moments and medial joint contact forces across subjects and activities. Arthritis & Rheumatology. 2014;66(5):1218-27.
27. Walter JP, D'Lima DD, Colwell Jr CW, Fregly BJ. Decreased knee adduction moment does not guarantee decreased medial contact force during gait. Journal of Orthopaedic Research. 2010;28(10):1348-54.
28. Chehab EF, Favre J, Erhart-Hledik JC, Andriacchi TP. Baseline knee adduction and flexion moments during walking are both associated with 5 year cartilage changes in patients with medial knee osteoarthritis. Osteoarthritis and Cartilage. 2014;22(11):1833-9.
29. Favre J, Erhart-Hledik JC, Andriacchi TP. Age-related differences in sagittal-plane knee function at heel-strike of walking are increased in osteoarthritic patients. Osteoarthritis and Cartilage. 2014;22(3):464-71.
30. Messier SP, Gutekunst DJ, Davis C, DeVita P. Weight loss reduces knee-joint loads in overweight and obese older adults with knee osteoarthritis. Arthritis & Rheumatism. 2005;52(7):2026-32.

31. Dilley JE, Bello MA, Roman N, McKinley T, Sankar U. Post-traumatic osteoarthritis: A review of pathogenic mechanisms and novel targets for mitigation. Bone Reports. 2023:101658.
32. Roos EM, Arden NK. Strategies for the prevention of knee osteoarthritis. Nature Reviews Rheumatology. 2016;12(2):92-101.
33. Swärd P, Kostogiannis I, Neuman P, Von Porat A, Boegård T, Roos H. Differences in the radiological characteristics between post-traumatic and non-traumatic knee osteoarthritis. Scandinavian Journal of Medicine & Science in Sports. 2010;20(5):731-9.
34. Robbins SM, Birmingham TB, Jones IC, Sischek EL, Dietzsch M, Giffin JR. Comparison of gait characteristics between patients with nontraumatic and posttraumatic medial knee osteoarthritis. Arthritis Care & Research. 2016;68(9):1215-23.
35. Robbins S, Abram F, Boily M, Pelletier J-P, Martel-Pelletier J. Relationship between alignment and cartilage thickness in patients with non-traumatic and post-traumatic knee osteoarthritis. Osteoarthritis and Cartilage. 2019;27(4):630-7.
36. Hart HF, Culvenor AG, Collins NJ, Ackland DC, Cowan SM, Machotka Z, et al. Knee kinematics and joint moments during gait following anterior cruciate ligament reconstruction: a systematic review and meta-analysis. British journal of sports medicine. 2016;50(10):597-612.
37. Miyazaki T, Wada M, Kawahara H, Sato M, Baba H, Shimada S. Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. Annals of the Rheumatic Diseases. 2002;61(7):617-22.
38. Chapple CM, Nicholson H, Baxter GD, Abbott JH. Patient characteristics that predict progression of knee osteoarthritis: a systematic review of prognostic studies. Arthritis Care & Research. 2011;63(8):1115-25.
39. Zheng H, Chen C. Body mass index and risk of knee osteoarthritis: systematic review and meta-analysis of prospective studies. BMJ Open. 2015;5(12):e007568.
40. Berenbaum F, Wallace IJ, Lieberman DE, Felson DT. Modern-day environmental factors in the pathogenesis of osteoarthritis. Nature Reviews Rheumatology. 2018;14(11):674-81.
41. Heilbronn L, Smith S, Ravussin E. Failure of fat cell proliferation, mitochondrial function and fat oxidation results in ectopic fat storage, insulin resistance and type II diabetes mellitus. International Journal of Obesity. 2004;28(4):S12-S21.
42. Wang X, Hunter D, Xu J, Ding C. Metabolic triggered inflammation in osteoarthritis. Osteoarthritis and Cartilage. 2015;23(1):22-30.
43. Gelber AC, Hochberg MC, Mead LA, Wang N-Y, Wigley FM, Klag MJ. Body mass index in young men and the risk of subsequent knee and hip osteoarthritis. The American Journal of Medicine. 1999;107(6):542-8.
44. Lohmander LS, De Verdier MG, Rollof J, Nilsson PM, Engström G. Incidence of severe knee and hip osteoarthritis in relation to different measures of body mass: a population-based prospective cohort study. Annals of the Rheumatic Diseases. 2009;68(4):490-6.
45. Toivanen AT, Heliövaara M, Impivaara O, Arokoski JP, Knekt P, Lauren H, et al. Obesity, physically demanding work and traumatic knee injury are major risk factors for knee osteoarthritis—a population-based study with a follow-up of 22 years. Rheumatology. 2010;49(2):308-14.
46. Pedroso MG, de Almeida AC, Aily JB, de Noronha M, Mattiello SM. Fatty infiltration in the thigh muscles in knee osteoarthritis: a systematic review and meta-analysis. Rheumatology International. 2019;39(4):627-35.

47. Kumar D, Karampinos DC, MacLeod TD, Lin W, Nardo L, Li X, et al. Quadriceps intramuscular fat fraction rather than muscle size is associated with knee osteoarthritis. Osteoarthritis and Cartilage. 2014;22(2):226-34.
48. Kumar D, Link TM, Jafarzadeh SR, LaValley MP, Majumdar S, Souza RB. Quadriceps adiposity is associated with increase in lesions of the knee cartilage, meniscus, or bone marrow over 3-years. Arthritis Care & Research. 2021;73(8):1134.
49. Raynauld JP, Pelletier JP, Roubille C, Dorais M, Abram F, Li W, et al. Magnetic resonance imaging–assessed vastus medialis muscle fat content and risk for knee osteoarthritis progression: relevance from a clinical trial. Arthritis Care & Research. 2015;67(10):1406-15.
50. Papalia R, Zampogna B, Torre G, Lanotte A, Vasta S, Albo E, et al. Sarcopenia and its relationship with osteoarthritis: risk factor or direct consequence? Musculoskeletal Surgery. 2014;98(1):9-14.
51. Ikemoto-Uezumi M, Matsui Y, Hasegawa M, Fujita R, Kanayama Y, Uezumi A, et al. Disuse atrophy accompanied by intramuscular ectopic adipogenesis in vastus medialis muscle of advanced osteoarthritis patients. The American Journal of Pathology. 2017;187(12):2674-85.
52. Teichtahl AJ, Wluka AE, Wang Y, Wijethilake PN, Strauss BJ, Proietto J, et al. Vastus medialis fat infiltration–a modifiable determinant of knee cartilage loss. Osteoarthritis and Cartilage. 2015;23(12):2150-7.
53. Meyer DC, Hoppeler H, von Rechenberg B, Gerber C. A pathomechanical concept explains muscle loss and fatty muscular changes following surgical tendon release. Journal of Orthopaedic Research. 2004;22(5):1004-7.
54. Goodpaster BH, Carlson CL, Visser M, Kelley DE, Scherzinger A, Harris TB, et al. Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. Journal of Applied Physiology. 2001;90(6):2157-65.
55. Yoshida Y, Marcus RL, Lastayo PC. Intramuscular adipose tissue and central activation in older adults. Muscle & Nerve. 2012;46(5):813-6.
56. Panagiotopoulos E, Strzelczyk P, Herrmann M, Scuderi G. Cadaveric study on static medial patellar stabilizers: the dynamizing role of the vastus medialis obliquus on medial patellofemoral ligament. Knee Surgery, Sports Traumatology, Arthroscopy. 2006;14(1):7-12.
57. Øiestad BE, Juhl CB, Culvenor AG, Berg B, Thorlund JB. Knee extensor muscle weakness is a risk factor for the development of knee osteoarthritis: an updated systematic review and meta-analysis including 46 819 men and women. British Journal of Sports Medicine. 2022;56(6):349-55.
58. Culvenor AG, Ruhdorfer A, Juhl C, Eckstein F, Øiestad BE. Knee extensor strength and risk of structural, symptomatic, and functional decline in knee osteoarthritis: a systematic review and meta-analysis. Arthritis Care & Research. 2017;69(5):649-58.
59. Jungmann PM, Baum T, Nevitt MC, Nardo L, Gersing AS, Lane NE, et al. Degeneration in ACL injured knees with and without reconstruction in relation to muscle size and fat content—data from the osteoarthritis initiative. PLOS One. 2016;11(12):e0166865.
60. Kim H-J, Lee J-H, Ahn S-E, Park M-J, Lee D-H. Influence of anterior cruciate ligament tear on thigh muscle strength and hamstring-to-quadriceps ratio: A meta-analysis. PLOS One. 2016;11(1):e0146234.
61. Øiestad BE, Engebretsen L, Storheim K, Risberg MA. Winner of the 2008 systematic review competition: knee osteoarthritis after anterior cruciate ligament injury. The American Journal of Sports Medicine. 2009;37(7):1434-43.

62. Murray D, Liddle A, Dodd C, Pandit H. Unicompartmental knee arthroplasty: is the glass half full or half empty? The Bone & Joint Journal. 2015;97(10_Supple_A):3-8.
63. Liddle AD, Judge A, Pandit H, Murray DW. Adverse outcomes after total and unicompartmental knee replacement in 101 330 matched patients: a study of data from the National Joint Registry for England and Wales. The Lancet. 2014;384(9952):1437-45.
64. Willis-Owen CA, Brust K, Alsop H, Miraldo M, Cobb JP. Unicondylar knee arthroplasty in the UK National Health Service: an analysis of candidacy, outcome and cost efficacy. The Knee. 2009;16(6):473-8.
65. Jones G, Kotti M, Wiik A, Collins R, Brevadt M, Strachan R, et al. Gait comparison of unicompartmental and total knee arthroplasties with healthy controls. The Bone & Joint Journal. 2016;98(10_Supple_B):16-21.
66. Wilson HA, Middleton R, Abram SG, Smith S, Alvand A, Jackson WF, et al. Patient relevant outcomes of unicompartmental versus total knee replacement: systematic review and meta-analysis. British Medical Journal. 2019;364.
67. Evans JT, Walker RW, Evans JP, Blom AW, Sayers A, Whitehouse MR. How long does a knee replacement last? A systematic review and meta-analysis of case series and national registry reports with more than 15 years of follow-up. The Lancet. 2019;393(10172):655-63.
68. Dagneaux L, Bourlez J, Degeorge B, Canovas F. Return to sport after total or unicompartmental knee arthroplasty: an informative guide for residents to patients. EFORT Open Reviews. 2017;2(12):496-501.
69. Hanreich C, Martelanz L, Koller U, Windhager R, Waldstein W. Sport and physical activity following primary total knee arthroplasty: a systematic review and meta-analysis. The Journal of Arthroplasty. 2020;35(8):2274-85. e1.
70. Waldstein W, Kolbitsch P, Koller U, Boettner F, Windhager R. Sport and physical activity following unicompartmental knee arthroplasty: a systematic review. Knee Surgery, Sports Traumatology, Arthroscopy. 2017;25(3):717-28.
71. Kuster MS, Stachowiak GW. Factors affecting polyethylene wear in total knee arthroplasty. Orthopedics. 2002;25(2):S235-S42.
72. Schmalzried TP, Shepherd EF, Dorey FJ, Jackson WO, dela Rosa M, McKellop HA, et al. Wear is a function of use, not time. Clinical Orthopaedics and Related Research. 2000;381:36-46.
73. Healy WL, Sharma S, Schwartz B, Iorio R. Athletic activity after total joint arthroplasty. Journal of Bone and Joint Surgery. 2008;90(10):2245-52.
74. D'Lima DD, Patil S, Steklov N, Slamin JE, Colwell Jr CW. Tibial forces measured in vivo after total knee arthroplasty. The Journal of Arthroplasty. 2006;21(2):255-62.
75. D'Lima DD, Steklov N, Patil S, Colwell CW. The Mark Coventry Award: in vivo knee forces during recreation and exercise after knee arthroplasty. Clinical Orthopaedics and Related Research. 2008;466(11):2605-11.
76. Andriacchi T, Andersson G, Fermier R, Stern D, Galante J. A study of lower-limb mechanics during stair-climbing. The Journal of Bone and Joint Surgery. 1980;62(5):749-57.
77. Dahlkvist N, Mayo P, Seedhom B. Forces during squatting and rising from a deep squat. Engineering in Medicine. 1982;11(2):69-76.
78. Ericson MO, Bratt A, Nisell R, Nemeth G, Ekholm J. Load moments about the hip and knee joints during ergometer cycling. Scandinavian Journal of Rehabilitation Medicine. 1986;18(4):165-72.
79. Winter DA. Moments of force and mechanical power in jogging. Journal of Biomechanics. 1983;16(1):91-7.

80. Crawford DA, Adams JB, Hobbs GR, Berend KR, Lombardi Jr AV. Higher activity level following total knee arthroplasty is not deleterious to mid-term implant survivorship. The Journal of Arthroplasty. 2020;35(1):116-20.
81. Crawford DA, Adams JB, Lombardi Jr AV, Berend KR. Activity level does not affect survivorship of unicondylar knee arthroplasty at 5-year minimum follow-up. The Journal of Arthroplasty. 2019;34(7):1364-8.
82. Mont MA, Marker DR, Seyler TM, Gordon N, Hungerford DS, Jones LC. Knee arthroplasties have similar results in high-and low-activity patients. Clinical Orthopaedics and Related Research. 2007;460:165-73.
83. Mayr HO, Reinhold M, Bernstein A, Suedkamp NP, Stoehr A. Sports activity following total knee arthroplasty in patients older than 60 years. The Journal of Arthroplasty. 2015;30(1):46-9.
84. Presti ML, Costa GG, Cialdella S, Agrò G, Grassi A, Caravelli S, et al. Return to sports after unicompartmental knee arthroplasty: reality or utopia? A 48-month follow-up prospective study. The Journal of Knee Surgery. 2019;32(02):186-91.
85. Argenson J-N, Boisgard S, Parratte S, Descamps S, Bercovy M, Bonnevialle P, et al. Survival analysis of total knee arthroplasty at a minimum 10 years' follow-up: a multicenter French nationwide study including 846 cases. Orthopaedics & Traumatology: Surgery & Research. 2013;99(4):385-90.
86. Lavernia CJ, Sierra RJ, Hungerford DS, Krackow K. Activity level and wear in total knee arthroplasty: a study of autopsy retrieved specimens. The Journal of Arthroplasty. 2001;16(4):446-53.
87. Ponzio DY, Chiu Y-F, Salvatore A, Lee Y-Y, Lyman S, Windsor RE. An analysis of the influence of physical activity level on total knee arthroplasty expectations, satisfaction, and outcomes: increased revision in active patients at five to ten years. Journal of Bone and Joint Surgery. 2018;100(18):1539-48.
88. Juhl C, Christensen R, Roos EM, Zhang W, Lund H. 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(3):622-36.
89. Roddy E, Zhang W, Doherty M, Arden N, Barlow J, Birrell F, et al. Evidence-based recommendations for the role of exercise in the management of osteoarthritis of the hip or knee—the MOVE consensus. Rheumatology. 2005;44(1):67-73.
90. Eitner A, Hofmann GO, Schaible H-G. Mechanisms of osteoarthritic pain. Studies in humans and experimental models. Frontiers in Molecular Neuroscience. 2017;10:349.
91. Rice D, Nijs J, Kosek E, Wideman T, Hasenbring MI, Koltyn K, et al. Exercise-induced hypoalgesia in pain-free and chronic pain populations: state of the art and future directions. The Journal of Pain. 2019;20(11):1249-66.
92. Sluka KA, Law LF, Bement MH. Exercise-induced pain and analgesia? Underlying mechanisms and clinical translation. Pain. 2018;159(Suppl 1):S91.
93. Srikandarajah S, Gilron I. Systematic review of movement-evoked pain versus pain at rest in postsurgical clinical trials and meta-analyses: a fundamental distinction requiring standardized measurement. Pain. 2011;152(8):1734-9.
94. Wideman TH, Finan PH, Edwards RR, Quartana PJ, Buenaver LF, Haythornthwaite JA, et al. Increased sensitivity to physical activity among individuals with knee osteoarthritis: relation to pain outcomes, psychological factors, and responses to quantitative sensory testing. Pain. 2014;155(4):703-11.

95. Arendt-Nielsen L. Pain sensitisation in osteoarthritis. Clinical and Experimental Rheumatology. 2017;35(Suppl 107):68-74.
96. Corbett DB, Simon CB, Manini TM, George SZ, Riley III JL, Fillingim RB. Movement-evoked pain: transforming the way we understand and measure pain. Pain. 2019;160(4):757.
97. Litcher-Kelly L, Martino SA, Broderick JE, Stone AA. A systematic review of measures used to assess chronic musculoskeletal pain in clinical and randomized controlled clinical trials. The Journal of Pain. 2007;8(12):906-13.
98. Wideman TH, Edwards RR, Finan PH, Haythornthwaite JA, Smith MT. Comparing the predictive value of task performance and task-specific sensitivity during physical function testing among people with knee osteoarthritis. Journal of Orthopaedic & Sports Physical Therapy. 2016;46(5):346-56.
99. Woznowski-Vu A, Aternali A, Gervais A, Pavilanis AD, Nijs J, Sullivan MJ, et al. The prospective prognostic value of biopsychosocial indices of sensitivity to physical activity among people with back pain. The Clinical Journal of Pain. 2021;37(10):719-29.
100. Woznowski-Vu A, Uddin Z, Flegg D, Aternali A, Wickens R, Sullivan MJ, et al. Comparing novel and existing measures of sensitivity to physical activity among people with chronic musculoskeletal pain. The Clinical Journal of Pain. 2019;35(8):656-67.
101. Harden RN, Wallach G, Gagnon CM, Zereshki A, Mukai A, Saracoglu M, et al. The osteoarthritis knee model: psychophysical characteristics and putative outcomes. The Journal of Pain. 2013;14(3):281-9.
102. Sullivan MJ, Larivière C, Simmonds M. Activity-related summation of pain and functional disability in patients with whiplash injuries. Pain. 2010;151(2):440-6.
103. Lambin DI, Thibault P, Simmonds M, Lariviere C, Sullivan MJ. Repetition-induced activity-related summation of pain in patients with fibromyalgia. Pain. 2011;152(6):1424-30.
104. Reid M. Sensitivity to Physical Activity: Identifying Important Predictors and Outcomes in Pain-Free Older Adults Using a Simple Activity-Related Measure. Pain Medicine. 2018;19(8):1512-3.
105. Cruz-Almeida Y, Cardoso J, Riley III JL, Goodin B, King CD, Petrov M, et al. Physical performance and movement-evoked pain profiles in community-dwelling individuals at risk for knee osteoarthritis. Experimental Gerontology. 2017;98:186-91.

# Preface to Chapter 3

Chapter 2 discussed the potential role of obesity, quadriceps muscle weakness and joint injury in knee OA pathogenesis through the creation of an abnormal loading environment at the knee. Considering there are differences in gait metrics between patients with non-traumatic and post-traumatic knee OA, the relationship between measures of disease progression (e.g., cartilage thickness) and knee joint loading (estimated via knee joint moments) might also differ between these knee OA subtypes. This has not been previously examined. A greater understanding of this relationship would provide valuable insight into the potential difference in mechanisms affecting disease progression between these OA subtypes. Therefore, a starting point in this thesis was to examine the relationship between external knee joint moments during gait and cartilage thickness, measured using MRI, in patients with non-traumatic and post-traumatic knee OA.

# Chapter 3: The relationship between knee loading during gait and cartilage thickness in non-traumatic and post-traumatic knee osteoarthritis

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## 3.1 Abstract

The relationship between knee moments and markers of knee OA progression have not been examined in different knee OA subtypes. The objective was to examine relationships between external knee moments during gait and tibiofemoral cartilage thickness in patients with non-traumatic and post-traumatic knee OA. For this cross-sectional study, participants with knee OA were classified into two groups: non-traumatic (n = 22; mean age: 60 years) and post-traumatic (n = 19; mean age: 56 years, history of anterior cruciate ligament rupture [ACL]). Gait data were collected with a 3D motion capture system sampled at 100 Hertz (Hz) and force plates sampled at 2000 Hz. External knee moments were calculated using inverse dynamics. Cartilage thickness was determined with magnetic resonance imaging (T1-weighted, 3D sagittal gradient echo sequence). Linear regression analyses examined relationships between cartilage thickness with knee moments, group, and their interaction. A higher knee adduction moment impulse was negatively associated with medial-to-lateral cartilage thickness ratio (B = -1.97). This relationship differed between participants in the non-traumatic OA group (r = -0.56) and post-traumatic OA group (r = -0.30). A higher late stance knee extension moment was associated with greater medial femoral condyle cartilage thickness (B = -0.86) and medial-to-lateral cartilage thickness (B = -0.73). These relationships also differed between participants in the non-traumatic OA group (r = -0.61 and r = -0.51, respectively) and post-traumatic OA group (r = 0.10 and r = 0.25, respectively).

**Clinical Significance**: The relationship between knee moments with tibiofemoral cartilage thickness differs between patients with non-traumatic and post-traumatic knee OA. The potential influence of mechanical knee loading on articular cartilage differs between these subtypes.

## 3.2 Introduction

OA is the most common joint disorder worldwide and is often associated with significant disability (1) with at least 19% of Americans aged 45 years and older being affected by knee OA (2). Medial knee joint loading has a role in knee OA progression (3). Specifically, the knee adduction moment (KAM) is a proxy for medial/lateral load distribution within the knee (4, 5). The KAM is associated with radiographic knee OA severity, where a higher KAM is associated with greater disease severity (6-8). Furthermore, a higher KAM is associated with longitudinal cartilage loss measured using MRI (9, 10) and radiographic knee OA progression (3) in patients with medial tibiofemoral knee OA.

The knee flexion moment (KFM) and extension moment (KEM) represent the net muscular contribution to the knee and have also been shown to play an important role in knee loading in individuals with knee OA. For instance, the KFM has been shown to influence medial knee joint contact forces (11, 12), and baseline KFM values were shown to predict 5-year tibiofemoral cartilage changes in individuals with medial compartment knee OA (10). However, another longitudinal study found no association between baseline peak KFM on any medial knee OA progression outcome measures after 2 years (13). Patients with severe knee OA also exhibit smaller knee extension angles and a reduced KEM in late stance when compared with asymptomatic individuals and older individuals with moderate knee OA (14). This has been hypothesized to be a compensatory strategy to increase knee joint stiffness and reduce the external load on the knee joint in individuals with knee OA (15). Consequently, further investigation is required to better understand how the KFM and KEM may impact knee OA-related cartilage changes.

Knee OA can be categorized as non-traumatic (patients with no history of a previous knee injury or trauma) or post-traumatic (OA diagnosed secondary to trauma, injury, surgery) (16).

Previous research suggests that there are differences in the structural changes that occur between non-traumatic and post-traumatic knee OA progression (16-19). Patients with knee OA and concomitant ACL tears have demonstrated more frequent OA-related findings in the lateral compartment, including increased denuded area and bone surface area, bone marrow lesions, and meniscal alterations, compared to patients with knee OA with an intact ACL (19). Radiographic findings such as joint space narrowing and osteophytes were found to be predominantly in the medial compartment of the knee joint in patients with non-traumatic knee OA, whereas it was found to be evenly distributed between medial and lateral compartments in patient with post-traumatic knee OA (16). Lastly, frontal plane knee kinetics during gait (20) and the relationship between knee alignment and cartilage thickness differ between patients with and non-traumatic and post-traumatic medial compartment knee OA (21). Therefore, differences in structural OA-related changes and knee mechanics exist between patients with non-traumatic and post-traumatic knee OA.

Considering there are differences in gait metrics between non-traumatic and post-traumatic knee OA, the relationship between measures of disease progression (e.g., cartilage thickness) and knee moments might also differ between these knee OA subtypes. This has not been previously examined. A greater understanding of this relationship would provide valuable insight into the potential difference in mechanisms affecting disease progression between these OA subtypes. The objective of this study was to examine the relationship between external knee joint moments (KAM, KFM, and KEM) during gait and cartilage thickness, measured using MRI, in patients with non-traumatic and post-traumatic knee OA. We hypothesized that the relationship between knee joint moments during gait and cartilage thickness would differ between participants with non-traumatic and post-traumatic knee OA.

## 3.3 Methods

### 3.3.1 Participants

This observational, cross-sectional study (level II evidence) recruited participants diagnosed with symptomatic knee OA, according to clinical criteria from the American College of Rheumatology (22). Participants were recruited from three tertiary hospitals in Montreal, Canada and the local community from January 2015 to March 2017. They were between the ages of 35 and 75. Exclusion criteria included knee trauma or surgery within the last 12 months, history of joint arthroplasty in the lower extremities, neurological conditions (e.g., previous stroke), severe cardiovascular conditions (e.g., angina pectoris), or any other conditions affecting gait. Participants were part of an ongoing longitudinal study (21, 23), and all available participants were analyzed for the current study. Participants provided written, informed consent before enrollment. Procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Jewish General Hospital) and with the Helsinki Declaration of 1975, as revised in 2000.

Participants that reported no previous knee trauma resulting in an ACL rupture were classified as non-traumatic OA (n = 22). Participants in the post-traumatic knee OA group (n = 19) had a history of ACL injury. This post-traumatic OA group included participants with an ACL deficiency (n = 9) or reconstructed ACL (n = 10). Other traumatic injuries (e.g., posterior cruciate ligament tear, isolated meniscal tear) were excluded from the study to ensure homogeneity. ACL status for all participants (injured, normal, and/or reconstructed) was confirmed on MRI by a fellowship trained, musculoskeletal radiologist with 8 years of experience. Participants provided

an estimate of when the ACL tear occurred. In patients with bilateral knee OA, the side with the most severe symptoms was selected based on participants' reporting of pain intensity.

Demographic variables were self-reported (i.e., age and sex) from participants (Table 3.1). Height was measured with a measuring tape and mass using a force plate. Pain was assessed using the Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP), which is a multidimensional, 11-item measure designed to comprehensively evaluate the pain experience in people with hip or knee OA. The ICOAP has demonstrated excellent test-retest reliability, internal consistency, and convergent validity with other instruments used to assess OA pain (24-26).

### 3.3.2 Radiographs

Participants underwent hip to ankle, anterior-posterior radiographs in standing. The participants stood barefoot, with feet and toes facing forward and the patella centered on the femoral condyles (27). Kellgren–Lawrence disease severity scores (0 = no OA to 4 = severe OA) provided a measure of disease severity (28).

### 3.3.3 Gait data collection

Gait was measured using an eight camera, motion capture system (OQUS 300 + , Qualisys) sampled at 100 Hz and two synchronized force plates (BP400600, AMTI) sampled at 2000 Hz. Marker and force plate data were captured with commercial software (Qualisys Track Manager, Qualisys). Similar procedures have previously demonstrated acceptable test-retest reliability (29, 30). Thirty-four reflective markers (12.7mm diameter) were placed on the participants according to guidelines (29). Eighteen individual markers were placed with adhesive tape over boney landmarks including: acromion, anterior and posterior superior iliac spines, femoral greater

trochanters and lateral epicondyles, lateral malleoli, first and fifth metatarsal heads, and calcanei. Four reflective marker clusters of four markers were also placed on the mid-shank and mid-thigh bilaterally using a Velcro strap. Six additional markers were placed bilaterally during static standing trials only to determine joint center position: femoral medial epicondyles, medial malleoli, and second metatarsal heads.

Data collection began with participants completing a standing trial on a force plate to identify knee and ankle joint centers and to measure body mass. Afterward, they completed two trials (one trial per side) to identify functional hip joint centers. These trials required participants to flex/extend and abduct/adduct their hip three times in each direction (31, 32). Before collecting gait trials, participants were allowed at least four practice gait trials to adjust to the environment. Participants were then required to walk barefoot, at self-selected speeds, along an 8-m walkway for seven successful trials for each leg. Participants were instructed to walk at their normal walking speed. A trial was deemed successful if an adequate force plate strike was achieved with one foot. Only five trials were processed. Additional trials were collected to account for potential errors.

### 3.3.4 Gait data processing

Data processing was completed using Visual3D (v 5.02, C-motion). Marker and force plate data were filtered with dual pass, Butterworth filters (fourth order) with cut-off frequencies of 6 Hz and 20 Hz, respectively. Inverse dynamics using Newton–Euler equations with previously published segment inertial properties were used to calculate net external knee moments (33). Moments were calculated about the knee joint coordinate system, amplitude normalized to body mass, and time normalized to 100% gait cycle. Gait parameters included peak KAM during early stance, peak KFM during early stance, and peak KEM in late stance. The KAM impulse during

stance was also determined from waveforms not normalized to 100% gait cycle. Gait speed was determined by tracking the speed of the posterior superior iliac spine markers. Discrete parameters were determined for each trial and averaged across five trials for each participant, and thus average values were used in subsequent statistical analyses.

### 3.3.5 Cartilage thickness measurement

Images of articular cartilage at the tibiofemoral joint were obtained with a 3-Tesla MRI system (GE Discovery MR750) with a knee coil. The sequence was a 3D sagittal T1* spoiled gradient-echo sequence with fat suppression (TR = 13 ms, TE = 4 ms, Number of excitations = 0.6, FoV = 160 mm, matrix = 512 × 512 pixels (Px), flip angle = 14°, Px bandwidth = 434 Hz/Px). To limit patient movement during the MRI, a strict immobilization protocol was used.

Cartilage thickness was determined according to a previously described and validated method, which has demonstrated excellent test-retest reliability (Pearson correlation coefficients of 0.97 for the global knee, 0.96 for the femur, and 0.83 for the tibia) with low measurement error (−0.3 ± 1.6% for the global knee, 0.14 ± 1.7% for the femur) (34). To briefly summarize, the bone was first segmented using a ray-casting approach (35), then the cartilage was quantified using a texture analysis process in a bone proximity resampled MRI image (34). For the bones (i.e., femur and tibia), the image was resampled in a polar coordinate system using a ray casting method following a coarse localization of the joint. The bone contours were localized along the radii using characteristics of a Gaussian of Laplacian filter. A spline surface representing the bone surface was built using the selected 3D positions. For the femur and tibia cartilage assessment, the MRI image was resampled perpendicularly to each surface independently. A texture analysis based on spatial gray level dependency properties allowed for the delineation of the cartilage-to-soft-tissues

interface while helping with the tuning of the bone-to-cartilage interface. Some final processing allowed for the consideration of fluid exclusion, and image inhomogeneity. Cartilage thickness was quantified for the following regions: medial femoral condyle, lateral femoral condyle, medial tibial plateau, and lateral tibial plateau. The ratio of medial:lateral cartilage thickness from these compartments was also determined. These regional cartilage thickness measures were chosen to increase the sensitivity to detect regional differences in cartilage thickness associated to different joint moments.

### 3.3.6 Statistical Analysis

Descriptive statistics were determined for each group for sample descriptors, discrete gait parameters, and cartilage thickness measures. An independent student t-test was used to compare the age, gait speed, and ICOAP between groups (non-traumatic and post-traumatic). A Welch test was used to compare body mass index (BMI) between groups given a statistically significant Levene test for homogeneity of variance. $\chi 2$ test compared Kellgren–Lawrence grades and sex proportions between groups.

Multiple regression analyses examined relationships between cartilage thickness measures (dependent variable) with gait parameters, OA group, and their interaction. Four analyses were conducted for each of the cartilage thickness measures. Each analysis varied in the gait parameter examined (peak KAM, KAM impulse, peak KFM, and peak KEM). Age, sex, BMI, and radiographic disease severity (Kellgren–Lawrence grades) were entered first, as covariates. Gait parameter and OA group (0 = non-traumatic and 1 = post-traumatic) were entered in the second and third steps, respectively. Next, their interaction was entered and was only retained if it was significant. Unstandardized regression coefficients (B) with 95% confidence intervals (CI) and

total explained variance ($R^2$) were reported. Statistical significance was set at $P < 0.05$. Appropriateness of the analyses was evaluated by examining data normality, residuals, and multicollinearity using histogram of residuals, plots of residuals, collinearity statistics, or variance proportions. Analyses were performed with SPSS (v24, IBM Corp).

## 3.4 Results

Participant demographics and group descriptors showed that there were no significant differences between groups for age, radiographic disease severity, gait speed, and pain (Table 3.1). However, significant differences were found between groups for BMI and sex in which the non-traumatic knee OA group had a greater mean BMI and higher proportion of women when compared with the post-traumatic OA group. Regression coefficients are provided in Table 3.2.

### 3.4.1 Peak KAM

Higher peak KAM was associated with lower medial femoral condyle cartilage thickness ($P = 0.01$), lower medial:lateral cartilage thickness ratio ($P < 0.01$), higher lateral femoral condyle cartilage thickness ($P = 0.02$), and higher lateral tibial plateau cartilage thickness ($P < 0.01$), after accounting for the covariates. For all five analyses, OA group and its interaction with peak KAM were not statistically significant. The explained variance ($R^2$) in cartilage thickness for the regression models ranged from 28% to 50%, depending on the regions evaluated (Table 3.2).

### 3.4.2 KAM Impulse

Higher KAM impulse was associated with lower medial femoral condyle cartilage thickness ($P = 0.04$), higher lateral femoral condyle cartilage thickness ($P = 0.04$), and higher

lateral tibial plateau cartilage thickness ($P$ = 0.02). For medial:lateral cartilage thickness, KAM impulse, OA group, and their interaction significantly explained the variance in the medial:lateral cartilage thickness ratio. Higher KAM impulse was associated with lower medial:lateral cartilage thickness ratio (r = −0.56) in the non-traumatic OA group, while this relationship was weaker in the post-traumatic OA group (r = −0.30, Figure 3.1). KAM impulse was not significantly associated with medial tibial plateau cartilage thickness ($P$ = 0.06). The explained variance ($R^2$) in cartilage thickness for the regression models ranged from 28% to 47%, depending on the regions evaluated (Table 3.2).

### 3.4.3 Peak KEM

Peak KEM, OA group, and their interaction significantly explained the variance in medial femoral condyle thickness. Peak KEM was negatively associated with medial femoral condyle cartilage thickness (r = −0.61) in the non-traumatic OA group, while this relationship was found to be weaker in the post-traumatic OA group (r = 0.10, Figure 3.2). Additionally, higher peak KEM was associated with lower medial:lateral cartilage thickness. The relationship with KEM was stronger in the non-traumatic (r = −0.51) than the post-traumatic OA group (r = 0.25, Figure 3.3). Peak KEM was not significantly associated with medial tibial plateau, lateral tibial plateau, or lateral femoral condyle cartilage thickness measures. The explained variance ($R^2$) in cartilage thickness for the regression models ranged from 20% to 46%, depending on the regions evaluated (Table 3.2).

### 3.4.4 Peak KFM

There were no statistically significant associations between peak KFM and regional cartilage thickness. OA group and their interaction did not significantly explain the variance in cartilage thickness (Table 3.2).

**Table 3.1.** Participant characteristics for individuals with non-traumatic and post-traumatic knee osteoarthritis.

| Measure | Non-Traumatic OA (n = 22) | Post-Traumatic OA (n = 19) | *P*-value |
|---|---|---|---|
| **Age (y)** | 60 (7) | 56 (9) | 0.191 |
| **Sex, n (%)** | | | |
| Men | 6 (27) | 11 (58) | **0.047** |
| Women | 16 (73) | 8 (42) | |
| **Body Mass Index (kg/m$^2$)** | 29.6 (7.5) | 26.0 (3.2) | **0.023** |
| **Gait Speed (m/s)** | 1.14 (0.14) | 1.23 (0.15) | 0.265 |
| **ICOAP** | | | |
| Constant Pain (/100) | 19 (24) | 16 (19) | 0.704 |
| Intermittent Pain (/100) | 31 (20) | 27 (21) | 0.512 |
| Total Score (/100) | 26 (21) | 22 (19) | 0.584 |
| **Radiographic Knee OA Severity, n (%)** | | | |
| Grade 1 | 2 (10) | 1 (5) | |
| Grade 2 | 6 (28) | 11 (58) | |
| Grade 3 | 8 (38) | 5 (26) | |
| Grade 4 | 5 (24) | 2 (11) | 0.297 |

Mean (with standard deviation [SD]) and number of participants (n) are provided for group descriptors. **ICOAP**: Intermittent and Constant Osteoarthritis Pain, **OA**: osteoarthritis. Significant associations ($P < 0.05$) are in bold. The *P*-value for Radiographic Knee OA severity is for all Kellgren-Lawrence grades.

**Table 3.2**. Associations between cartilage measures and knee joint moment, osteoarthritis group and their interaction (knee joint moment x osteoarthritis group).

| Gait Variable | Cartilage Region | Gait Variable B (95% CI) | OA Group B (95% CI) | Interaction B (95% CI) | Model Explained Variance ($R^2$) |
|---|---|---|---|---|---|
| Peak KAM | Med Femoral Condyle | **-0.58** (-1.02, -0.14) | -0.01 (-0.18, 0.15) | - | 41.7% |
| | Lat Femoral Condyle | **0.58** (0.10, 1.06) | 0.06 (-0.12, 0.24) | - | 34.1% |
| | Med Tibial Plateau | -0.50 (-1.02, 0.02) | -0.06 (-0.25, 0.13) | - | 27.5% |
| | Lat Tibial Plateau | **1.05** (0.35, 1.75) | -0.01 (-0.27, 0.26) | - | 36.9% |
| | Med:Lat Cartilage | **-0.67** (-0.97, -0.38) | -0.02 (-0.13, 0.09) | - | 49.5% |
| KAM Impulse | Med Femoral Condyle | **-1.13** (-2.24, -0.03) | -0.03 (-0.20, 0.14) | - | 37.6% |
| | Lat Femoral Condyle | **1.23** (0.05, 2.41) | 0.07 (-0.11, 0.25) | - | 31.5% |
| | Med Tibial Plateau | -1.21 (-2.46, 0.04) | -0.07 (-0.26, 0.13) | - | 27.5% |
| | Lat Tibial Plateau | **2.07** (0.30, 3.84) | 0.02 (-0.25, 0.29) | - | 31.1% |
| | Med:Lat Cartilage | **-1.97** (-2.92, -1.01) | **-0.27** (-0.52, -0.01) | **1.47** (0.01, 2.93) | 47% |
| Peak KFM | Med Femoral Condyle | -0.18 (-0.66, 0.29) | -0.05 (-0.23, 0.13) | - | 30.6% |
| | Lat Femoral Condyle | 0.28 (-0.23, 0.79) | 0.10 (-0.09, 0.29) | - | 24.9% |
| | Med Tibial Plateau | -0.20 (-0.74, 0.34) | -0.09 (-0.29, 0.11) | - | 20.3% |
| | Lat Tibial Plateau | 0.72 (-0.02, 1.47) | 0.07 (-0.21, 0.35) | - | 27.7% |
| | Med:Lat Cartilage | -0.34 (-0.70, 0.02) | -0.07 (-0.20, 0.07) | - | 25.5% |
| Peak KEM | Med Femoral Condyle | **-0.86** (-1.50, -0.22) | **0.42** (0.05, 0.79) | **1.42** (0.40, 2.44) | 45.9% |
| | Lat Femoral Condyle | 0.37 (-0.25, 0.99) | 0.10 (-0.09, 0.29) | - | 25.3% |
| | Med Tibial Plateau | -0.37 (-1.03, 0.28) | -0.09 (-0.29, 0.11) | - | 22.2% |
| | Lat Tibial Plateau | 0.22 (-0.74, 1.18) | 0.05 (-0.24, 0.34) | - | 19.7% |

| | | | | | |
|---|---|---|---|---|---|
| | Med:Lat Cartilage | **-0.73** (-1.23, -0.22) | 0.25 (-0.05, 0.54) | **0.94** (0.14, 1.75) | 35.9% |

**OA:** osteoarthritis, **KAM:** knee adduction moment, **KEM:** knee extension moment, **KFM:** knee flexion moment, **Med:** medial, **Lat:** lateral, **CI:** confidence interval. Age, sex, BMI and radiographic knee OA severity were controlled for in the regression analyses. Unstandardized coefficients (B) with 95% confidence intervals are provided. Significant associations ($P < 0.05$) are in bold. Only significant interactions were retained in the model.

**Figure 3.1**. Relationship between knee adduction moment impulse & medial:lateral cartilage thickness ratio. Non-traumatic osteoarthritis group (solid line, filled circles): r = -0.56. Post-traumatic osteoarthritis group (dashed line, empty circles): r = -0.30. Nm = Newton metre.

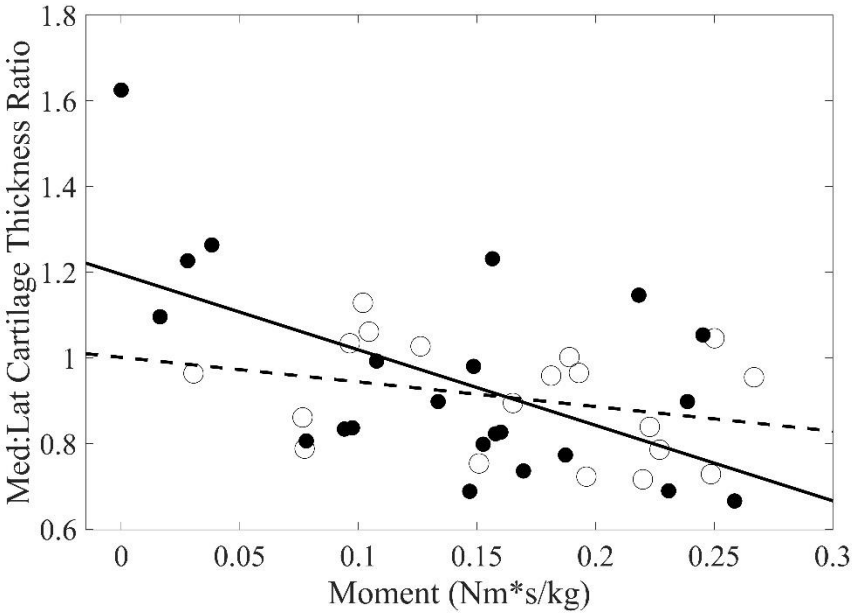


**Figure 3.2**. Relationship between peak knee extension moment & medial femoral condyle cartilage thickness. Non-traumatic osteoarthritis group (solid line, filled circles): r = -0.61. Post-traumatic osteoarthritis group (dashed line, empty circles): r = 0.10. Nm/kg = Newton metre per kilogram.

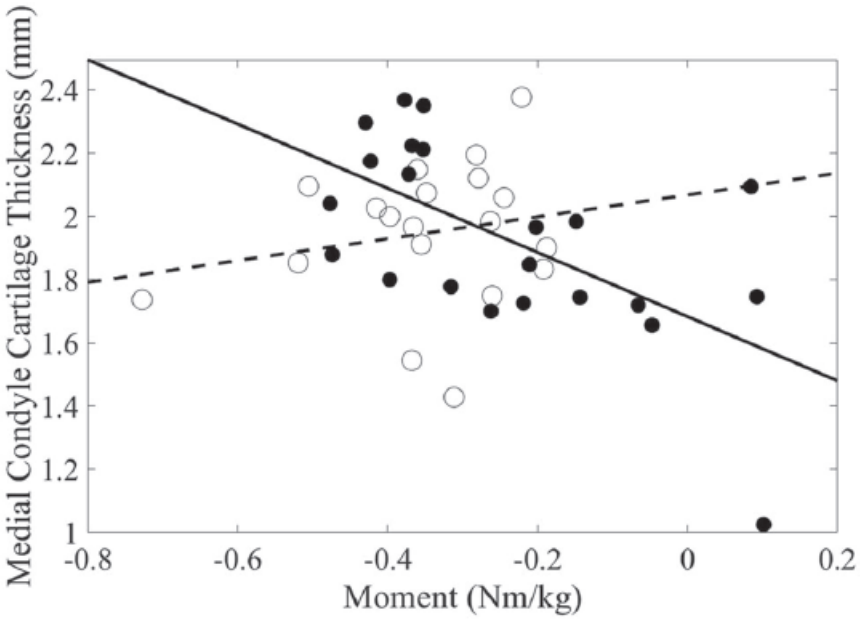
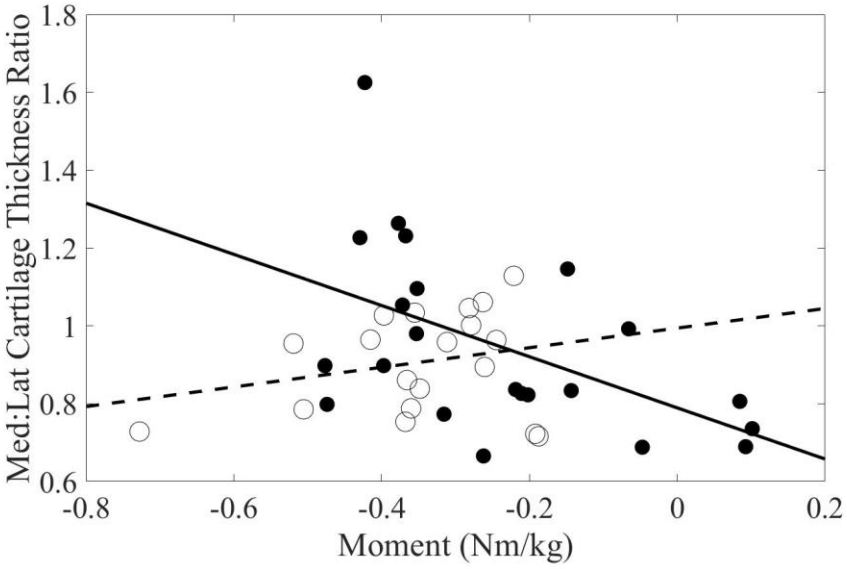


**Figure 3.3**. Relationship between peak knee extension moment & medial:lateral cartilage thickness ratio. Non-traumatic osteoarthritis group (solid line, filled circles): r = -0.51. Post-traumatic osteoarthritis group (dashed line, empty circles): r = 0.25. Nm/kg = Newton metre per kilogram.



## 3.5 Discussion

This study demonstrated that there is a relationship between knee mechanics during gait and cartilage thickness. Higher KAM values were related to lower medial compartment and higher lateral compartment cartilage thickness. Furthermore, the relationship between knee moments and cartilage thickness differed between non-traumatic and post-traumatic knee OA subtypes for the KAM impulse and peak KEM. Considering that the relationship between mechanical factors and knee OA progression differ between these OA subtypes, perhaps treatments that target these mechanical factors (e.g., tibial osteotomy) to slow OA progression should also differ.

The inverse relationship between the peak KAM and medial compartment cartilage thickness for both OA groups suggests that the peak KAM relates to medial tibiofemoral OA progression. This is consistent with previous studies examining the relationship between peak KAM and radiographic knee OA severity (8), radiographic knee OA progression (3), and cartilage thickness loss determined using MRI (10). However, other studies have demonstrated conflicting results (9, 36). This discrepancy could be explained by differences in the regions of cartilage thickness measured and the distribution of OA changes in the participants. Nonetheless, our data are concordant with the fact that an increase in medial knee joint loading has been shown to play a role in medial tibiofemoral OA progression (3). Given the KAM is a proxy for medial to lateral tibiofemoral compartment loading, a higher peak KAM would imply greater loading on the medial compartment. This could be detrimental in individuals with altered gait kinematics (i.e., individuals with knee OA or post knee injury), as a shift can occur in the contact location to cartilage regions not normally conditioned to increased loading. The inability of these cartilage regions to adapt to changes in load bearing could lead to degenerative changes in the medial tibiofemoral compartment (6). We also found a higher KAM impulse to be negatively associated

with the medial:lateral cartilage thickness ratio in the non-traumatic OA group, while this relationship was weaker in the post-traumatic OA group. Our findings could be explained by several factors. First, the relationship between the KAM impulse and cartilage thickness measures may vary based on the OA subtype. This would indicate that the influence of cumulative medial knee joint loading (i.e., KAM impulse) on articular cartilage, rather than the medial knee joint load magnitude (i.e., peak KAM), may differ between patients with non-traumatic and post-traumatic knee OA. Second, participants in the non-traumatic knee OA group had a significantly greater BMI than participants in the post-traumatic knee OA group. Previous research would suggest that higher dynamic knee joint loading and KAM impulse, but not peak KAM, is a significant risk factor for medial tibial cartilage volume loss (9). As a result, the altered loading patterns (37) and increased tibiofemoral compressive and shear contact forces and dynamic loads during gait (38) seen in patients with knee OA with a higher BMI may further contribute to medial knee OA progression. However, BMI was accounted for in statistical analyses. Lastly, the KAM impulse has been shown to be more sensitive at distinguishing between radiographic knee OA severities (39). Consequently, our results could be due to the fact that the non-traumatic OA group had a greater proportion of participants with moderate to severe radiographic knee OA. Although, radiographic disease severity was accounted for in our analyses. Longitudinal research is needed to better understand the potential influence of the peak KAM and KAM impulse on tibiofemoral cartilage thickness loss between individuals with non-traumatic and post-traumatic knee OA. A greater understanding of this relationship would provide valuable insight into if mechanisms affecting disease progression differ between these OA subtypes.

In addition, higher late stance KEM (i.e., more negative values) was associated with greater medial femoral condyle cartilage thickness and medial:lateral cartilage thickness ratio in the non-

traumatic OA group. This relationship was weaker in the post-traumatic OA group. The history of injury could account for these findings. Participants in the post-traumatic OA group may have continued to experience persistent alterations in lower extremity neuromuscular function and movement patterns post ACL injury or reconstruction, which would ultimately alter walking kinematics and knee joint loading patterns (40-42). Alternatively, the non-traumatic OA group had a greater proportion of participants with moderate or severe OA. This could potentially account for our findings, as greater OA severity has been associated with diminished late stance KEM (14, 43), although severity was accounted for in the analyses. Our findings may suggest that the role of the peak KEM on MRI measures of tibiofemoral cartilage thickness differs between individuals with non-traumatic and post-traumatic knee OA.

Lastly, the KFM was not associated with any regions of cartilage thickness. Longitudinal studies examining the relationship between baseline KFM and cartilage thickness measures demonstrate conflicting results (10, 13). Further research is needed to better understand the relationship between KEM/KFM and measures of cartilage thickness in individuals with non-traumatic and post-traumatic knee OA.

This study has limitations. First, this study was cross-sectional and does not allow for the inference of causal relationships. Second, between-group differences in sex and BMI may have confounded the results. However, these factors were accounted for in the analyses. Third, the post-traumatic knee OA group consisted of both participants with a ruptured ACL and participants with a surgically reconstructed ACL to increase the sample size. However, this is less of a concern, given ACL reconstruction does not decrease knee OA prevalence (44), nor fully restore normal knee joint kinematics when compared with ACL-deficient knees (45). Lastly, our results are not

generalizable to patients with other traumatic knee injuries (i.e., posterior cruciate ligament tear, meniscal tear in isolation, etc.).

To conclude, relationships existed between peak KAM, KAM impulse, and peak KEM during gait with regional tibiofemoral cartilage thickness. In addition, the relationship between KAM impulse and peak KEM with regional tibiofemoral cartilage thickness was dependent on the OA subtype (non-traumatic vs. post-traumatic knee OA). The influence of knee joint moments on regional cartilage thickness in patients with non-traumatic and post-traumatic knee OA had not been previously examined. As a result, our findings provide new insight into the pathomechanics of knee OA and support the hypothesis that the potential influence of mechanical knee loading on articular cartilage differs between patients with non-traumatic and post-traumatic knee OA. This has important implications for clinical practice. For instance, addressing alterations in walking kinematics and knee joint loading patterns between patients with non-traumatic and post-traumatic knee OA may warrant different treatment approaches and should be explored further. Future research should also examine the longitudinal influence of gait kinematics and kinetics on indicators of disease progression in both knee OA subtypes.

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**Declaration of Competing Interest**

Jean-Pierre Pelletier and Johanne Martel-Pelletier are shareholders in ArthroLab Inc; company assessing the MRI images. Mr. Teoli provides continuing education courses on knee osteoarthritis best practice for rehabilitation professionals. The remaining authors have nothing to disclose.

## 3.6 Chapter 3 References


1. Litwic A, Edwards MH, Dennison EM, Cooper C. Epidemiology and burden of osteoarthritis. British Medical Bulletin. 2013;105(1):185-99.
2. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part II. Arthritis & Rheumatism. 2008;58(1):26-35.
3. Miyazaki T, Wada M, Kawahara H, Sato M, Baba H, Shimada S. Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. Annals of the Rheumatic Diseases. 2002;61(7):617-22.
4. Andriacchi TP. Dynamics of knee malalignment. Orthopedic Clinics of North America. 1994;25(3):395-403.
5. Zhao D, Banks SA, Mitchell KH, D'Lima DD, Colwell Jr CW, Fregly BJ. Correlation between the knee adduction torque and medial contact force for a variety of gait patterns. Journal of Orthopaedic Research. 2007;25(6):789-97.
6. Andriacchi TP, Mündermann A, Smith RL, Alexander EJ, Dyrby CO, Koo S. A framework for the in vivo pathomechanics of osteoarthritis at the knee. Annals of Biomedical Engineering. 2004;32(3):447-57.
7. Mündermann A, Dyrby CO, Hurwitz DE, Sharma L, Andriacchi TP. Potential strategies to reduce medial compartment loading in patients with knee osteoarthritis of varying severity: reduced walking speed. Arthritis & Rheumatism. 2004;50(4):1172-8.
8. Sharma L, Hurwitz DE, Thonar EJM, Sum JA, Lenz ME, Dunlop DD, et al. Knee adduction moment, serum hyaluronan level, and disease severity in medial tibiofemoral osteoarthritis. Arthritis & Rheumatism. 1998;41(7):1233-40.
9. Bennell KL, Bowles K-A, Wang Y, Cicuttini F, Davies-Tuck M, Hinman RS. Higher dynamic medial knee load predicts greater cartilage loss over 12 months in medial knee osteoarthritis. Annals of the Rheumatic Diseases. 2011;70(10):1770-4.
10. Chehab EF, Favre J, Erhart-Hledik JC, Andriacchi TP. Baseline knee adduction and flexion moments during walking are both associated with 5 year cartilage changes in patients with medial knee osteoarthritis. Osteoarthritis and Cartilage. 2014;22(11):1833-9.
11. Trepczynski A, Kutzner I, Bergmann G, Taylor WR, Heller MO. Modulation of the relationship between external knee adduction moments and medial joint contact forces across subjects and activities. Arthritis & Rheumatology. 2014;66(5):1218-27.
12. Walter JP, D'Lima DD, Colwell Jr CW, Fregly BJ. Decreased knee adduction moment does not guarantee decreased medial contact force during gait. Journal of Orthopaedic Research. 2010;28(10):1348-54.
13. Chang AH, Moisio KC, Chmiel JS, Eckstein F, Guermazi A, Prasad PV, et al. External knee adduction and flexion moments during gait and medial tibiofemoral disease progression in knee osteoarthritis. Osteoarthritis and Cartilage. 2015;23(7):1099-106.
14. Favre J, Erhart-Hledik JC, Andriacchi TP. Age-related differences in sagittal-plane knee function at heel-strike of walking are increased in osteoarthritic patients. Osteoarthritis and Cartilage. 2014;22(3):464-71.
15. Messier SP, Gutekunst DJ, Davis C, DeVita P. Weight loss reduces knee-joint loads in overweight and obese older adults with knee osteoarthritis. Arthritis & Rheumatism. 2005;52(7):2026-32.

16. Swärd P, Kostogiannis I, Neuman P, Von Porat A, Boegård T, Roos H. Differences in the radiological characteristics between post-traumatic and non-traumatic knee osteoarthritis. Scandinavian Journal of Medicine & Science in Sports. 2010;20(5):731-9.
17. Nishimori M, Deie M, Adachi N, Kanaya A, Nakamae A, Motoyama M, et al. Articular cartilage injury of the posterior lateral tibial plateau associated with acute anterior cruciate ligament injury. Knee Surgery, Sports Traumatology, Arthroscopy. 2008;16:270-4.
18. Scarvell JM, Smith PN, Refshauge KM, Galloway HR, Woods KR. Association between abnormal kinematics and degenerative change in knees of people with chronic anterior cruciate ligament deficiency: a magnetic resonance imaging study. Australian Journal of Physiotherapy. 2005;51(4):233-40.
19. Stein V, Li L, Lo G, Guermazi A, Zhang Y, Kent Kwoh C, et al. Pattern of joint damage in persons with knee osteoarthritis and concomitant ACL tears. Rheumatology International. 2012;32:1197-208.
20. Robbins SM, Birmingham TB, Jones IC, Sischek EL, Dietzsch M, Giffin JR. Comparison of gait characteristics between patients with nontraumatic and posttraumatic medial knee osteoarthritis. Arthritis Care & Research. 2016;68(9):1215-23.
21. Robbins S, Abram F, Boily M, Pelletier J-P, Martel-Pelletier J. Relationship between alignment and cartilage thickness in patients with non-traumatic and post-traumatic knee osteoarthritis. Osteoarthritis and Cartilage. 2019;27(4):630-7.
22. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis & Rheumatism. 1986;29(8):1039-49.
23. Robbins SM, Morelli M, Martineau PA, St-Onge N, Boily M, Dimentberg R, et al. A comparison of muscle activation and knee mechanics during gait between patients with non-traumatic and post-traumatic knee osteoarthritis. Osteoarthritis and Cartilage. 2019;27(7):1033-42.
24. Hawker G, Davis A, French M, Cibere J, Jordan J, March L, et al. Development and preliminary psychometric testing of a new OA pain measure–an OARSI/OMERACT initiative. Osteoarthritis and Cartilage. 2008;16(4):409-14.
25. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual analog scale for pain (vas pain), numeric rating scale for pain (nrs pain), mcgill pain questionnaire (mpq), short-form mcgill pain questionnaire (sf-mpq), chronic pain grade scale (cpgs), short form-36 bodily pain scale (sf-36 bps), and measure of intermittent and constant osteoarthritis pain (icoap). Arthritis Care & Research. 2011;63(S11):S240-S52.
26. Manolarakis GE, Kontodimopoulos N, Sifaki-Pistolla D, Niakas D. Establishing the psychometric properties of the ICOAP questionnaire through intra-articular treatment of osteoarthritic pain: implementation for the Greek version. Arthritis. 2016;2016.
27. Specogna AV, Birmingham TB, DaSilva JJ, Milner JS, Kerr J, Hunt MA, et al. Reliability of lower limb frontal plane alignment measurements using plain radiographs and digitized images. The journal of Knee Surgery. 2004;17(04):203-10.
28. JS KJL. Radiological assessment of osteo-arthrosis. Annals of the Rheumatic Diseases. 1957;164:494-502.
29. Collins TD, Ghoussayni SN, Ewins DJ, Kent JA. A six degrees-of-freedom marker set for gait analysis: repeatability and comparison with a modified Helen Hayes set. Gait & Posture. 2009;30(2):173-80.

30. Robbins SM, Wilson JLA, Rutherford DJ, Hubley-Kozey CL. Reliability of principal components and discrete parameters of knee angle and moment gait waveforms in individuals with moderate knee osteoarthritis. Gait & Posture. 2013;38(3):421-7.
31. Begon M, Monnet T, Lacouture P. Effects of movement for estimating the hip joint centre. Gait & Posture. 2007;25(3):353-9.
32. Besier TF, Sturnieks DL, Alderson JA, Lloyd DG. Repeatability of gait data using a functional hip joint centre and a mean helical knee axis. Journal of Biomechanics. 2003;36(8):1159-68.
33. Dempster WT. Space requirements of the seated operator, geometrical, kinematic, and mechanical aspects of the body with special reference to the limbs. WADC Technical Report. Wright-Patterson Air Force, OH; 1955.
34. Dodin P, Pelletier J-P, Martel-Pelletier J, Abram F. Automatic human knee cartilage segmentation from 3-D magnetic resonance images. IEEE Transactions on Biomedical Engineering. 2010;57(11):2699-711.
35. Dodin P, Martel-Pelletier J, Pelletier J-P, Abram F. A fully automated human knee 3D MRI bone segmentation using the ray casting technique. Medical & Biological Engineering & Computing. 2011;49:1413-24.
36. Vanwanseele B, Eckstein F, Smith R, Lange A, Foroughi N, Baker M, et al. The relationship between knee adduction moment and cartilage and meniscus morphology in women with osteoarthritis. Osteoarthritis and Cartilage. 2010;18(7):894-901.
37. Griffin TM, Guilak F. The role of mechanical loading in the onset and progression of osteoarthritis. Exercise and Sport Sciences Reviews. 2005;33(4):195-200.
38. Harding GT, Dunbar MJ, Hubley-Kozey CL, Stanish WD, Wilson JLA. Obesity is associated with higher absolute tibiofemoral contact and muscle forces during gait with and without knee osteoarthritis. Clinical Biomechanics. 2016;31:79-86.
39. Kean CO, Hinman RS, Bowles KA, Cicuttini F, Davies-Tuck M, Bennell KL. Comparison of peak knee adduction moment and knee adduction moment impulse in distinguishing between severities of knee osteoarthritis. Clinical Biomechanics. 2012;27(5):520-3.
40. Gardinier ES, Manal K, Buchanan TS, Snyder-Mackler L. Gait and neuromuscular asymmetries after acute ACL rupture. Medicine and Science in Sports and Exercise. 2012;44(8):1490.
41. Kuenze CM, Hertel J, Weltman A, Diduch D, Saliba SA, Hart JM. Persistent neuromuscular and corticomotor quadriceps asymmetry after anterior cruciate ligament reconstruction. Journal of Athletic Training. 2015;50(3):303-12.
42. Otzel DM, Chow JW, Tillman MD. Long-term deficits in quadriceps strength and activation following anterior cruciate ligament reconstruction. Physical Therapy in Sport. 2015;16(1):22-8.
43. Astephen JL, Deluzio KJ, Caldwell GE, Dunbar MJ. Biomechanical changes at the hip, knee, and ankle joints during gait are associated with knee osteoarthritis severity. Journal of Orthopaedic Research. 2008;26(3):332-41.
44. Harris KP, Driban JB, Sitler MR, Cattano NM, Balasubramanian E, Hootman JM. Tibiofemoral osteoarthritis after surgical or nonsurgical treatment of anterior cruciate ligament rupture: a systematic review. Journal of Athletic Training. 2017;52(6):507-17.
45. Gao B, Zheng NN. Alterations in three-dimensional joint kinematics of anterior cruciate ligament-deficient and-reconstructed knees during walking. Clinical Biomechanics. 2010;25(3):222-9.

# Preface to Chapter 4

There has also been growing interest in local measures of adiposity, such as intermuscular fat (between muscles and beneath fascia) and intramuscular fat (stored within the muscle), and how they may influence OA status and clinical outcomes in patients with knee OA. More specifically, previous research would suggest that VM intramuscular fat is a modifiable determinant of knee cartilage loss. Further studies are needed to determine whether VM intramuscular fat differs between patients with knee OA and healthy adults, and to clarify the relationship between VM intramuscular fat with radiographic knee OA severity and quadriceps muscle strength. In addition, our findings from Chapter 3 suggested that the potential influence of mechanical knee loading on articular cartilage differs between patients with non-traumatic and post-traumatic knee OA. However, there is minimal research comparing thigh intramuscular fat between different knee OA subtypes, including non-traumatic and post-traumatic knee OA. Therefore, we aimed to: 1) compare VM intramuscular fat between knee OA subtypes and healthy adults and 2) estimate the extent to which VM intramuscular fat relates to OA severity and quadriceps muscle strength in patients with non-traumatic and post-traumatic knee OA.

# Chapter 4: Vastus medialis intramuscular fat is associated with reduced quadriceps strength, but not knee osteoarthritis severity

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## 4.1 Abstract

**Background**: VM intramuscular fat has been proposed to be a modifiable determinant of knee cartilage loss in patients with knee OA. The objective was to determine whether VM intramuscular fat relates to OA severity and quadriceps muscle strength in patients with non-traumatic and post-traumatic knee OA.

**Methods**: For this cross-sectional study, participants with knee OA were classified into two groups: non-traumatic (n = 22; mean age = 60 years) and post-traumatic (n = 19; mean age = 56 years). Healthy adults were included (n = 22; mean age = 59 years). A 3-Tesla magnetic resonance imaging was used to measure VM cross-sectional area and intramuscular fat. Isometric knee extensor muscle torque was assessed using an isokinetic dynamometer and normalized to body mass (Nm/kg). Knee OA severity was assessed using standing antero-posterior radiographs (Kellgren-Lawrence scores). Regression analyses examined relationships between 1) VM intramuscular fat with knee OA severity and OA group, after accounting for sex and body mass index, and 2) knee extensor muscle torque with VM intramuscular fat, after accounting for sex and VM cross-sectional area.

**Findings**: VM intramuscular fat was positively associated with body mass index (B = 0.321, $P < 0.001$), but not with OA severity or group ($P > 0.05$). Higher VM intramuscular fat was associated with reduced knee extensor muscle torque (B = -0.040, $P = 0.018$).

**Interpretation**: Greater VM intramuscular fat was associated with lower quadriceps muscle strength in patients with knee OA. It is unclear whether this is due to the accumulation of VM intramuscular fat or other potential factors, such as diet and physical inactivity.

## 4.2 Introduction

Obesity is a modifiable risk factor for knee OA and is an important contributor to the increasing prevalence of knee OA (1, 2). Mechanisms linking obesity with the increased risk of developing knee OA are multifactorial, involving both mechanical (i.e., increased joint load) and systemic factors (i.e., production and release of cytokines and adipokines by adipose tissue which promote low-grade systemic inflammation) (3). Consequently, there has been extensive research examining how global measures of adiposity (e.g., BMI) relate to knee joint health (4-6).

There has also been growing interest in local measures of adiposity, such as intermuscular fat (between muscles and beneath fascia) and intramuscular fat (stored within the muscle) (7), and how they may influence OA status and clinical outcomes in patients with knee OA (8-17). A recent systematic review and meta analysis demonstrated that patients with knee OA had greater thigh intermuscular (n = 6 studies) and intramuscular (n = 1 study) fat content compared to individuals without knee OA (7). Sarcopenia is thought to be accelerated in individuals with knee OA and quadriceps muscle atrophy is hypothesized to be followed by an increase in fat infiltration, in part due to physical inactivity and disuse secondary to joint pain (18). This is consistent with previous research demonstrating an association between higher quadriceps intramuscular fat with worse pain and physical function in patients with knee OA (13). Similarly, women with advanced knee OA demonstrated greater ectopic adipogenesis in the VM muscle following disuse atrophy when compared to women without knee OA (19).

There is also evidence to suggest that quadriceps intramuscular fat (particularly VM intramuscular fat) relates to OA status and cartilage measures. Higher quadriceps intramuscular fat fractions have been shown to be associated with radiographic disease severity (13). VM intramuscular fat was associated with cartilage loss, as well as the occurrence and progression of

bone marrow lesions over a 2-year period (16). Similarly, VM intramuscular fat (but not intramuscular fat of other quadriceps muscles) was associated with increased cartilage, meniscus, and bone marrow lesions after 3 years, after accounting for age, sex and BMI (14). Furthermore, reducing VM intramuscular fat via lifestyle interventions, such as exercise and weight loss, has been shown to have a beneficial effect on knee cartilage preservation in healthy adults (20).

Intramuscular quadriceps adiposity has been linked to knee OA pathogenesis via several potential mechanisms. The release of proinflammatory cytokines by intramuscular fat may disrupt knee joint cartilage homeostasis, leading to further OA progression (21). Intramuscular fat can also alter muscle metabolism (22) and change fiber orientation (23), potentially leading to impaired muscle function, reduced knee joint stability and abnormal knee joint loading. This is consistent with previous research demonstrating that greater thigh intramuscular fat is associated with an impairment in neuromuscular activation and decreased quadriceps strength in healthy adults (24) and older adults (25), although previous studies in patients with knee OA report conflicting findings (19). The VM muscle also has an important role in functional knee stability (26) and reduced quadriceps muscle strength is a risk factor for the development (27) and progression (28) of knee OA. Consequently, VM intramuscular fat may impact knee joint structure and muscle function and warrants further investigation. Given the paucity of studies conducted on the topic (7), further studies are necessary to determine whether VM intramuscular fat differs between patients with knee OA and healthy adults, and to clarify the relationship between VM intramuscular fat with radiographic knee OA severity and quadriceps muscle strength.

There is also minimal research comparing thigh intramuscular fat between different knee OA subtypes, including non-traumatic and post-traumatic knee OA (29). Impairments in muscle strength and activation occur in patients with knee OA (27) or after a knee trauma (30). However,

it is unclear if impairments in muscle function may be explained by potential differences in intramuscular fat content between patients with knee OA with or without a history of knee trauma (e.g., ligament rupture). Considering that previous knee trauma is a major risk factor for knee OA initiation and progression (31), the relationship between disease severity and intramuscular fat might also vary between these OA subtypes.

The objectives of this study were to: 1) compare VM intramuscular fat between knee OA subtypes and healthy adults and 2) estimate the extent to which VM intramuscular fat relates to OA severity and quadriceps muscle strength in patients with non-traumatic and post-traumatic knee OA. We hypothesized that patients with knee OA would have a greater proportion (%) of VM intramuscular fat when compared to healthy adults, and that increased VM intramuscular fat would be associated with worse radiographic knee OA severity and reduced quadriceps muscle strength in patients with knee OA.

## 4.3 Methods

### 4.3.1 Participants

This study used an observational, cross-sectional design (level II evidence) and adhered to the STROBE statement guidelines for cross-sectional studies (32). Participants with knee OA were recruited from three tertiary hospitals in Montreal, Canada and the local community from January 2015 to March 2017. Knee OA diagnosis was determined using the clinical criteria from the American College of Rheumatology (33).

Participants with knee OA were classified into two groups: non-traumatic and post-traumatic, defined as a history of ACL confirmed on MRI done within the context of the study, and not at the time of ACL injury. An experienced radiologist confirmed ACL status for all

participants using MRI. Participants provided an estimate of when the ACL tear occurred. For participants with bilateral knee OA, participants were asked to select the knee with the greatest pain intensity over the last month. Exclusion criteria for the participants with knee OA included knee trauma or surgery within the last 12 months, history of joint arthroplasty in the lower extremities, neurological conditions (e.g., previous stroke), severe cardiovascular conditions (e.g., angina pectoris), or any other conditions affecting gait. Participants with a self-report history of other traumatic knee injuries (e.g., knee ligament tear other than the ACL or meniscal tear) that did not occur at the time of ACL injury were excluded. Healthy adults were recruited for comparison. Exclusion criteria for the healthy participants included the same exclusion criteria listed above, as well as a diagnosis of lower extremity OA (33) or current lower extremity pain. The study limb was randomly selected by healthy participants by choosing one of two folded papers, which concealed the words "left" or "right". Participants were part of an ongoing longitudinal study (34). All available participants were analyzed for the current study. Participants provided written, informed consent prior to enrollment. Procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Jewish General Hospital, Montreal, Canada) and with the Helsinki Declaration of 1964, as revised in 2000.

Demographic variables were self-reported (i.e., age, sex) from participants. Height and mass were measured with a measuring tape and a force plate, respectively. BMI was calculated from these values. Pain was assessed using the constant pain and intermittent pain subscales of the ICOAP (35). Subscale scores were transformed to a score ranging from 0 (severe knee problems) to 100 (no knee problems) (36).

### 4.3.2 Vastus medialis cross-sectional area & intramuscular fat

MRI acquisitions of the VM muscle were obtained using a 3T MRI (GE Discovery MR750) with a T1-weighted axial spin echo sequence; slice thickness: 3 mm, repetition time (TR): 450 ms, echo time (TE): 12 ms, Px bandwidth: 100–150 kHz, flip angle: 140°. VM cross-sectional area and intramuscular fat were determined with commercial software (Arthrolab Inc., Montreal, Quebec, Canada) as previously described (16), with a modification. The modification was that the MR images did not need to be reformatted from sagittal to axial since the acquisition was made in axial. The VM was segmented by trained expert readers by drawing a contour along muscle boundaries, which was followed by a fully automated optimization, selection, and quantification of VM area and fat area. First, a filtering of the segmented region was performed to reduce segmentation noise. For this purpose, the analysis of 1 pixel around the segmented region allowed for a threshold to be computed, expressed as a means intensity, to determine the peripheral pixels to be filtered out providing an optimized segmented VM region. The area ($mm^2$) of the VM region was then computed from its number of pixels. Next, the segmentation of fat structures is completed. Fat pixels were defined by using a threshold which was computed as the point of greatest distance to the solid line of the dark side of the distribution in the normalized histogram of the VM region histogram. The fat area ($mm^2$) was then computed from the number of pixels of the fat structures. The area of the fat structures was normalized by computing the fat proportion as a percentage of fat in the VM (%fat), in which the number of pixels of fat structures was divided by the number of pixels of the VM region. The VM segmentation process delineates the whole VM muscle present in the MRI field of view (FoV). However, the assessment of VM muscle cross-sectional area and fat proportion were performed using the two most proximal selected slices. The selection of the slices was made from most to least proximal in accordance with trans-patient and per-patient rules: selected slices must be contiguous and show a comparable, good quality. The

VM area and %fat were then computed from the information available in these selected slices. Previous research has demonstrated low error estimation for VM area (0.6 $cm^2$) and VM %fat (0.6%) (16). An example of VM muscle and fat segmentation is provided in Appendix 1.1.

### 4.3.3 Maximum voluntary isometric contractions

Participants completed a series of maximum voluntary isometric contractions (MVICs) using an isokinetic dynamometer (Humac Cybex NORM, Computer Sports Medicine Inc., Massachusetts, United States). A similar protocol has demonstrated good test-retest reliability in patients with knee OA (37). For this study, only knee extensor torque (Nm) was explored. Participants performed a seated knee extension MVIC with 45° of knee flexion. The thigh was secured with Velcro straps, the resistance pad was placed distally on the shin, above the medial malleolus, and the lateral femoral epicondyle was aligned with the axis of the dynamometer lever arm. Each participant completed one practice trial, followed by two 5-second MVIC trials with a 30-second rest period between trials. Participants were instructed to provide maximal effort. Standardized verbal encouragement was provided throughout the MVIC trial. A 4th order recursive Butterworth filter with a 10 Hz cut-off frequency filtered torque data. The maximum torque for each MVIC trial was identified using a 500 ms moving-average window. The highest of the two torque values was used as the isometric torque for the MVIC exercise and was normalized to body mass (Nm/kg).

### 4.3.4. Radiographs

Participants in the OA groups underwent standing hip to ankle, anterior-posterior radiographs. Participants stood barefoot, with feet and toes facing forward and the patella centered

on the femoral condyles (38). Kellgren-Lawrence (KL) disease severity scores (0 = no OA to 4 = severe OA) provided a measure of disease severity (39).

### 4.3.5 Statistical Analysis

Descriptive statistics were determined for each group for sample descriptors, OA status and radiographic knee OA measures. One-way analysis of variance (ANOVA) with modified Bonferroni corrections compared age, BMI, knee extensor muscle torque, VM muscle cross-sectional area, VM %fat and ICOAP scores between groups (healthy, non-traumatic OA, post-traumatic OA). Chi-squared tests compared sex proportions and KL grades between groups.

Pearson's correlations examined relationships between VM %fat, knee extensor muscle torque, VM cross-sectional area, age and BMI. Relationships between these variables with sex and radiographic knee OA severity were investigated using point-biserial correlation ($r_{pb}$) and Kendall's $\tau$ (due to the large number of tied ranks) (40), respectively. The relationship between sex and radiographic knee OA severity was examined using a chi-squared test of independence with Cramer's V statistic.

Multiple regression analyses examined relationships between VM %fat (dependent variable) with radiographic OA severity (0 = KL grades 1–2 [doubtful/mild], 1 = KL grades 3–4 [moderate/severe]) and OA group, after accounting for sex (41) and BMI (5). Sex and BMI were entered on the first step. OA group (0 = non-traumatic, 1 = post-traumatic), radiographic OA severity and their interaction were entered on the second, third and fourth step, respectively. Potential interactions between OA group and radiographic OA severity were only retained if statistically significant. Due to our sample size, radiographic knee OA severity was transformed into a dichotomous variable to limit the number of dummy variables in the regression analysis.

Additionally, multiple regression analyses examined the relationship between knee extensor muscle torque (dependent variable) with VM %fat in the participants with knee OA, after accounting for sex (0 = female, 1 = male) (41) and VM muscle cross-sectional area (42). Although BMI was not accounted for, knee extensor muscle torque was normalized to body mass (kg). This was done to limit the number of variables included in the model. Sex and VM muscle cross-sectional area were entered on the first step, followed by VM %fat on the second step. Statistical significance for analyses was set at $P < 0.05$. For regression analyses, unstandardized regression coefficients (B) with 95% CI were provided. Total explained variance ($R^2$) for the regression models were also reported. Appropriateness of the analyses was evaluated by examining data normality, residuals and multicollinearity using histogram of residuals, plots of residuals, collinearity statistics, or variance proportions. The presence of potential outliers and high leverage data points, and their potential influence on regression models, were assessed. Analyses were performed with SPSS (v24, IBM Corp, New York, United States).

## 4.4 Results

Participant demographics and group descriptors can be found in Table 4.1. Participants with knee OA were classified into two groups: non-traumatic (n = 22) and post-traumatic (n = 19). In the post-traumatic knee OA group, 9 participants did not have ACL reconstruction following ACL injury (5 partial ACL tears and 4 complete ACL tears), and 10 participants had reconstructed ACLs. The mean time from initial ACL injury was 24 years (standard deviation [SD]: 12 years). Furthermore, 3 participants in the post-traumatic knee OA group had evidence of a previous partial knee ligament tear (1 posterior cruciate ligament, 1 lateral collateral ligament, 1 medial collateral ligament) on their MRI. Healthy adults (n = 22) were recruited for comparison. One participant in

the non-traumatic OA group refused to undergo radiographs and consequently, did not have a KL-score. One participant in the healthy group and non-traumatic knee OA group had missing data for knee extensor muscle torque due to a malfunction of the equipment. Their data were excluded from relevant analyses.

There were statistically significant between-group differences in ICOAP constant pain scores (F = 6.683, $P = 0.002$), ICOAP intermittent pain scores (F = 15.324, $P < 0.001$) and VM %fat (F = 3.401, $P = 0.040$). However, no significant difference in VM %fat between groups was observed once adjustments were done for multiple pairwise comparisons using Bonferroni corrections (*P*-value range: 0.080 to 1.000). ICOAP constant and intermittent pain scores in the non-traumatic ($P = 0.004$ and $P < 0.001$, respectively) and post-traumatic ($P = 0.020$ and $P < 0.001$, respectively) OA groups remained significantly greater when compared to healthy adults, but did not differ between OA groups ($P = 1.000$ for both). There were no other statistically significant differences between groups ($P > 0.05$).

Results of the correlational analyses can be found in Appendix 1.2. VM intramuscular fat was associated with knee extensor muscle torque (r = -0.455, $P = 0.003$) and BMI (r = 0.640, $P < 0.001$). Knee extensor muscle torque was associated with VM muscle cross-sectional area (r = 0.448, $P = 0.004$), age (r = -0.453, $P = 0.003$), sex ($r_{pb} = 0.427$, $P = 0.006$) and BMI (r = -0.374, $P = 0.017$).

Results for the multiple regression analyses are provided in Tables 4.2 and 4.3. Multiple regression analyses examining the relationship between VM %fat (dependent variable) with radiographic OA severity (KL grades) and OA group (Table 4.2) revealed no significant associations between VM %fat with OA group ($P = 0.857$) or radiographic OA severity ($P = 0.329$). The interaction between OA group and radiographic OA severity was not statistically

significant ($P$ = 0.263) and was not retained in the final model. There was a significant positive association between BMI and VM %fat ($P$ < 0.001), whereby a higher VM %fat was associated with a higher BMI (Figure 4.1). Total explained variance ($R^2$) in VM %fat for the regression model was 48%, with sex and BMI accounting for most of the variance.

Multiple regression analyses examining the relationship between knee extensor muscle torque (dependent variable) and VM %fat in participants with knee OA (Table 4.3) revealed that a higher VM %fat was significantly associated with a reduction in knee extensor muscle torque ($P$ = 0.018, Figure 4.2). There were no significant associations between knee extensor muscle torque with sex ($P$ = 0.568) or VM muscle cross-sectional area ($P$ = 0.140). Total explained variance ($R^2$) in knee extensor muscle torque for the regression model was 34%.

There were no influential outliers in the regression models (Cook's distance <1) (40). However, there were two high leverage data points (values >2 times the average leverage) (40) for each regression model. Regression analyses were conducted a second time without high leverage data points. The high leverage data points were retained, as they did not appear to strongly influence the results. A comparison of regression analyses with and without high leverage data points can be found in Appendix 1.3 and Appendix 1.4, respectively.

**Table 4.1.** Participant characteristics for healthy and knee osteoarthritis groups.

| Measure | Healthy (n = 22) | Non-Traumatic Knee OA (n = 22) | Post-Traumatic Knee OA (n = 19) | *P* |
|---|---|---|---|---|
| **Age (y)** | 59 (7) | 60 (7) | 56 (9) | 0.354 |
| **Sex, n (%)** | | | | |
| Men | 6 (27) | 6 (27) | 11 (58) | 0.068 |
| Women | 16 (73) | 16 (73) | 8 (42) | |
| **BMI (kg/m$^2$)** | 27.0 (4.6) | 29.6 (7.5) | 26.0 (3.2) | 0.093 |
| **VM intramuscular fat infiltration (%fat)** | 4.3 (2.2) | 6.3 (4.0) | 4.2 (2.0) | **0.040** |
| **VM muscle cross-sectional area (mm$^2$)** | 1194 (488) | 1098 (365) | 1420 (499) | 0.077 |
| **Knee Extensor Muscle Torque (Nm/kg)*** | 1.2 (0.4) | 1.1 (0.4) | 1.2 (0.3) | 0.335 |
| **ICOAP** | | | | |
| Constant Pain (/100) | 0 (0) | 18 (24) | 17 (19) | **0.002** |
| Intermittent Pain (/100) | 3 (8) | 31 (21) | 28 (20) | **<0.001** |
| **Radiographic Knee OA Severity, n (%)*** | | | | |
| Grade 1 | N/A | 2 (10) | 1 (5) | 0.297 |
| Grade 2 | | 6 (28) | 11 (58) | |
| Grade 3 | | 8 (38) | 5 (26) | |
| Grade 4 | | 5 (24) | 2 (11) | |

Mean (with standard deviation [SD]) and number of participants (n) are provided for group descriptors, unless otherwise noted. **OA**: osteoarthritis, **BMI**: body mass index, **VM**: vastus medialis, **ICOAP**: Intermittent and Constant Osteoarthritis Pain. Significant differences are in bold ($P < 0.05$).*One participant from the non-traumatic OA group was missing a KL-score. One participant in the healthy group and one participant in the non-traumatic OA group were missing data on knee extensor muscle torque.

**Table 4.2.** Unstandardized regression coefficients examining the relationship between vastus medialis intramuscular fat with osteoarthritis group and radiographic knee osteoarthritis severity (n = 40).

| | Sex<br>B (95% CI) | BMI<br>B (95% CI) | Knee OA Group*<br>B (95% CI) | Radiographic Knee OA Severity<br>B (95% CI) |
|---|---|---|---|---|
| Vastus Medialis Intramuscular Fat | -1.512<br>(-3.298, 0.274) | **0.321**<br>**(0.173, 0.469)** | -0.167<br>(-2.040, 1.705) | 0.857<br>(-0.902, 2.617) |

Unstandardized coefficients (B) with 95% confidence intervals (CI) are provided. Sex (0 = females, males = 1) and body mass index (BMI) were accounted for in the regression model. Significant associations are in bold ($P < 0.05$). Only significant interactions were retained in the model. **OA**: osteoarthritis. Units for VM intramuscular fat are in percent (%) fat. *One participant from the non-traumatic OA group was missing a KL-score.

**Table 4.3.** Unstandardized regression coefficients examining the between body weight normalized knee extensor muscle torque with vastus medialis intramuscular fat and vastus medialis muscle cross-sectional area (n = 40).

| | Sex<br>B (95% CI) | VM Cross-sectional Area<br>B (95% CI) | VM Intramuscular Fat<br>B (95% CI) |
|---|---|---|---|
| Knee Extensor Muscle Torque* | 0.086<br>(-0.218, 0.391) | <0.001<br>(0.000, 0.001) | **-0.040**<br>**(-0.072, -0.007)** |

Unstandardized coefficients (B) with 95% confidence intervals are provided. Sex (0 = females, males = 1) and vastus medialis (VM) muscle cross-sectional area were accounted for in the regression analyses. Significant associations are in bold ($P < 0.05$). Units for VM cross-sectional area and intramuscular fat are in $mm^2$ and percent (%) fat, respectively. *One participant in the non-traumatic OA group was missing data on knee extensor muscle torque.

**Figure 4.1.** The relationship between vastus medialis intramuscular fat and body mass index in participants with knee osteoarthritis (n = 41), r = 0.640, $P < 0.001$.

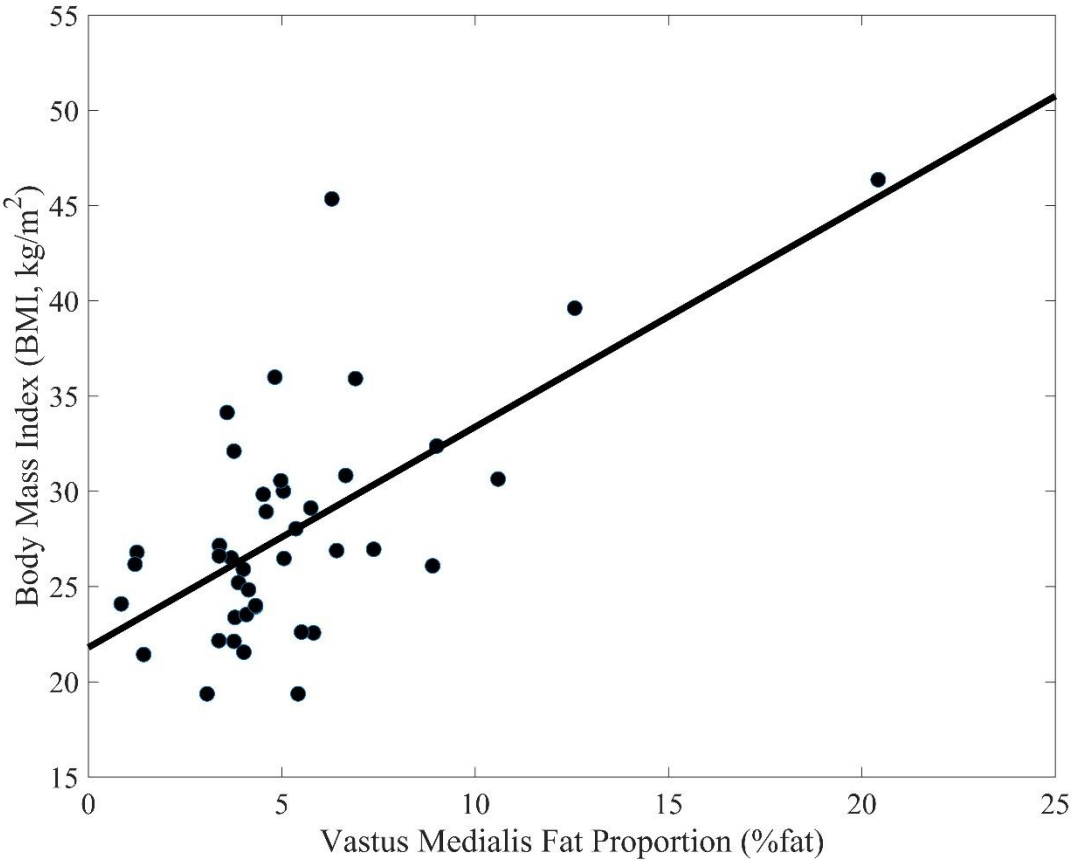
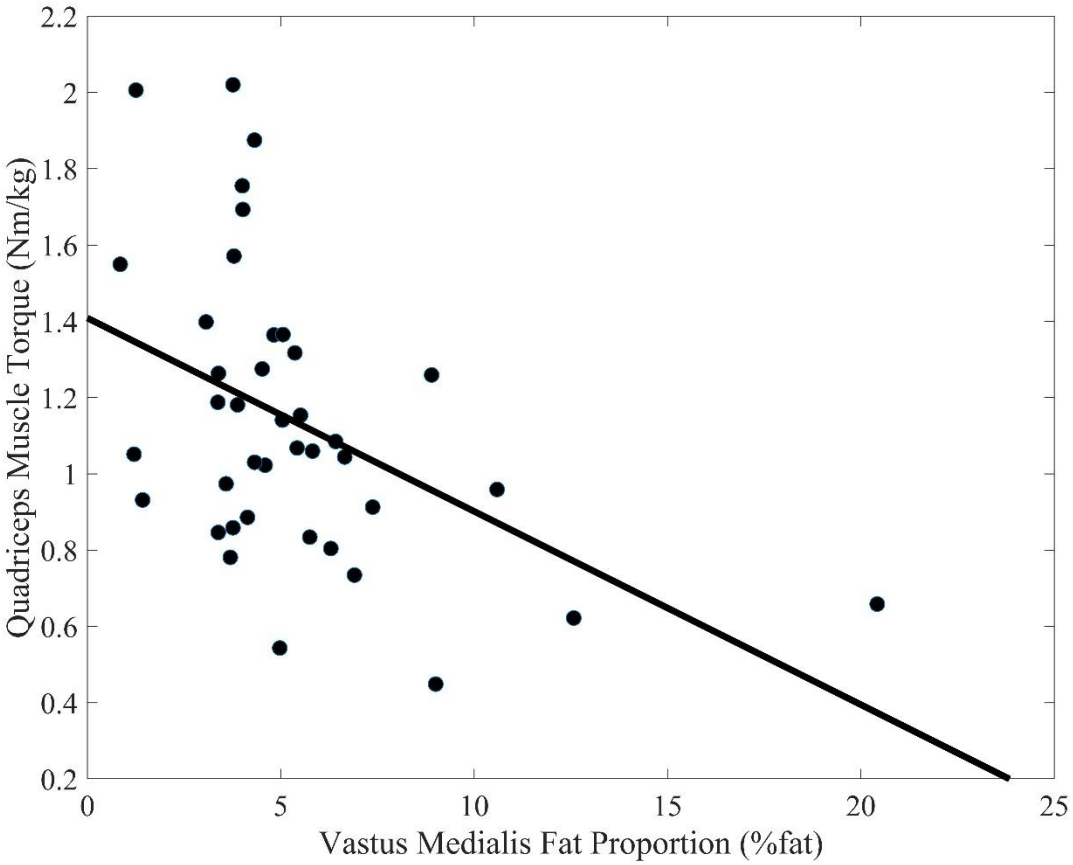


**Figure 4.2.** The relationship between body weight-normalized knee extensor muscle torque and vastus medialis intramuscular fat in participants with knee osteoarthritis (n = 40), r = -0.455, *P* = 0.003.



## 4.5 Discussion

The main findings of this study are: 1) VM %fat did not differ between patients with non-traumatic knee OA, post-traumatic knee OA and healthy participants; 2) higher VM %fat was associated with a higher BMI and lower knee extensor muscle torque, but not with radiographic knee OA severity. The findings of this study are novel and contribute to the growing body of research examining the potential influence of thigh muscle intramuscular fat on OA status and clinical outcomes in patients with knee OA.

Our results would suggest that VM intramuscular fat does not differ between patients with knee OA and healthy participants, nor between knee OA subtypes. There was a 2% difference in VM %fat between the non-traumatic knee OA group and the post-traumatic knee OA and healthy groups. This difference may be explained by the higher BMI in the non-traumatic knee OA group compared to the post-traumatic knee OA group (mean difference: -3.6 $kg/m^2$) and healthy participants (mean difference: -2.6 $kg/m^2$). This observation is supported by the strong correlation between VM %fat and BMI in our knee OA sample ($r = 0.640$, $P < 0.001$). Our findings are contrary to a previous study demonstrating greater quadriceps intramuscular fat fractions in patients with knee OA ($P = 0.018$) (13), despite the difference in groups being similar (1.5% vs. 2% in our study). Nonetheless, it is unclear the magnitude of the difference between groups that would be considered clinically meaningful. The Goutallier classification system has been used to qualitatively evaluate muscle fat infiltration (43). Previous research in patients undergoing rotator cuff repair has suggested a Goutallier Grade of 2 (fat is evident but is less than muscle tissue) or more to be pathological (43). However, little research has examined the application of this classification system in the thigh muscles of patients with knee OA (29). Further research is needed to determine whether thigh intramuscular fat differs between healthy adults and patients with knee

OA (and between knee OA subtypes), and to determine whether this difference is clinically meaningful.

We also observed no statistically significant association between VM %fat with radiographic severity, regardless of OA subtype. These findings contrast with a previous study demonstrating a weak association (r = 0.25, *P* = 0.002) between quadriceps intramuscular fat with radiographic knee OA severity (13). However, correlation analyses did not consider potential confounding factors such as age, sex and BMI, which could have influenced this relationship (13). Additionally, the OA group consisted predominantly of patients with moderate-to-severe OA (13), whereas our study sample consisted of patients with predominantly mild-to-moderate knee OA. Thus, studying a more severe knee OA population could have demonstrated a stronger relationship between VM intramuscular fat and OA severity. Furthermore, greater VM intramuscular fat has been shown to be associated with increased cartilage loss and bone marrow lesions over a 2-year (16) and 3-year period (14). The KL Classification System and the MRI assessment of cartilage provide different measures of OA severity (44), potentially explaining the discrepancy in study findings (13, 14, 16). Nonetheless, it remains unclear as to whether greater VM intramuscular fat found in patients with knee OA is a contributing factor to knee OA progression (14, 16), or simply a consequence of disuse and age-related muscle changes (sarcopenia) (18, 19).

Lastly, higher VM %fat was associated with lower knee extensor muscle torque after accounting for sex and VM cross-sectional area. A loss in muscle strength may be explained by a reduction in muscle mass (i.e., reduced anatomical cross-sectional area) or by a loss in muscle quality (i.e., limited central neural activation of the muscle fibers) (18). Given VM cross-sectional area was accounted for in regression analyses, the inverse relationship between knee extensor muscle torque and VM intramuscular fat may be better explained by reduced quadriceps muscle

quality and impairment in quadriceps muscular function due to the accumulation of VM intramuscular fat. The release of pro-inflammatory cytokines by intramuscular adipose tissue may impair normal muscle function (22, 23), leading to abnormal loading patterns and an increased susceptibility to joint damage and failure to repair. These findings are consistent with previous research demonstrating an association between thigh intramuscular fat and an impairment in neuromuscular activation and muscle strength in healthy adults (24) and older adults (25, 45). This is important, considering reduced quadriceps muscle strength is a risk factor for the development (27) and progression (28) of knee OA. Therefore, VM (and quadriceps) intramuscular fat may be a potential target for therapeutic interventions. Interventions such as exercise and weight loss can reduce VM intramuscular fat and improve muscle quality via hypertrophy, which may in turn help to restore optimal VM (and quadriceps) muscle function, enhance knee joint stability and minimize subsequent knee OA progression (20). However, the relationship between thigh intramuscular fat and thigh muscle strength has not been corroborated in patients with knee OA (12, 13). A previous study in twenty women with knee OA found no association between quadriceps or hamstrings intramuscular fat fraction with knee extensor or flexor strength or power, after controlling for mean peak muscle activation (12). This discrepancy with our findings could be explained by between-study differences in the sample (i.e., only women were included in their study) and the method of measuring intramuscular fat (i.e., in their study, a region-growing algorithm was used whereby fat compartments were analyzed sequentially) (12). Interestingly, knee extensor and flexor power (but not peak isometric torque) were positively associated with quadriceps and hamstrings lean muscle mass (12), suggesting that maintaining lean muscle tissue may help preserve muscle power in patients with knee OA, regardless of intramuscular fat content. Further research is needed to clarify whether impairments in muscle strength and power in the knee OA population are due to the

accumulation of thigh intramuscular fat, the loss of lean muscle mass, other factors (physical inactivity, pain, joint effusion), or a combination thereof.

We acknowledge that this study has limitations. This study was cross-sectional and does not allow for the inference of causal relationships. The post-traumatic OA group included participants with a partially or fully torn ACL and participants with a reconstructed ACL. Although surgical status was not accounted for due to our small sample size, lower limb strength deficits have been shown to persist for years following an ACL injury, regardless of surgical status (30, 46). Furthermore, functional outcomes, as well as radiographic knee OA prevalence and severity are similar at 5 years follow-up (47) and 20 years follow-up (48), regardless of operative or non-operative treatment for an ACL tear. Additionally, the small sample size and predominantly mild to moderate knee OA severity in our sample may have limited our ability to detect a statistically significant relationship between VM intramuscular fat and radiographic OA severity. Lastly, given the sample size in our study, other factors that may affect knee extensor muscle torque in patients with knee OA, such as age (18) and pain (49), were not accounted for in regression analyses.

## 4.6 Conclusions

In conclusion, VM intramuscular fat did not differ between patients with non-traumatic knee OA, post-traumatic knee OA and healthy adults. In addition, VM intramuscular fat may impair quadriceps muscle strength in patients with knee OA. However, additional work is needed to determine whether VM intramuscular fat relates to longitudinal measures of disease progression apart from global measures of adiposity (e.g., BMI) and to shed light on whether changes in thigh intramuscular fat influence changes in muscle strength and function in patients with knee OA.

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**Declaration of Competing Interest**

Jean-Pierre Pelletier and Johanne Martel-Pelletier are shareholders in ArthroLab Inc.; the company assessing the MRI images. François Abram is an employee of ArthroLab Inc. Mr. Teoli provides continuing education courses on knee osteoarthritis best practice for rehabilitation professionals. All remaining authors have no conflicts of interest to disclose.

## 4.7 Chapter 4 References


1. Deshpande BR, Katz JN, Solomon DH, Yelin EH, Hunter DJ, Messier SP, et al. Number of persons with symptomatic knee osteoarthritis in the US: impact of race and ethnicity, age, sex, and obesity. Arthritis Care & Research. 2016;68(12):1743-50.
2. Zheng H, Chen C. Body mass index and risk of knee osteoarthritis: systematic review and meta-analysis of prospective studies. BMJ Open. 2015;5(12):e007568.
3. Berenbaum F, Wallace IJ, Lieberman DE, Felson DT. Modern-day environmental factors in the pathogenesis of osteoarthritis. Nature Reviews Rheumatology. 2018;14(11):674-81.
4. Gelber AC, Hochberg MC, Mead LA, Wang N-Y, Wigley FM, Klag MJ. Body mass index in young men and the risk of subsequent knee and hip osteoarthritis. The American Journal of Medicine. 1999;107(6):542-8.
5. Lohmander LS, De Verdier MG, Rollof J, Nilsson PM, Engström G. Incidence of severe knee and hip osteoarthritis in relation to different measures of body mass: a population-based prospective cohort study. Annals of the Rheumatic Diseases. 2009;68(4):490-6.
6. Toivanen AT, Heliövaara M, Impivaara O, Arokoski JP, Knekt P, Lauren H, et al. Obesity, physically demanding work and traumatic knee injury are major risk factors for knee osteoarthritis—a population-based study with a follow-up of 22 years. Rheumatology. 2010;49(2):308-14.
7. Pedroso MG, de Almeida AC, Aily JB, de Noronha M, Mattiello SM. Fatty infiltration in the thigh muscles in knee osteoarthritis: a systematic review and meta-analysis. Rheumatology International. 2019;39(4):627-35.
8. Beattie KA, MacIntyre NJ, Ramadan K, Inglis D, Maly MR. Longitudinal changes in intermuscular fat volume and quadriceps muscle volume in the thighs of women with knee osteoarthritis. Arthritis Care & Research. 2012;64(1):22-9.
9. Chopp-Hurley JN, Wiebenga EG, Bulbrook BD, Keir PJ, Maly MR. Evaluating the relationship between quadriceps muscle quality captured using ultrasound with clinical severity in women with knee osteoarthritis. Clinical Biomechanics. 2020;80:105165.
10. Conroy MB, Kwoh CK, Krishnan E, Nevitt MC, Boudreau R, Carbone LD, et al. Muscle strength, mass, and quality in older men and women with knee osteoarthritis. Arthritis Care & Research. 2012;64(1):15-21.
11. Dannhauer T, Ruhdorfer A, Wirth W, Eckstein F. Quantitative relationship of thigh adipose tissue with pain, radiographic status, and progression of knee osteoarthritis: longitudinal findings from the osteoarthritis initiative. Investigative Radiology. 2015;50(4):268-74.
12. Davison MJ, Maly MR, Keir PJ, Hapuhennedige SM, Kron AT, Adachi JD, et al. Lean muscle volume of the thigh has a stronger relationship with muscle power than muscle strength in women with knee osteoarthritis. Clinical Biomechanics. 2017;41:92-7.
13. Kumar D, Karampinos DC, MacLeod TD, Lin W, Nardo L, Li X, et al. Quadriceps intramuscular fat fraction rather than muscle size is associated with knee osteoarthritis. Osteoarthritis and Cartilage. 2014;22(2):226-34.
14. Kumar D, Link TM, Jafarzadeh SR, LaValley MP, Majumdar S, Souza RB. Quadriceps adiposity is associated with increase in lesions of the knee cartilage, meniscus, or bone marrow over 3-years. Arthritis Care & Research. 2021;73(8):1134.
15. Maly MR, Calder KM, MacIntyre NJ, Beattie KA. Relationship of intermuscular fat volume in the thigh with knee extensor strength and physical performance in women at risk of or with knee osteoarthritis. Arthritis Care & Research. 2013;65(1):44-52.

16. Raynauld JP, Pelletier JP, Roubille C, Dorais M, Abram F, Li W, et al. Magnetic resonance imaging–assessed vastus medialis muscle fat content and risk for knee osteoarthritis progression: relevance from a clinical trial. Arthritis Care & Research. 2015;67(10):1406-15.
17. Ruhdorfer A, Wirth W, Dannhauer T, Eckstein F. Longitudinal (4 year) change of thigh muscle and adipose tissue distribution in chronically painful vs painless knees–data from the Osteoarthritis Initiative. Osteoarthritis and Cartilage. 2015;23(8):1348-56.
18. Papalia R, Zampogna B, Torre G, Lanotte A, Vasta S, Albo E, et al. Sarcopenia and its relationship with osteoarthritis: risk factor or direct consequence? Musculoskeletal Surgery. 2014;98(1):9-14.
19. Ikemoto-Uezumi M, Matsui Y, Hasegawa M, Fujita R, Kanayama Y, Uezumi A, et al. Disuse atrophy accompanied by intramuscular ectopic adipogenesis in vastus medialis muscle of advanced osteoarthritis patients. The American Journal of Pathology. 2017;187(12):2674-85.
20. Teichtahl AJ, Wluka AE, Wang Y, Wijethilake PN, Strauss BJ, Proietto J, et al. Vastus medialis fat infiltration–a modifiable determinant of knee cartilage loss. Osteoarthritis and Cartilage. 2015;23(12):2150-7.
21. Wang X, Hunter D, Xu J, Ding C. Metabolic triggered inflammation in osteoarthritis. Osteoarthritis and Cartilage. 2015;23(1):22-30.
22. Heilbronn L, Smith S, Ravussin E. Failure of fat cell proliferation, mitochondrial function and fat oxidation results in ectopic fat storage, insulin resistance and type II diabetes mellitus. International Journal of Obesity. 2004;28(4):S12-S21.
23. Meyer DC, Hoppeler H, von Rechenberg B, Gerber C. A pathomechanical concept explains muscle loss and fatty muscular changes following surgical tendon release. Journal of Orthopaedic Research. 2004;22(5):1004-7.
24. Inhuber S, Sollmann N, Schlaeger S, Dieckmeyer M, Burian E, Kohlmeyer C, et al. Associations of thigh muscle fat infiltration with isometric strength measurements based on chemical shift encoding-based water-fat magnetic resonance imaging. European Radiology Experimental. 2019;3(1):1-10.
25. Yoshida Y, Marcus RL, Lastayo PC. Intramuscular adipose tissue and central activation in older adults. Muscle & Nerve. 2012;46(5):813-6.
26. Panagiotopoulos E, Strzelczyk P, Herrmann M, Scuderi G. Cadaveric study on static medial patellar stabilizers: the dynamizing role of the vastus medialis obliquus on medial patellofemoral ligament. Knee Surgery, Sports Traumatology, Arthroscopy. 2006;14(1):7-12.
27. Øiestad B, Juhl C, Eitzen I, Thorlund J. Knee extensor muscle weakness is a risk factor for development of knee osteoarthritis. A systematic review and meta-analysis. Osteoarthritis and Cartilage. 2015;23(2):171-7.
28. Culvenor AG, Ruhdorfer A, Juhl C, Eckstein F, Øiestad BE. Knee extensor strength and risk of structural, symptomatic, and functional decline in knee osteoarthritis: a systematic review and meta-analysis. Arthritis Care & Research. 2017;69(5):649-58.
29. Jungmann PM, Baum T, Nevitt MC, Nardo L, Gersing AS, Lane NE, et al. Degeneration in ACL injured knees with and without reconstruction in relation to muscle size and fat content—data from the osteoarthritis initiative. PLOS One. 2016;11(12):e0166865.
30. Kim H-J, Lee J-H, Ahn S-E, Park M-J, Lee D-H. Influence of anterior cruciate ligament tear on thigh muscle strength and hamstring-to-quadriceps ratio: A meta-analysis. PLOS One. 2016;11(1):e0146234.

31. Øiestad BE, Engebretsen L, Storheim K, Risberg MA. Winner of the 2008 systematic review competition: knee osteoarthritis after anterior cruciate ligament injury. The American Journal of Sports Medicine. 2009;37(7):1434-43.
32. Erik von Elm M, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Annals of Internal Medicine. 2007;147(8):573.
33. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis & Rheumatism. 1986;29(8):1039-49.
34. Robbins SM, Morelli M, Martineau PA, St-Onge N, Boily M, Dimentberg R, et al. A comparison of muscle activation and knee mechanics during gait between patients with non-traumatic and post-traumatic knee osteoarthritis. Osteoarthritis and Cartilage. 2019;27(7):1033-42.
35. Hawker G, Davis A, French M, Cibere J, Jordan J, March L, et al. Development and preliminary psychometric testing of a new OA pain measure–an OARSI/OMERACT initiative. Osteoarthritis and Cartilage. 2008;16(4):409-14.
36. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual analog scale for pain (vas pain), numeric rating scale for pain (nrs pain), mcgill pain questionnaire (mpq), short-form mcgill pain questionnaire (sf-mpq), chronic pain grade scale (cpgs), short form-36 bodily pain scale (sf-36 bps), and measure of intermittent and constant osteoarthritis pain (icoap). Arthritis Care & Research. 2011;63(S11):S240-S52.
37. Hubley-Kozey CL, Robbins SM, Rutherford DJ, Stanish WD. Reliability of surface electromyographic recordings during walking in individuals with knee osteoarthritis. Journal of Electromyography and Kinesiology. 2013;23(2):334-41.
38. Specogna AV, Birmingham TB, DaSilva JJ, Milner JS, Kerr J, Hunt MA, et al. Reliability of lower limb frontal plane alignment measurements using plain radiographs and digitized images. The journal of Knee Surgery. 2004;17(04):203-10.
39. JS KJL. Radiological assessment of osteo-arthrosis. Annals of the Rheumatic Diseases. 1957;164:494-502.
40. Field A. Discovering statistics using IBM SPSS statistics: Sage; 2017.
41. Visser A, de Mutsert R, Loef M, Le Cessie S, den Heijer M, Bloem J, et al. The role of fat mass and skeletal muscle mass in knee osteoarthritis is different for men and women: the NEO study. Osteoarthritis and Cartilage. 2014;22(2):197-202.
42. Wang Y, Wluka AE, Berry PA, Siew T, Teichtahl AJ, Urquhart DM, et al. Increase in vastus medialis cross-sectional area is associated with reduced pain, cartilage loss, and joint replacement risk in knee osteoarthritis. Arthritis & Rheumatism. 2012;64(12):3917-25.
43. Goutallier D, Postel J-M, Bernageau J, Lavau L, Voisin M-C. Fatty muscle degeneration in cuff ruptures: pre-and postoperative evaluation by CT scan. Clinical Orthopaedics and Related Research. 1994;304:78-83.
44. Kohn MD, Sassoon AA, Fernando ND. Classifications in brief: Kellgren-Lawrence classification of osteoarthritis. Clinical Orthopaedics and Related Research. 2016;474:1886-93.
45. Goodpaster BH, Carlson CL, Visser M, Kelley DE, Scherzinger A, Harris TB, et al. Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. Journal of Applied Physiology. 2001;90(6):2157-65.

46. Lisee C, Lepley AS, Birchmeier T, O'Hagan K, Kuenze C. Quadriceps strength and volitional activation after anterior cruciate ligament reconstruction: a systematic review and meta-analysis. Sports Health. 2019;11(2):163-79.
47. Frobell RB, Roos HP, Roos EM, Roemer FW, Ranstam J, Lohmander LS. Treatment for acute anterior cruciate ligament tear: five year outcome of randomised trial. British Medical Journal. 2013;346.
48. van Yperen DT, Reijman M, van Es EM, Bierma-Zeinstra SM, Meuffels DE. Twenty-year follow-up study comparing operative versus nonoperative treatment of anterior cruciate ligament ruptures in high-level athletes. The American Journal of Sports Medicine. 2018;46(5):1129-36.
49. de Zwart AH, Dekker J, Lems W, Roorda LD, Van Der Esch M, Van Der Leeden M. Factors associated with upper leg muscle strength in knee osteoarthritis: A scoping review. Journal of Rehabilitation Medicine. 2018;50(2):140-50.

# Preface to Chapter 5

Along the same lines as Chapter 3 and 4, Chapter 5 will continue to explore knee joint loading. However, Chapter 5 will focus on the impact of knee joint loading on implant-replated outcomes in patients following knee arthroplasty for knee OA.

Recommendations regarding PA and sports limitations following knee arthroplasty are mainly based on expert consensus and have been put into question in recent years due to evidence suggesting no increased risk of implant wear or failure with greater levels of PA and sports participation. The first steps in establishing guidance on PA and sports participation following UKA and TKA are to understand the scientific evidence available to inform recommendations, to understand how studies on the topic are conducted and to identify where further research is needed. As a result, we conducted a scoping review to: 1) describe the available scientific literature examining the impact of PA and sports participation on implant integrity and failure following a UKA and TKA for tibiofemoral knee OA, and to 2) identify knowledge gaps on the topic and provide recommendations for future research.

# Chapter 5: Understanding the impact of physical activity level and sports participation on implant integrity and failure in patients following unicompartmental and total knee arthroplasty: A scoping review

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## Chapter 5.1 Abstract

**Background**: PA and sports participation recommendations following UKA and TKA have been questioned in recent years. This review aimed to summarize the scientific literature examining the impact of PA level and sports participation on implant integrity and failure in patients following UKA and TKA.

**Methods**: This scoping review was conducted according to the Arksey and O'Malley framework. Five databases (Medline, Embase, SCOPUS, CINAHL, ProQuest) were searched up until August 19, 2022. Retrospective, prospective and cross-sectional studies were included if they assessed the impact of PA level and/or sports participation on implant integrity and/or failure at ≥1 year following UKA or TKA. Two authors independently conducted abstract/full text reviews and data charting. Extracted data were summarized using descriptive analysis.

**Results**: Of 1719 potential records, 18 studies (UKA: n = 5, TKA: n = 13) met inclusion criteria. Data from 1517 patients following UKA (56% females, mean age: 52-66 years) and 5625 patients following TKA (57% females, mean age: 62-74 years) were included. Following UKA, no studies reported a deleterious effect of PA level or sports participation on implant integrity or failure (mean follow-up: 3.3-10.3 years). Following TKA, four studies reported a potentially deleterious effect of PA level, but not sports participation, on implant integrity or failure (mean follow-up: 1-11.4 years).

**Conclusions**: No studies demonstrated an association between greater levels of PA and sports participation with increased implant wear or failure up to ten years post UKA, whereas results were mixed following TKA. There is a need for large, high-quality prospective cohort studies with long-term (>10 years) follow-up.

## 5.2 Background

Regular exercise and PA are crucial for the management of knee OA (1) and play a fundamental role in the post-operative rehabilitation of patients following UKA and TKA (2, 3). Additionally, regular exercise and PA have been shown to be effective in the treatment of 26 chronic diseases and primary prevention of at least 35 chronic diseases (4). This is especially important, given that 35-40% of patients with OA are diagnosed with cardiovascular disease (5, 6), 59% have metabolic syndrome (7), 14% have Type 2 Diabetes Mellitus (8) and 33% report back pain (6). As a result, patients are encouraged to remain active following their knee arthroplasty. Furthermore, some patients desire an increased functional capacity post knee arthroplasty, with evolving expectations towards being able to participate in physical activities or sports (9). Most patients return to PA and sports following knee arthroplasty, with a trend towards participation in low-impact activities and sports (10-12). This trend may be explained by the fact that higher-impact activities and sports are typically discouraged following knee arthroplasty to reduce the potential negative impact on implant component survivorship due to a greater number of loading cycles and greater knee joint forces (13, 14).

Recommendations regarding PA and sports limitations following knee arthroplasty are mainly based on expert consensus (15), with insight from studies that assessed knee forces in vivo (13, 16), and using estimates from joint models (17-20). However, these recommendations have been put into question in recent years due to evidence suggesting no increased risk of implant wear or failure with greater levels of PA (21-23) and sports participation (24, 25). For instance, a study by Mont et al. (23), demonstrated that high activity levels and participation in low-to-moderate impact sports had no effect on TKA implant failure at 4 years follow-up. Similarly, there was no evidence of additional wear or loosening and revision rates were similar in patients performing

high-impact activity when compared to those performing medium or low- impact activities at 6 years post TKA (24). However, other studies have reported conflicting findings (26-28). Thus, whether participation in sport and high-impact activities increases the risk of knee arthroplasty implant failure remains unclear, and may explain the often inconsistent and contradictory recommendations provided to patients in clinical practice.

The first steps in establishing guidance on PA and sports participation following UKA and TKA are to understand the scientific evidence available to inform recommendations, to understand how studies on the topic are conducted and to identify where further research is needed. While a recent systematic review assessed the effect of PA and rehabilitation on implant revision rates among elderly patients (>65 years of age) who underwent TKA or total hip arthroplasty (THA) (3), no reviews have included both primary UKA and TKA for knee OA in adults of all ages. Patients post UKA are a relevant patient population to include, considering they are physically active and regularly participate in sports post-operatively (11). Furthermore, younger patients who undergo TKA tend to spend more time being physically active (29) and are more likely to participate in sports post-operatively (30). Thus, a broad overview of the available scientific literature on patients of all ages following both primary UKA and TKA for knee OA is needed.

The primary aim of this scoping review was to describe the available scientific literature examining the impact of PA and sports participation on implant integrity and failure in adult patients of all ages following a UKA and TKA for tibiofemoral knee OA. The secondary aim was to identify knowledge gaps on the topic and provide recommendations for future research.

## 5.3 Methods

This scoping review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (31) (Appendix 1.5). A scoping review design and methodology was used due to the descriptive and exploratory nature of the research question and study objectives (32, 33). We used the Arksey and O'Malley (34) framework to guide our review, with refinements proposed by more recently published guidelines (32, 33, 35). The scoping review protocol was not registered previously.

Our research question was: "What is known on the impact of PA and sports participation on implant integrity and implant failure in adults following UKA and TKA for tibiofemoral OA? In accordance with the PCC framework (33), our population (P) was defined as "adults with primary UKA or TKA for tibiofemoral OA", the concept (C) was defined as "the impact of PA and sports participation on implant integrity and implant failure following UKA and TKA" and the Context (C) was "non-specific", meaning evidence could come from any settings. Consistent with the definition by the World Health Organization, PA was defined as, "any bodily movement produced by skeletal muscles that results in energy expenditure" (36). PA refers to all movement, including occupational, transport, domestic and leisure time (37). Sports participation also involves PA, but differs in that sports adhere to a common set of rules or expectations, and a defined goal exists. They can also be undertaken individually or as part of a team (37). Lastly, implant integrity (e.g., implant wear) differs from implant failure in that it provides information on the general status of an implant that has not yet failed. This is an important distinction with clinically relevant implications for interpreting and generalizing study findings.

### 5.3.1 Data sources and search strategy

Relevant studies were identified by searching five online databases: Medline, Embase+Embase Classic, SCOPUS, CINAHL and ProQuest Theses & Dissertations, from inception to June 8, 2021. An updated search of the same five online databases was also conducted on August 19, 2022 to identify more recent potentially relevant articles. Databases were selected based on their relevance to the topic and to ensure the search strategy was comprehensive. ProQuest Theses & Dissertations was included to ensure that potentially relevant grey literature sources were not missed. Keywords and constructs (i.e., MeSH, Boolean phrases) used to execute each search were developed a priori from a preliminary search, search strategies from relevant review articles (3, 11, 12, 38), and in consultation with team members and an academic librarian. The following general search terms (in brackets) were adapted based on the database and were grouped by construct: 1) Patient Population (knee arthroplasty or knee replacement), 2) Implant Survivorship (prosthesis failure or reoperation or survivorship or revision or durability or wear or adverse or complications or failure) and 3) Physical Activity and Sports Participation (exercise or physical fitness or activity level or physical activity or sport or athlete or athletic). The full search strategies for each database can be found in Appendix 1.6a to 1.6e.

### 5.3.2 Study Selection

Studies were included if they were published in English or French, and assessed the impact of PA level and/or sports participation on implant integrity and/or failure ≥1 year following primary UKA or TKA for tibiofemoral OA in adults (18+ years). Studies reporting on multiple surgical interventions (i.e., TKA & THA) had to report the results of the knee arthroplasty group separately. Studies that assessed PA level and sports participation using a self-report questionnaire developed by the study authors were included if at least one parameter regarding the physical

activities/sports under study was reported (i.e., frequency, intensity, duration, etc.). This was done to facilitate robust and clinically relevant review findings. Studies reporting on multiple patient populations (i.e., OA, rheumatoid arthritis [RA], etc.) needed to have the majority (>50%) of patients with tibiofemoral OA. Studies with no direct statistical analysis examining the impact of PA level and/or sports participation on implant integrity and/or failure were included if they reported on implant-related outcomes (i.e., number of revisions) for relevant sub-groups (i.e., high activity level vs. low activity level). The authors of potential articles were contacted by the primary author if study information was missing (e.g., primary diagnoses for participants). See Table 5.1 for more information on inclusion and exclusion criteria.

### 5.3.3 Study Screening

Results for individual database searches were merged in EndNote 20.1, and duplicates removed. Remaining records were imported into Rayyan (Rayyan Systems Inc, https://rayyan.ai/). Prior to title and abstract reviews, two raters (A.T. & P.I.) independently screened a random sample of 30 titles and abstracts to assess the applicability of the exclusion criteria, as well as the inter-rater agreement and Cohen's kappa (K) between the two raters. Reviewers reached almost perfect level of agreement (97%, K = 0.87) (39), and as result, proceeded with reviewing the remainder of the titles and abstracts. Afterwards, the same two independent raters (A.T. & P.I.) performed full-text screening to determine final study selection. Once again, prior to the full article reviews, two raters (A.T. & P.I.) independently screened a random sample of 15 full-text articles to assess the applicability of the exclusion criteria, as well as the inter-rater agreement and Cohen's kappa (K) between the two raters. Reviewers reached almost perfect level of agreement (93%, K = 0.84) (39), and as result, proceeded with reviewing the remainder of the full-text articles. Consensus was

reached on disagreements, first between raters (A.T. & P.I.) and if required, with a third author (S.M.R.). We reviewed reference lists of included studies, relevant review articles, and clinical guidelines to identify additional relevant records.

### 5.3.4 Data Charting

We extracted the following information from included studies: 1. Study characteristics: year, design, location, mean follow-up, 2. Surgery and implant: type of surgery, implant-related information (company, model, etc.), 3. Study population: sample size, baseline participant characteristics (primary diagnosis, age, sex, etc.), 4. Assessment of PA and sports participation, 5. Assessment of implant integrity and failure, 6. Statistical analysis, 7. Key study findings, and 8. Funding sources and disclosures of interest. Data extraction was completed by two independent raters (A.T. & P.I.) using a customized Microsoft Excel form (33). The form was first piloted by comparing data extracted by the two independent raters (A.T. & P.I.) across a random sample of 5 studies to ensure accurate and relevant data were extracted (33).

### 5.3.5 Data Synthesis

A descriptive analysis approach was used to summarize study characteristics, participant demographic information, as well as information regarding PA level, sports participation, implant integrity and implant failure across studies. We reported means, SDs, ranges, proportions, and rates for numerical variables. Categorical variables were described by number (n) and percentage (%). Findings pertaining to studies involving patients post UKA and TKA were summarized separately.

### 5.3.6 Risk of bias assessment

Risk of bias (rating: low, moderate, or high) was assessed by the primary author (A.T.) in included studies was assessed using the National Institute of Health (NIH) Study Quality Assessments Tool for Case-Control Studies, and the NIH Study Quality Assessment tool for Observational Cohort and Cross-Sectional Studies (40). Consistent with the secondary aim of this scoping review, risk of bias was assessed to better provide recommendations for future research.

**Table 5.1.** Study inclusion and exclusion criteria

| Variable | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| Language | English or French language | Not English or French language |
| Study Population | Human participants | Animal models |
| | Adults (18+ years) | Not adults (<18 years) |
| | Primary unilateral knee replacement (UKA) or total knee replacement (TKA) for tibiofemoral osteoarthritis (OA) | Surgical procedure other than UKA/TKA or following revision knee arthroplasty |
| Study Design | Retrospective, prospective or cross-sectional quantitative studies (case–control studies, randomized controlled trials, longitudinal cohort studies, case series), theses and dissertations | Case study, case reports, reviews and meta-analyses, qualitative studies |
| Article Format | Peer-reviewed research article or theses/dissertations | Editorial, commentary, conference abstract, report |
| Exposure | Assessed physical activity level and/or sports participation | No/inappropriate assessment of physical activity level and/or sports participation |
| Main outcome | Any outcome related to implant integrity and/or implant failure | No outcome related to implant integrity or implant failure |
| Statistical Analysis | Direct analysis examining the impact of physical activity level/sports participation on implant integrity and/or implant failure<br>OR<br>Reported on implant integrity and/or implant failure for relevant sub-groups | No direct analysis and did not report on implant integrity or implant failure for relevant sub-groups |

## 5.4 Results

Of 1503 potential records generated from the original database search on June 9, 2021, 1003 records underwent title/abstract screening, 106 were reviewed in full, and 19 articles were included (21-28, 41-51) (Figure 5.1). Two studies were excluded because the primary diagnosis of participants receiving TKA was either not available (52) or no response was received from the corresponding author regarding missing data (53). An updated search conducted on August 19, 2022, generated 216 additional records. Of these, 134 underwent title/abstract screening and 16 were reviewed in full. No additional articles were included in the scoping review.

### 5.4.1 Study & Participant Characteristics

A summary of study characteristics and baseline participant demographics are provided in Appendix 1.7. In total, 18 studies reported in 19 articles across 6 countries (North America: n = 9 studies, Europe: n = 9 studies) were included. Two articles reported on the same dataset at a mean follow-up of 6.1 years (41) and 10.3 years (45) post UKA. As a result, these two articles were combined and counted as one study for the purpose of this review. Of the 18 studies, eight were retrospective cohort studies (21, 22, 26-28, 44, 49, 51), four were prospective cohort studies (41, 43, 45, 50), two were matched case-control studies (46, 47), and four were cross-sectional studies (23, 24, 42, 48).

Five studies (28%) included patients post UKA (22, 25, 41, 45, 49, 51) and thirteen studies (72%) included patients post TKA (21, 23, 24, 27, 28, 42-44, 46-48, 50). Implant-related information (i.e., company, design, bearing and fixation) can be found in Appendix 1.8. Data from 1517 patients following UKA (1788 knees, 56% females, mean age range: 52-66 years) and 5625 patients following TKA (6306 knees, 57% females, mean age range: 62-74 years) were included.

The proportion of the study sample with a diagnosis of knee OA as the primary indicator for surgery ranged between 86-100% in UKA studies, and between 65-100% in TKA studies. UKA procedures were done for medial compartment knee OA for all participants in four studies (22, 25, 41, 45, 49), and 89% of participants in one study (51). Mean follow-up periods ranged from 3.3 to 10.3 years in UKA studies, and from 1 to 11.4 years in TKA studies.

Information on funding sources and potential disclosures of interest for included studies can be found in Appendix 1.9. To summarize, funding sources were mentioned in seven studies (39%). However, no studies specified the role of the funding sources in their study. Disclosures of interest were declared in eleven studies (61%).

### 5.4.2 Risk of Bias Assessment

A summary of the risk of bias assessment using the NIH Study Quality Assessment can be found in Appendices 1.10a and 1.10b. All UKA studies (n = 5) had a "moderate" risk of bias (22, 25, 41, 45, 49, 51). For TKA studies (n = 13), seven studies had a "high" risk of bias (23, 24, 26, 27, 44, 46, 48), three studies had a "moderate" risk of bias (42, 43, 50), and three studies had a "low" risk of bias (21, 28, 47). Common reasons for not meeting criteria in observational cohort and cross-sectional studies were not clearly defining the study population (present in 38% of studies), not providing a sample size justification (present in 19% of studies), and not adjusting for potential confounders (present in 19% of studies). Common reasons for not meeting criteria in case-control studies were not including a sample size justification (present in 19% of studies), not indicating whether cases and/or controls were randomly selected from those eligible (unable to determine for all studies), and not using concurrent controls (present in zero studies).

### 5.4.3 Physical Activity & Sports Participation

A summary of how PA and sports participation was assessed in UKA and TKA studies is provided in Table 5.2. Fourteen studies (78%) reported assessing PA level using self-reports measures and one study (6%) reported assessing PA using annual walk cycles estimated from a pedometer. Five studies (28%) reported assessing sports participation using either a self-report questionnaire developed by the study authors (n = 4) or the Modifiable Activity Questionnaire (n = 1).

### 5.4.4 Implant Integrity & Failure

A summary of the different implant-related outcomes and how they were assessed in UKA and TKA studies is provided in Table 5.3. Implant-related outcomes were separated into two categories: outcomes related to implant integrity and outcomes related to implant failure. Implant integrity and failure, in relation to PA level or sports participation, were assessed in 12 studies (67%) and 14 studies (78%), respectively.

### 5.4.5 The Effect of Physical Activity & Sports Participation on Implant Integrity

A summary of key constructs and key study findings for each study can be found in Appendix 1.11. In UKA studies (n = 5), the association between PA and sports participation with implant integrity was assessed in three studies (60%) and one study (20%), respectively. No studies reported a deleterious effect of PA level or sports participation on implant integrity, regardless of mean follow-up period.

In TKA studies (n = 13), the association between PA and sports participation with implant integrity was assessed in nine studies (69%) and two studies (15%), respectively. Only one study

(27) reported a potentially deleterious effect of pre-operative (but not post-operative) PA levels on implant integrity. In this retrospective study (27), twenty-eight TKA implant polyethylene inserts were retrieved at autopsy from twenty-three patients and assessed for wear at a mean follow-up of 6.2 years. Participants who were classified as a 5 or 6 on the University of California at Los Angeles (UCLA) activity scale (occasional or regular participation in moderate PA) pre-operatively demonstrated greater extent ($P = 0.001$) and severity ($P < 0.001$) of polyethylene insert creep or deformation compared to less active patients (27).

### 5.4.6 The Effect of Physical Activity & Sports Participation on Implant Failure

In UKA studies (n = 5), the association between PA and sports participation with implant failure was assessed in three studies (60%) and one study (20%), respectively. No studies reported a deleterious effect of PA level or sports participation on implant failure, regardless of mean follow-up. Interestingly, one study reported a potential protective effect of PA level on implant failure, with increasing Tegner Activity Scale scores being associated with increased implant survival (41). Each increase in one point on the Tegner Activity Scale score was associated with approximately 30% fewer revisions (hazard ratio for revision: 0.71 per one unit increase in Tegner Activity Scale score, 95% CI: 0.52 to 0.96, $P = 0.025$) (41).

In TKA studies (n = 13), the association between PA and sports participation with implant failure was assessed in eight studies (62%) and 3 studies (23%), respectively. Three studies reported a potentially deleterious effect of PA level (26, 28, 46), but not sports participation, on implant failure. One retrospective study of 828 patients post TKA with a mean follow-up of 10 years demonstrated a statistically significant correlation between revision rate with activity level assessed using the Devane classification ($P = 0.03$), whereby risk of TKA implant mechanical

complications increased with greater activity (26). Similarly, a retrospective study classified 2016 patients post TKA as active (Lower Extremity Activity Scale score between 13-18, n = 1008) or inactive (Lower Extremity Activity Scale score between 7-12, n = 1008) (28). Revision rates were significantly greater at 5 to 10 years post TKA for active patients (3.2% revision rate) when compared to inactive patients (1.6% revision rate, $P = 0.019$) (28). Lastly, in a matched case-control study, the revision group (cases, n = 12 knees) had higher activity levels compared to the control group ($P = 0.02$) (46). Conversely, one study reported a potential protective effect of PA level on implant failure, with higher UCLA activity level scores being associated with increased implant survival (21). Kaplan-Meier analysis revealed that the all-cause 12-year survivorship was 98% for the high activity group and 95.3% for the low activity group ($P = 0.003$) (21). No studies reported a negative impact of sports participation on implant failure.

**Figure 5.1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews flow chart. [a]Ali et al. 2016 & Hamilton et al. 2017 reported on the same dataset with different follow-up periods and were counted as one study for the purpose of this scoping review.

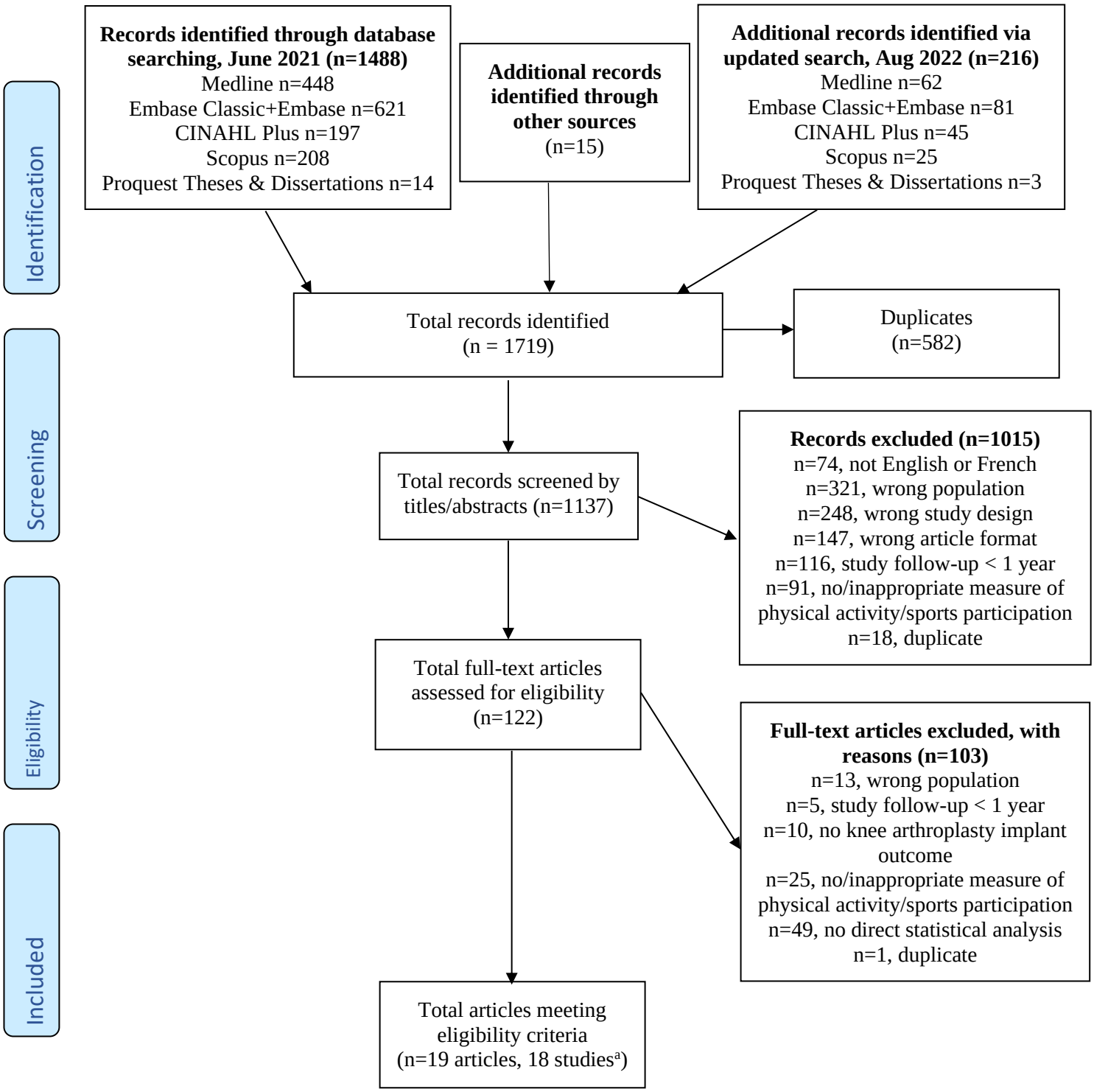

**Table 5.2.** Assessment of physical activity and sports participation across studies.

| | Outcome[a] | Assessment Method | n |
|---|---|---|---|
| **UKA Studies (n = 5)** | Physical Activity | Tegner Activity Scale (41, 45, 51) | 2[b] |
| | | University of California at Los Angeles (UCLA) activity scale (22, 49) | 2 |
| | Sports Participation | Self-report questionnaire developed by authors (25, 49) | 1 |
| | **Outcome[a]** | **Assessment Method** | **n** |
| **TKA Studies (n = 13)** | Physical Activity | University of California at Los Angeles (UCLA) activity scale (21, 27, 42, 43, 48) | 5 |
| | | Devane Classification (26) | 1 |
| | | Modified OASDI Activity Level Scoring System (46) | 1 |
| | | Lower Extremity Activity Scale (28) | 1 |
| | | Estimated annual walking cycles (50) | 1 |
| | Sports Participation | Self-report questionnaire developed by authors (44) | 1 |
| | Both Physical Activity & Sports Participation | Modifiable Activity Questionnaire (MAQ), MET-hours per week (47) | 1 |
| | | Total Knee Replacement Questionnaire, weighted activity score based on frequency and impact of specific activity or sport, developed by authors (23) | 1 |
| | | Scoring system based on the impact and quantity of the specific activity or sport, developed by authors (24) | 1 |

[a]Only physical activity and sports participation outcomes involved in analyses with implant-related outcomes are reported for each study.

[b]Ali et al. 2016 & Hamilton et al. 2017 reported on the same dataset with different follow-up periods and were counted as one study for the purpose of this scoping review.

**UKA**: unicompartmental knee arthroplasty, **TKA**: total knee arthroplasty

**Table 5.3.** Assessment of implant-related outcomes across studies.

| | Implant-Related Outcome[a] | | Assessment Method | n |
|---|---|---|---|---|
| **UKA Studies (n = 5)** | Implant Failure | Implant survivorship | Kaplan-Meier survival analysis (22, 41, 45) | 2[b] |
| | | Number of revisions | Frequency count (22, 25, 41, 49) | 4 |
| | | Time to implant failure | Not applicable (45) | 1 |
| | Implant Integrity | Meniscal bearing thickness | Radiograph (22) | 1 |
| | | Implant position | Radiograph (49) | 1 |
| | | Width of lateral compartment | Radiograph (49) | 1 |
| | | Radiolucent lines | Radiograph (51) | 1 |
| | **Implant-Related Outcome*** | | **Assessment Method** | **n** |
| **TKA Studies (n = 13)** | Implant Failure | Implant survivorship | Kaplan-Meier survival analysis (21, 43) | 2 |
| | | Number of revisions | Frequency count (21, 23, 26, 28, 42-44, 46, 47) | 9 |
| | | Time to implant failure | Not applicable (21, 28) | 2 |
| | | Risk of implant revision | Odds ratio (28, 47) | 2 |
| | Implant Integrity | Implant loosening | Radiograph (26, 42, 50) | 2 |
| | | | Scintigraphy (24) | 1 |
| | | Osteolysis | Radiograph (28, 42, 50) | 3 |
| | | Implant wear | Radiograph (21, 24, 28, 42) | 4 |
| | | Radiolucent lines | Radiograph (21, 24, 43) | 3 |
| | | Implant alignment | Radiograph (24, 50) | 2 |
| | | Polyethylene wear at autopsy | Linear wear measured using a caliper (27). Visual wear assessed via visual inspection (27). Volumetric wear measured using a specially designed device (27). | 1 |
| | | Blood serum metal ion concentrations | Measured via blood samples (48, 50) | 2 |

[a]Only implant-related outcomes involved in analyses with physical activity/sports participation outcomes are reported for reach study.

[b]Ali et al. 2016 & Hamilton et al. 2017 reported on the same dataset with different follow-up periods and were counted as one study for the purpose of this scoping review.

**UKA**: unicompartmental knee arthroplasty, **TKA**: total knee arthroplasty

## 5.5 Discussion

This scoping review is a first step to informing evidence-based guidance on PA and sports participation following UKA and TKA. To date, no studies have shown an association between greater levels of PA and sports participation with increased implant wear or failure rates up to ten years post UKA, whereas results are mixed following TKA. However, there is a need for higher-quality studies with larger samples sizes and long-term follow-up periods.

### 5.5.1 The Effect of Physical Activity & Sports Participation on Implant Integrity & Failure

Following UKA, no studies reported a potentially deleterious effect of greater PA levels and sports participation on implant integrity or failure. Although encouraging, these findings could alternatively be explained by other factors such as the specific patient selection criteria for UKA in included studies, or study follow-up periods that may not have been long enough to observe UKA implant wear or failure.

Four TKA studies reported an association between greater PA (but not sports participation) with greater implant wear (27) and implant failure rates (26, 28, 46). However, the conclusions drawn from these studies were hampered by certain methodological limitations. For instance, Lavernia et al. found that only preoperative (but not postoperative) activity level was associated with polyethylene wear post-operatively (27). The findings by Heck et al. are potentially confounded by the physical job demands of the included cases (e.g., plumber, construction worker) (46). The Devane classification used to assess activity level in the study by Argenson et al. provides limited information on activity levels (26). Lastly, Ponzio et al. found that revision rates were higher for active patients compared to inactive patients at 5-10 years post TKA (28). However, activity level was not a risk factor for implant revision in the multivariate model after accounting

for confounding variables (i.e., sex, BMI, age, etc.) (28). Therefore, the results of these studies must be interpreted with caution, as it remains unclear whether PA level is a significant risk factor for premature implant wear and failure following TKA.

### 5.5.2 Clinical Implications

Although our findings are encouraging, we remain cautious in our interpretation. Considering that 82% of TKAs and 70% of UKAs last 25 years (54), studies with long-term follow-up (>10 years) are needed. Furthermore, there are many factors to consider when recommending a specific PA or sport following knee arthroplasty (14). Knee arthroplasty implant design and materials have evolved significantly over time, improving both patient outcomes and implant longevity postoperatively (55). This may, in part, explain why older studies (27, 46) have shown less favorable results for active patients compared to less active patients. The specific contact geometry of knee arthroplasty implants must also be considered (56). For instance, higher contact stresses occur in knee flexion due to the fact that the femoral and tibial radiuses are conforming near extension and nonconforming in flexion (56). As a result, activities involving knee joint loading at greater angles of flexion (i.e., hiking, jogging, downhill skiing) may place undue stress on the implant bearing surface and accelerate wear of the polyethylene insert (14). Lastly, when compared to a TKA, a UKA generally provides improved range of motion, knee kinematics and physical function (57, 58). This may allow patients to return to more technically demanding and higher-level activities or sports.

Previous research has also suggested that implant wear is a function of use, and not time (59). As a result, athletic activities with a greater number of loading cycles, joint loads and/or technical demands may induce important stress at the bone-implant fixation surface and accelerate

wear of implant components, leading to premature implant failure and revision. Furthermore, activities and sports that are more technically demanding and high level should only be recommended in patients with experience in these specific activities. Previous research would suggest that inexperienced patients may be at a greater risk of sustaining sports-related injuries, and knee joint loads may be significantly greater for beginners when compared with experienced individuals (14). Therefore, patients should be made aware of the potential risks of higher activity levels or high-impact sports on long-term implant survival, which are not entirely known. This would allow for patients to make an informed decision, with guidance from their orthopaedic surgeon and physiotherapist, regarding which physical activities and sports to participate in following their knee arthroplasty.

### 5.5.3 Future Directions

A secondary aim of this scoping review was to identify knowledge gaps and provide recommendations for future research. There is a need for large high-quality, multicenter prospective cohort studies with long-term (>10 years) follow-up. Authors should ensure that the study population is clearly defined, a sample size justification is provided, and key potential confounding variables (i.e., age, sex, BMI) are accounted for in statistical analyses, among other considerations for methodological quality. To ensure transparency, it is crucial that authors declare funding sources and their role in the study, as well as potential disclosures of interest. Considering the significant between-study variability in the assessment of PA levels and sports participation, a more consistent approach is needed in future research. Furthermore, the categorical nature of self-report questionnaires provides fairly broad descriptions of various activities associated with each level on a given scale, but fail to provide relevant information such as the intensity and frequency

of activities. One potential solution may be the use of objective measures (e.g., pedometer, fitness watch) to improve estimates of PA and sports participation duration, intensity, and frequency. Lastly, research examining the impact of PA and sports participation on implant integrity or failure in different patient sub-groups is needed. For instance, outcomes could be stratified by age, seeing as implant revision rates have been shown to increase with decreasing age (60). There is also limited research on patient populations that participate in vigorous PA and/or high-impact sports. This is likely due to the fact that these types of activities are often discouraged by orthopaedic surgeons post-operatively.

### 5.5.4 Limitations

The broad research question and search strategy resulted in a comprehensive description of the current evidence-base. We also evaluated the risk of bias in included studies to better inform our conclusions and recommendations for future research. That being said, there are certain limitations that must be considered. First, there was significant between-study variability in the assessment of PA levels and sports participation, as well as implant integrity and failure. In addition, there was a lack of standardized, objective measures for the assessment of PA and sports participation, with little information regarding relevant parameters (i.e., duration, frequency, intensity). Together, these limitations make it difficult to summarize outcomes of individual studies, as well as make between-study comparisons. Second, only one author did the risk of bias assessment, and most included studies had a moderate to high risk of bias. Third, there was a wide follow-up range (1-11.4 years) for included studies. Therefore, studies with shorter follow-up periods (<5 years) may not have had sufficient time to observe any potential negative impact of PA level or sports participation on implant integrity or failure. Furthermore, several potentially

relevant articles were excluded due to language (61) and not having conducted analyses between relevant sub-groups (i.e., low vs. high PA or high-impact sport) (53, 61-65). However, these excluded studies also support the notion that higher levels of PA (61) and participation in higher impact sports such as tennis (65) and downhill skiing (63) appear to be safe in the short- to mid-term following TKA. We also acknowledge that only four prospective cohort studies were deemed eligible, including two with fewer than 45 subjects, and few included studies reported on long-term outcomes (>10 years). As a result, our conclusions are generalizable to mid-term follow-up after knee arthroplasty.

## 5.6 Conclusions

To date, no studies have shown an association between greater levels of PA and sports participation with increased implant wear or failure rates in the short- (<5 years) to mid-term (5-10 years) post UKA (mean follow-up range: 3.3-10.3 years), whereas results are mixed following TKA (mean follow-up range: 1-11.4 years). However, there were a limited number of large, high-quality multicenter prospective cohort studies with long-term (>10 years) follow-up. There was also significant between-study variability in the assessment of PA levels and sports participation, as well as implant integrity and failure. Lastly, there was a lack of standardized, objective measures for the assessment of PA and sports participation. As a result, the evidence remains inconclusive regarding whether PA level and sports participation are detrimental to long-term (>10 years) implant survivorship in patients following UKA and TKA.

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**Declaration of Competing Interest**

Mr. Teoli provides paid continuing education courses and webinars on knee osteoarthritis best practice for rehabilitation professionals. Dr. Antoniou participates on a Data Safety Monitoring Board or Advisory Board for the Canadian Orthopaedic Association and the Orthopedic Research Society, has a leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid (Trepso Therapeutics), and has patents planned, issued or pending: PCT/CA2014/000656: “Methods and Compositions for Treatment of Cartilage and Disc Disorders”. All remaining authors have no financial or non-financial competing interests to disclose.

## 5.7 Chapter 5 References


1. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee: a Cochrane systematic review. British Journal of Sports Medicine. 2015;49(24):1554-7.
2. Mistry JB, Elmallah RD, Bhave A, Chughtai M, Cherian JJ, McGinn T, et al. Rehabilitative guidelines after total knee arthroplasty: a review. The Journal of Knee Surgery. 2016;29(03):201-17.
3. Papalia R, Campi S, Vorini F, Zampogna B, Vasta S, Papalia G, et al. The role of physical activity and rehabilitation following hip and knee arthroplasty in the elderly. Journal of Clinical Medicine. 2020;9(5):1401.
4. Pedersen BK, Saltin B. Exercise as medicine–evidence for prescribing exercise as therapy in 26 different chronic diseases. Scandinavian Journal of Medicine & Science in Sports. 2015;25:1-72.
5. Hall AJ, Stubbs B, Mamas MA, Myint PK, Smith TO. Association between osteoarthritis and cardiovascular disease: systematic review and meta-analysis. European Journal of Preventive Cardiology. 2016;23(9):938-46.
6. Swain S, Sarmanova A, Coupland C, Doherty M, Zhang W. Comorbidities in Osteoarthritis: A systematic review and meta-analysis of observational studies. Arthritis Care & Research. 2020;72(7):991-1000.
7. Puenpatom RA, Victor TW. Increased prevalence of metabolic syndrome in individuals with osteoarthritis: an analysis of NHANES III data. Postgraduate Medicine. 2009;121(6):9-20.
8. Louati K, Vidal C, Berenbaum F, Sellam J. Association between diabetes mellitus and osteoarthritis: systematic literature review and meta-analysis. RMD Open. 2015;1(1):e000077.
9. Dagneaux L, Bourlez J, Degeorge B, Canovas F. Return to sport after total or unicompartmental knee arthroplasty: an informative guide for residents to patients. EFORT Open Reviews. 2017;2(12):496-501.
10. Hanreich C, Martelanz L, Koller U, Windhager R, Waldstein W. Sport and physical activity following primary total knee arthroplasty: a systematic review and meta-analysis. The Journal of Arthroplasty. 2020;35(8):2274-85. e1.
11. Waldstein W, Kolbitsch P, Koller U, Boettner F, Windhager R. Sport and physical activity following unicompartmental knee arthroplasty: a systematic review. Knee Surgery, Sports Traumatology, Arthroscopy. 2017;25(3):717-28.
12. Witjes S, Gouttebarge V, Kuijer P, van Geenen RC, Poolman RW, Kerkhoffs GM. Return to sports and physical activity after total and unicondylar knee arthroplasty: a systematic review and meta-analysis. Sports Medicine. 2016;46(2):269-92.
13. D'Lima DD, Steklov N, Patil S, Colwell CW. The Mark Coventry Award: in vivo knee forces during recreation and exercise after knee arthroplasty. Clinical Orthopaedics and Related Research. 2008;466(11):2605-11.
14. Kuster MS, Stachowiak GW. Factors affecting polyethylene wear in total knee arthroplasty. Orthopedics. 2002;25(2):S235-S42.
15. Healy WL, Sharma S, Schwartz B, Iorio R. Athletic activity after total joint arthroplasty. Journal of Bone and Joint Surgery. 2008;90(10):2245-52.
16. D'Lima DD, Patil S, Steklov N, Slamin JE, Colwell Jr CW. Tibial forces measured in vivo after total knee arthroplasty. The Journal of Arthroplasty. 2006;21(2):255-62.

17. Andriacchi T, Andersson G, Fermier R, Stern D, Galante J. A study of lower-limb mechanics during stair-climbing. The Journal of Bone and Joint Surgery. 1980;62(5):749-57.
18. Dahlkvist N, Mayo P, Seedhom B. Forces during squatting and rising from a deep squat. Engineering in Medicine. 1982;11(2):69-76.
19. Ericson MO, Bratt A, Nisell R, Nemeth G, Ekholm J. Load moments about the hip and knee joints during ergometer cycling. Scandinavian Journal of Rehabilitation Medicine. 1986;18(4):165-72.
20. Winter DA. Moments of force and mechanical power in jogging. Journal of Biomechanics. 1983;16(1):91-7.
21. Crawford DA, Adams JB, Hobbs GR, Berend KR, Lombardi Jr AV. Higher activity level following total knee arthroplasty is not deleterious to mid-term implant survivorship. The Journal of Arthroplasty. 2020;35(1):116-20.
22. Crawford DA, Adams JB, Lombardi Jr AV, Berend KR. Activity level does not affect survivorship of unicondylar knee arthroplasty at 5-year minimum follow-up. The Journal of Arthroplasty. 2019;34(7):1364-8.
23. Mont MA, Marker DR, Seyler TM, Gordon N, Hungerford DS, Jones LC. Knee arthroplasties have similar results in high-and low-activity patients. Clinical Orthopaedics and Related Research. 2007;460:165-73.
24. Mayr HO, Reinhold M, Bernstein A, Suedkamp NP, Stoehr A. Sports activity following total knee arthroplasty in patients older than 60 years. The Journal of Arthroplasty. 2015;30(1):46-9.
25. Presti ML, Costa GG, Cialdella S, Agrò G, Grassi A, Caravelli S, et al. Return to sports after unicompartmental knee arthroplasty: reality or utopia? A 48-month follow-up prospective study. The Journal of Knee Surgery. 2019;32(02):186-91.
26. Argenson J-N, Boisgard S, Parratte S, Descamps S, Bercovy M, Bonnevialle P, et al. Survival analysis of total knee arthroplasty at a minimum 10 years' follow-up: a multicenter French nationwide study including 846 cases. Orthopaedics & Traumatology: Surgery & Research. 2013;99(4):385-90.
27. Lavernia CJ, Sierra RJ, Hungerford DS, Krackow K. Activity level and wear in total knee arthroplasty: a study of autopsy retrieved specimens. The Journal of Arthroplasty. 2001;16(4):446-53.
28. Ponzio DY, Chiu Y-F, Salvatore A, Lee Y-Y, Lyman S, Windsor RE. An analysis of the influence of physical activity level on total knee arthroplasty expectations, satisfaction, and outcomes: increased revision in active patients at five to ten years. Journal of Bone and Joint Surgery. 2018;100(18):1539-48.
29. Kersten RF, Stevens M, van Raay JJ, Bulstra SK, van den Akker-Scheek I. Habitual physical activity after total knee replacement. Physical Therapy. 2012;92(9):1109-16.
30. Williams DH, Greidanus NV, Masri BA, Duncan CP, Garbuz DS. Predictors of participation in sports after hip and knee arthroplasty. Clinical Orthopaedics and Related Research. 2012;470:555-61.
31. Tricco A, Lillie E, Zarin W, O'Brien K, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. . Annals of Internal Medicine. 2018;169(7):467-73.
32. Peters MD, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. JBI Evidence Implementation. 2015;13(3):141-6.

33. Peters MD, Marnie C, Tricco AC, Pollock D, Munn Z, Alexander L, et al. Updated methodological guidance for the conduct of scoping reviews. JBI Evidence Synthesis. 2020;18(10):2119-26.
34. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. International Journal of Social Research Methodology. 2005;8(1):19-32.
35. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implementation Science. 2010;5:1-9.
36. World Health Organization (WHO). Physical Activity. 2020. Available from: https://www.who.int/news-room/fact-sheets/detail/physical-activity.
37. Khan KM, Thompson AM, Blair SN, Sallis JF, Powell KE, Bull FC, et al. Sport and exercise as contributors to the health of nations. The Lancet. 2012;380(9836):59-64.
38. Jassim S, Douglas S, Haddad F. Athletic activity after lower limb arthroplasty: a systematic review of current evidence. The Bone & Joint Journal. 2014;96(7):923-7.
39. McHugh ML. Interrater reliability: the kappa statistic. Biochemia Medica. 2012;22(3):276-82.
40. National Institute of Health (NIH). National Institute of Health. Study Quality Assessment Tools. 2021. Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.
41. Ali AM, Pandit H, Liddle AD, Jenkins C, Mellon S, Dodd CA, et al. Does activity affect the outcome of the Oxford unicompartmental knee replacement? The Knee. 2016;23(2):327-30.
42. Bauman S, Williams D, Petruccelli D, Elliott W, de Beer J. Physical activity after total joint replacement: a cross-sectional survey. Clinical Journal of Sport Medicine. 2007;17(2):104-8.
43. Bercovy M, Langlois J, Beldame J, Lefebvre B. Functional results of the ROCC® mobile bearing knee. 602 cases at midterm follow-up (5 to 14 years). The Journal of Arthroplasty. 2015;30(6):973-9.
44. Bradbury N, Borton D, Spoo G, Cross MJ. Participation in sports after total knee replacement. The American Journal of Sports Medicine. 1998;26(4):530-5.
45. Hamilton TW, Pandit HG, Jenkins C, Mellon SJ, Dodd CA, Murray DW. Evidence-based indications for mobile-bearing unicompartmental knee arthroplasty in a consecutive cohort of thousand knees. The Journal of Arthroplasty. 2017;32(6):1779-85.
46. Heck DA, Clingman JK, Kettelkamp DG. Gross polyethylene failure in total knee arthroplasty. Orthopedics. 1992;15(1):23-8.
47. Jones DL, Cauley JA, Kriska AM, Wisniewski SR, Irrgang JJ, Heck DA, et al. Physical activity and risk of revision total knee arthroplasty in individuals with knee osteoarthritis: a matched case-control study. The Journal of Rheumatology. 2004;31(7):1384-90.
48. Luetzner J, Krummenauer F, Lengel AM, Ziegler J, Witzleb W-C. Serum metal ion exposure after total knee arthroplasty. Clinical Orthopaedics and Related Research. 2007;461:136-42.
49. Pietschmann MF, Wohlleb L, Weber P, Schmidutz F, Ficklscherer A, Gülecyüz MF, et al. Sports activities after medial unicompartmental knee arthroplasty Oxford III—what can we expect? International Orthopaedics. 2013;37:31-7.
50. Reiner T, Sorbi R, Müller M, Nees T, Kretzer JP, Rickert M, et al. Blood metal ion release after primary total knee arthroplasty: a prospective study. Orthopaedic Surgery. 2020;12(2):396-403.

51. Schai PA, Suh J-T, Thornhill TS, Scott RD. Unicompartmental knee arthroplasty in middle-aged patients: a 2-to 6-year follow-up evaluation. The Journal of Arthroplasty. 1998;13(4):365-72.
52. Rohrbach M, Lüem M, Ochsner PE. Patient and surgery related factors associated with fatigue type polyethylene wear on 49 PCA and DURACON retrievals at autopsy and revision. Journal of Orthopaedic Surgery and Research. 2008;3:1-10.
53. Mont MA, Marker DR, Seyler TM, Jones LC, Kolisek FR, Hungerford DS. High-impact sports after total knee arthroplasty. The Journal of Arthroplasty. 2008;23(6):80-4.
54. Evans JT, Walker RW, Evans JP, Blom AW, Sayers A, Whitehouse MR. How long does a knee replacement last? A systematic review and meta-analysis of case series and national registry reports with more than 15 years of follow-up. The Lancet. 2019;393(10172):655-63.
55. Causero A, Di Benedetto P, Beltrame A, Gisonni R, Cainero V, Pagano M. Design evolution in total knee replacement: which is the future. Acta Biomedica. 2014;85(Suppl 2):5-19.
56. Kuster MS, Horz S, Spalinger E, Stachowiak GW, Gächter A. The effects of conformity and load in total knee replacement. Clinical Orthopaedics and Related Research. 2000;375:302-12.
57. Jones G, Kotti M, Wiik A, Collins R, Brevadt M, Strachan R, et al. Gait comparison of unicompartmental and total knee arthroplasties with healthy controls. The Bone & Joint Journal. 2016;98(10_Supple_B):16-21.
58. Wilson HA, Middleton R, Abram SG, Smith S, Alvand A, Jackson WF, et al. Patient relevant outcomes of unicompartmental versus total knee replacement: systematic review and meta-analysis. British Medical Journal. 2019;364.
59. Schmalzried TP, Shepherd EF, Dorey FJ, Jackson WO, dela Rosa M, McKellop HA, et al. Wear is a function of use, not time. Clinical Orthopaedics and Related Research. 2000;381:36-46.
60. Khan M, Osman K, Green G, Haddad F. The epidemiology of failure in total knee arthroplasty: avoiding your next revision. The Bone & Joint Journal. 2016;98(1_Supple_A):105-12.
61. Valle C, Sperr M, Lemhöfer C, Bartel KE, Schmitt-Sody M. Does sports activity influence total knee arthroplasty durability? Analysis with a follow-up of 12 years. Sportverletzung Sportschaden. 2017;31(2):111-5.
62. Diduch DR, Insall JN, Scott WN, Scuderi GR, Font-Rodriguez D. Total knee replacement in young, active patients. Long-term follow-up and functional outcome. Journal of Bone and Joint Surgery. 1997;79(4):575-82.
63. Hofstaedter T, Fink C, Dorn U, Pötzelsberger B, Hepperger C, Gordon K, et al. Alpine Skiing With total knee ArthroPlasty (ASWAP): clinical and radiographic outcomes. Scandinavian Journal of Medicine & Science in Sports. 2015;25:10-5.
64. Mallon WJ, Callaghan JJ. Total knee arthroplasty in active golfers. The Journal of Arthroplasty. 1993;8(3):299-306.
65. Mont MA, Rajadhyaksha AD, Marxen JL, Silberstein CE, Hungerford DS. Tennis after total knee arthroplasty. The American Journal of Sports Medicine. 2002;30(2):163-6.

# Preface to Chapter 6

Chapters 3 to 5 focused on the role of knee joint loading on clinical outcomes in patients with knee OA, and implant survivorship in patients following knee arthroplasty. Chapter 6 sought to better understand evoked pain responses (i.e., SPA) in response to knee joint loading (i.e., during standardized physical tasks).

Past research has emphasized the need for standardized approaches to assessing pain during relevant physical activities. SPA is an approach to assessing the negative responses to engagement in PA. However, it is unclear which physical activities or tasks are most appropriate for assessing SPA in patients with knee OA. In addition, longitudinal studies are needed to determine the potential prognostic value of SPA measures (i.e., SPA-Pain) with respect to recovery trajectories in patients with knee OA. Therefore, we aimed to: 1) compare baseline evoked pain responses across five physical tasks in patients with knee OA and 2) evaluate the relative prognostic value of SPA-Pain indices in patients with knee OA for pain and physical function after an 8-week activity-based rehabilitation program.

# Chapter 6: Comparing evoked pain responses and the prospective prognostic value of measures of sensitivity to physical activity among people with knee osteoarthritis

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Unpublished

## 6.1 Abstract

**Background**: Indices of SPA have been used among patients with knee OA to evaluate the change in pain intensity in relation to a standardized physical task. It is unclear which physical tasks are most appropriate for assessing SPA, and the prospective value of SPA measures remains largely unexplored in patients with knee OA. This longitudinal observational study aimed to compare evoked pain responses across five physical tasks and evaluate the prognostic value of SPA indices in patients with knee OA.

**Methods:** Adults with knee OA (n = 81) were evaluated at baseline and following an 8-week activity-based rehabilitation program. Performance and activity-related changes in pain (SPA-Pain indices) across five physical tasks were assessed at baseline. OA-related pain and physical function were assessed using a self-report questionnaire at baseline and following the 8-week rehabilitation program. Multiple regression analyses were conducted to examine whether pain and physical function following the 8-week rehabilitation program were associated with baseline SPA-Pain indices.

**Results:** The 6-Minute Walk Test and the Stair Climb Test were the most evocative physical tasks. Baseline task-specific SPA-Pain indices were not significantly associated with KOOS-Pain or KOOS-ADL scores following an 8-week rehabilitation program after accounting for age, sex and baseline KOOS-Pain or KOOS ADL scores, respectively ($P > 0.05$).

**Conclusions:** The 6-Minute Walk Test and Stair Climb Test may be the most appropriate physical tasks for assessing SPA in patients with knee OA. Regression analyses did not support the prognostic value of baseline task-specific SPA-Pain indices for OA-related pain and physical function following an 8-week rehabilitation program in patients with knee OA.

## 6.2 Introduction

OA is a degenerative joint disorder that affects approximately 15% of Canadians (1) and more than 500 million people worldwide (2). Patients with knee OA commonly report pain in response to movement or weight-bearing activities, resulting in difficulty with activities such as walking and going up and down stairs (3). Furthermore, increased pain during exercise has been identified as a major barrier to engaging in activity-based interventions for individuals with knee OA (4, 5), and is associated with poor treatment adherence in outpatient physiotherapy clinics (6). As a result, movement-evoked pain has been suggested to be a particularly important measure of musculoskeletal pain above and beyond traditional pain assessments, and standardized approaches to assessing pain during relevant physical activities are needed to address these barriers (7, 8).

This research gap has begun to be addressed through the development of novel approaches to assessing the negative responses to engagement in PA, including increased pain intensity and negative pain-related thoughts and feelings, among others (9-12). The term SPA has been used to broadly capture the full range of these negative biopsychosocial responses to engagement in an activity. SPA has been observed among patients with knee OA, as well as in other chronic pain conditions, such as back pain (11, 12), whiplash (13) and fibromyalgia (14). In addition, high levels of SPA have been shown to be uniquely associated with worse pain, function, and physical performance beyond passive measures of mechanical pain in patients with knee OA (9, 10).

Past studies have used SPA-Pain indices among patients with musculoskeletal pain conditions, such as knee OA, to evaluate the change in pain intensity in relation to a standardized physical task such as the 6-Minute Walk Test (9, 10). Recent work has begun to shed light on the potential prognostic value of SPA-Pain indices in patients with low back pain (11, 15). However, studies in patients with knee OA have used primarily cross-sectional designs (9, 10, 16, 17). As a

result, longitudinal studies are needed to determine the potential prognostic value of SPA-Pain indices with respect to recovery trajectories in patients with knee OA. Furthermore, it is unclear which physical activities or tasks are most appropriate for assessing SPA in patients with knee OA (10). This is especially important for identifying physical tasks that both elicit SPA and can be feasibly performed in typical practice settings (18), as well as for mitigating potential floor and ceiling effects when assessing SPA in patients with knee OA (10). Therefore, a better understanding of the potential merits and limitations of SPA measures are needed and is an essential step in developing SPA as a potential clinical assessment tool and integrating sensitized responses to PA within clinical management. This study aims to address these gaps by 1) comparing baseline evoked pain responses across five physical tasks in patients with knee OA and by 2) evaluating the relative prognostic value of SPA-Pain indices in patients with knee OA for pain and physical function after an 8-week activity-based rehabilitation program. For objective #1, we hypothesized that the 6-Minute Walk Test and the Stair Climb Test would be the most evocative of the physical tasks, as increased pain is commonly reported by patients with knee OA during weight-bearing activities of longer duration or that are more physically demanding. For objective #2, we hypothesized that SPA-Pain indices would be associated with pain and physical function following an 8-week activity-based rehabilitation program, after accounting for age, sex and baseline OA-related pain or physical function.

## 6.3 Methods

This study used a longitudinal observational design, and was part of a larger longitudinal cohort study testing patients with knee OA once before and following an 8-week activity-based rehabilitation intervention. This study adhered to the STROBE statement guidelines for reporting

observational cohort studies (19). For the purpose of this study, only the baseline and 8-week follow-up timepoints were considered.

### 6.3.1 Participants & Recruitment

The cohort consisted of 81 patients with knee OA entering an 8-week activity-based rehabilitation program. Eligibility criteria included: 1) fluency in English or French; 2) diagnosis of knee OA by an orthopaedic surgeon based on American College of Rheumatology criteria (20); 3) scheduled for either rehabilitation interventions at our affiliated treatment centers; 4) no serious medical co-morbidities (e.g., heart failure, cancer) or contraindications to PA; and 5) absence of severe cognitive impairment or dementia. Participant recruitment and data collection occurred from September 2017 to February 2020 via a Montreal-based network (in QC, Canada) of ten rehabilitation clinics, which provide an 8-week rehabilitation program to approximately 300 patients meeting our eligibility criteria each year. Patients were referred to this program by a network of Montreal-area physicians and orthopaedic surgeons, typically because they were not current candidates for surgery and/or would benefit from physical conditioning and increased activity engagement. In addition, clerks at the reception of the ten rehabilitation clinics or physicians' offices asked patients whether they would like to be approached by a research staff member about a research study involving people with knee pain. If yes, the research staff member contacted the patient directly to assess interest in participating. Recruitment was fully integrated within established clinical protocols and trained members of our research team invited all patients referred to the rehabilitation program to participate in the study. Participants provided written, informed consent prior to enrollment. Research ethics approval was obtained by the McGill University, Faculty of Medicine Institutional Review Board (Certificate number: A09-B46-16A).

Procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964, as revised in 2000.

### 6.3.2 Treatment

A detailed summary of the 8-week rehabilitation program is provided in Appendix 1.12. For the rehabilitation program, participants received ten treatment sessions by a physiotherapist over the course of 8 weeks and were assigned a progressive home exercise program throughout the intervention. Physiotherapists received training on how to administer the 8-week rehabilitation program. Consistent with clinical guidelines (21, 22), treatment focused on education, manual therapy, and range of motion, flexibility, strengthening and aerobic exercises. The home program also included a walking program that aimed to work up to 30 minutes of walking per day. Protocols for manual therapy, strengthening exercises, stretching exercises and range of motion exercises were based on previous research (23). The specific choice of manual therapy technique and/or home exercise program prescribed was individualized based on the results of the clinical examination completed by the treating physiotherapist. It is important to note that while participants were recruited upon enrollment for the 8-week rehabilitation program, our analyses were not specifically targeting the outcomes of completed care, but rather captured the general trajectory of a cohort of people with knee OA who were participating in a rehabilitation program.

### 6.3.3 Procedures

As previously mentioned, only relevant timepoints (baseline, 8-week follow-up) and outcomes (discussed below) will be presented for the purpose of this study. The timing for the initial post-treatment assessment was selected as rehabilitation patients would have just completed

treatment and were expected to better tolerate the physical tasks by this time. Testing consisted of assessing participant information (i.e., demographics, height, weight), three self-report questionnaires, and five physical tasks and measures of pain response.

### 6.3.4 Measures - Self-report questionnaires

*6.3.4.1 Demographic Information*

A list of demographic and health-related questions was used to collect information to describe the study sample's characteristics (age, sex, ethnicity, level of education, pain duration and number of comorbidities). Height and weight were objectively measured with a measuring tape and scale, respectively. BMI was calculated from these values ($kg/m^2$).

*6.3.4.2 OA-related pain and physical function*

The Knee Injury and Osteoarthritis Outcome Score (KOOS) is a disease specific, self-report measure (42 items over 5 subscales) that is recommended for use in the knee OA population (24). The scoring system of the KOOS utilizes a 5-point Likert scale, with anchors of zero (no problems) to 4 (extreme problems). Subscale scores are transformed to a 0-to-100 scale, with zero representing extreme knee problems and 100 representing no knee problems (24). The KOOS pain and function in daily living subscales were the main outcomes of interest, and were assessed at baseline and following the 8-week rehabilitation program. The KOOS has demonstrated adequate internal consistency, test-retest reliability and construct validity in adults with knee OA (25).

*6.3.4.3 Psychological factors*

Psychological factors, such as pain catastrophizing and pain-related fear were assessed at both timepoints (baseline, 8 weeks). For the purpose of the study, only baseline scores were included to provide a more biopsychosocial description of the study sample. Pain catastrophizing was assessed using the Pain Catastrophizing Scale (PCS) (26). The PCS consists of 13 items, in which participants must indicate the degree to which they have the stated thoughts and feelings when experiencing pain, using a 0 (not at all) to 4 (all the time) scale. A total score (0-52) is yielded with higher scores indicating greater pain catastrophizing, along with three subscale scores assessing rumination, magnification, and helplessness (26). Previous research supports the internal consistency, construct validity and structural validity of PCS as a measure of pain catastrophizing in patients with knee OA (27). In addition, pain-related fear was assessed using the Tampa Scale of Kinesiophobia-11 (TSK-11) (28, 29). The TSK-11 consists of 11 items, scored on a 1 (strongly disagree) to 4 (strongly agree) scale, yielding a total score ranging from 11 to 44, with higher scores indicating greater pain-related fear. The TSK-11 has been deemed to be both a reliable and valid measure of fear of movement or (re)injury for patients with chronic pain (28, 29).

### 6.3.5 Indices of Sensitivity to Physical Activity

Previous research would suggest that repetitive physical tasks may have a cumulative impact on pain sensitivity in patients with knee OA (10). Therefore, SPA-Pain was assessed by measuring pain responses (pain severity) immediately before and after completion of five standardized physical tasks (described in detail below).

#### *6.3.5.1 Standardized Physical Tasks*

The standardized physical tasks were chosen based on OARSI recommendations for performance-based tests in patients with knee OA (30). Physical performance for each task was also measured. The standardized physical tasks included: 1) the 30-second Chair Stand Test, 2) the 40-Meter Fast-Paced Walk Test, 3) the Timed-Up-and-Go Test, 4) the 6-Minute Walk Test, and 5) the Stair Climb Test. The research assistant explained and demonstrated all tasks before participants initiated the first task. The order of the first three tasks was randomized for each participant, followed by the fourth and fifth task. This order was chosen because we expected evoked pain responses to be similar for the first three tasks, and for the fourth and fifth tasks to be most evocative. Participants were permitted to use a walking aid as required. Five-minute rest periods were provided between tasks to limit the amount of pain carried over to the next task.

The 30-Second Chair Stand Test required participants to stand up and sit down from a chair as many times as possible in 30 seconds. The number of repetitions was noted. The 40-meter Fast-Paced Walk Test required participants to walk 40 meters as quickly and safely as possible. A straight, flat 30-meter track was used. The time to complete the test (in seconds) was noted. For the Timed-Up-and-Go Test, participants were required to rise from a chair, walk 3 meters, turn around, walk back to the chair and sit down. The time to complete the test (in seconds) was noted. For the 6-Minute Walk Test, participants were required to walk as far as possible in 6 minutes. A straight, flat 30-meter track was used. The maximum distance achieved was noted. Lastly, the Stair Climb Test required participants to step on and off a single step for 30 repetitions. The time to complete the task was noted.

*6.3.5.2 Measurement of pain responses*

Consistent with previous approaches (9, 10), participants were required to verbally rate their pain before and after each physical task by using a 0 (no pain) to 100 (most pain imaginable) NRS. Task-specific SPA-Pain indices were then generated by subtracting the reported pain level before the physical task from the reported pain level immediately after the physical task. A greater SPA-Pain index would indicate a greater increase in movement-evoked pain from before to immediately following the physical task.

### 6.3.6 Data Analysis

#### *6.3.6.1 Missing Data Analysis*

Missing data analysis was conducted to determine the proportion and distribution of missing data, as well as the most likely type of missingness (missing completely at random, missing at random, not missing at random) (31, 32). Participants with complete data on main outcomes of interest (KOOS-Pain and KOOS-ADL subscale scores at 8 weeks) were compared with participants with incomplete data on main outcomes of interest using independent-samples t tests ($\chi 2$ tests for categorical variables) to determine if there were statistically significant differences ($P < 0.05$) on variables included in this study.

#### *6.3.6.2 Statistical Analyses*

Descriptive statistics (mean, SDs, proportions) were calculated for all variables included in the study's analyses and for the demographic information collected. Paired t-tests were used to evaluate whether post-task pain (P2) was significantly greater than the pre-task pain (P1) for each physical task at baseline. The proportion of participants who experienced a clinically important increase in pain (≥20-point increase in pain ratings on a 0-100 NRS) for each of the five tasks was

also calculated. The potential for floor effects was evaluated by determining the proportion of participants who scored 0/100 on the SPA post-task pain rating for each task at baseline. A higher proportion of these responses would indicate that the task may not have been adequate in evoking sufficient activity-related pain among participants. The potential for ceiling effects was evaluated by determining the proportion of participants who scored 100/100 on the SPA post-task pain rating for each task at baseline. A higher proportion of these responses would indicate that the task may have been too intense. A threshold of >15% was defined as a floor or ceiling effect (33).

Correlational analyses were conducted to examine relationships between baseline task-specific SPA-Pain indices with KOOS-Pain and KOOS-ADL at baseline and at 8 weeks. Since SPA-Pain measures were non-normally distributed, Spearman correlations were considered more appropriate than Pearson correlations (34). For these analyses, statistical assumptions were verified for violations and addressed when necessary.

Separate multiple regression analyses (10 in total) were conducted to examine whether self-reported pain (KOOS-pain) and physical function (KOOS-ADL) following an 8-week activity-based rehabilitation program (dependent variables) are associated with baseline task-specific SPA-Pain indices (independent variables), after accounting for baseline pain and physical function scores, respectively, as well as age and sex. Age and sex were accounted for in regression analyses because KOOS scores (dependent variable) have been shown to vary based on age and sex (35). In addition, women with knee OA tend to experience more debilitating pain than men (36), and both variables have been shown to be predictors of functional decline (i.e., worsening of pain and activity limitations) in patients with knee OA (37). For regression analyses, age, sex, baseline pain or physical function, and baseline task-specific SPA-pain index were entered on the first, second, third and fourth step, respectively. Statistical significance for analyses was set at $P < 0.05$.

Unstandardized regression coefficients (B) with 95% CI were provided. Total explained variance ($R^2$) for the regression models were also reported. Regression analyses were conducted once using pooled data from multiple imputations, and again using only available data (complete case analysis according to analysis-by-analysis) for comparison. Appropriateness of the analyses was evaluated by examining data normality, residuals and multicollinearity using histogram of residuals, plots of residuals, collinearity statistics, or variance proportions. The presence of potential outliers and high leverage data points, and their potential influence on regression models, were assessed. Analyses were performed with SPSS (v27, IBM Corp, New York, United States).

#### *6.3.6.3 Sample Size*

This study was planned to be powered for regression analyses that can include up to 4 predictor variables. With 4 predictor variables for each regression model (as described in the previous section), assuming an α is set at 0.05 and power is set at 0.80, the sample size calculation (G*Power, version 3.1.9.4) required the sample size to be at least 80 participants to detect a medium effect sized relationship ($f^2 = 0.16$).

## 6.4 Results

A participant flow diagram is provided in Appendix 1.13. Eighty-one participants participated in the study and had data at baseline available for analysis. Sixty-eight participants completed the main outcome measures of interest (KOOS-Pain and KOOS-ADL subscales) at 8-week follow-up. The most common reasons for loss to follow-up were not responding to requests for follow-up and loss of interest/willingness to continue with participation. Two participants were

also excluded from the 8-week follow-up as they had not completed the rehabilitation program. The average time between baseline and 8-week follow-up sessions was 78.5 days (SD: 18.3 days).

Information on baseline participant characteristics, as well as means and SDs for outcome measures at baseline can be found in Table 6.1 and Table 6.2, respectively. In summary, the mean age of our sample was 61.2 years (SD: 10.6 years), and 63% were women. The mean BMI was 31.0 kg/m$^2$ (SD: 6.3 kg/m$^2$) and 80% of participants reported having ≥1 comorbidities. Participants had moderate pain levels (mean KOOS-pain subscale score: 52/100) of long-term duration (mean: 6.0 years), and relatively low scores on psychosocial questionnaires (mean PCS score: 14.8/52, mean TSK-11 score: 28.0/44) at baseline.

### 6.4.1 Missing data

The proportion of missing data for variables used in analyses ranged from 1.2% to 16.0% (range for all variables: 1.2% to 21.0%). The proportion of missing data for both main outcomes of interest (KOOS-Pain and KOOS-ADL scores at 8 weeks) was 16.0%. However, only 4.1% of the total data was missing overall. Data were primarily missing due to item nonresponse and loss to follow-up. The most frequently occurring pattern among participants was that there was no missing data. All other patterns of missing data were shared by <10% of participants. This would suggest that missing data was subject to random chance rather than being systematically missing.

Participants with complete data (n = 68) and participants with incomplete data (n = 13) on main outcomes of interest (KOOS-Pain and KOOS-ADL subscale scores at 8 weeks) were compared on variables included in this study. Comparisons revealed that participants with incomplete data on main outcomes of interest had significantly worse performance on the 6-Minute Walk Test ($t$ = 2.32, $P$ = 0.023). There were no other significant differences noted for any other

variables. These findings, along with findings from the missing data analysis, would suggest that our data's type of missingness was likely "missing at random". Therefore, multiple imputation was warranted to reduce the risk of bias associated with analyzing only available data (31, 32).

### 6.4.2 Multiple Imputations

Multiple imputations by fully conditional specification (FCS) using predictive mean matching (PMM) were carried out. This approach is a more flexible method that does not rely on the assumption of multivariate normality and has been recommended as an approach to performing multiple imputations in the presence of non-normal data (38, 39). Furthermore, an important feature of FCS is its ability to handle different variable types (continuous, binary, unordered categorical and ordered categorical) because each variable is imputed using its own imputation model (39). Consistent with recommendations in the literature, multiple imputations were carried out using 5 imputations and 10 iterations (31, 32). Ten iterations achieved FCS model convergence since no pattern was observed in FCS charts, which appeared appropriately random (32). All the findings presented below are based on pooled data from these multiple imputations (n = 81).

### 6.4.3 Characteristics of SPA-Pain Indices

Performance on physical tasks and SPA indices characteristics at baseline can be found in Table 6.3. Two participants used a cane for all physical tasks except the 30-second Chair Stand Test. For SPA-Pain measures, paired t-tests revealed a statistically significant change in pain intensity for the 30-Second Chair-Stand Test ($t$ = -3.36, $P$ = 0.001), the 40-Meter Fast-Paced Walk Test (t = -4.33, $P$ < 0.001), the 6-Minute Walk Test ($t$ = -5.98, $P$ < 0.001) and the Stair Climb Test (t = -7.90, $P$ < 0.001), but not for the Timed-Up-and-Go Test ($t$ = -0.575, $P$ = 0.565).

The most evocative test was the Stair Climb Test (mean increase of 19.4 points on 100-point NRS), whereas the least evocative test was the Timed-Up-and-Go Test (mean increase of 0.5 points on 100-point NRS). A clinically important increase in pain (≥20-point increase in pain) was seen in 23% of participants for the 30-Second Chair-Stand Test, 19% of participants for the 40-Meter Fast-Paced Walk Test, 4% for the Timed-Up-and-Go Test, 40% of participants for the 6-Minute Walk Test, and 47% of participants for the Stair Climb Test. Conversely, a reduction in pain (negative SPA-Pain index) was observed in 7-11% of participants, depending on the physical task. Floor effects (post-task pain rating = 0/100) and ceiling effects (post-task pain rating = 100/100) across physical tasks are summarized in Table 6.3. In summary, floor effects for physical tasks ranged from 14% of participants in the Stair Climb Task to 49% of participants in the Timed-Up-and-Go Test. Ceiling effects were present in ≤1% of participants across physical tasks.

### 6.4.4 Correlations

Results of correlation analyses can be found in Table 6.4. Greater SPA-Pain for the 40-Meter Fast-Paced Walk Test was significantly associated with worse KOOS-Pain at baseline ($P$ = 0.004) and at 8 weeks ($P$ = 0.004), as well as worse KOOS-ADL at baseline ($P$ = 0.005) and at 8 weeks ($P$ = 0.012). Greater SPA-Pain for the 6-Minute Walk Test was significantly associated with worse KOOS-Pain ($P$ = 0.048) and KOOS-ADL ($P$ = 0.022) at baseline. Greater SPA-Pain for the Stair Climb Test was significantly associated with worse KOOS-Pain at baseline ($P$ = 0.025) and at 8 weeks ($P$ = 0.037). There were no other statistically significant correlations between variables ($P$ > 0.05).

### 6.4.5 Predictive Value of SPA-Pain Indices

Results for regression analyses using pooled data from multiple imputations (n = 81) are provided in Tables 6.5 and 6.6. Similar findings were observed for regression analyses when carried out with available data using complete case analysis (analysis-by-analysis, Appendix 1.14 and 1.15). None of the baseline task-specific SPA-Pain indices were significantly associated with KOOS-Pain scores following an 8-week rehabilitation program after accounting for age, sex and baseline KOOS-Pain scores (*P*-value range: 0.108 to 0.933, depending on the regression model) (Table 6.5). For all models, baseline KOOS-Pain scores were significantly associated with KOOS-Pain scores at 8 weeks (*P*-value range: 0.004 to 0.015, depending on the regression model). Age and sex were not associated with KOOS-Pain scores at 8 weeks ($P > 0.05$). Total explained variance ($R^2$) in KOOS-Pain scores at 8 weeks for regression models varied between 22.1% and 25.7%, with baseline KOOS-Pain scores accounting for most of the variance (20.7%).

None of the baseline task-specific SPA-Pain indices were significantly associated with KOOS-ADL scores following an 8-week rehabilitation program after accounting for age, sex and baseline KOOS-ADL scores (*P*-value range: 0.109 to 0.957, depending on the regression model) (Table 6.6). For all models, baseline KOOS-ADL scores were significantly associated with KOOS-ADL scores at 8 weeks (*P*-value range: <0.001 to 0.006, depending on the regression model). Age and sex were not associated with KOOS-ADL scores at 8 weeks ($P > 0.05$). Total explained variance ($R^2$) in KOOS-ADL scores at 8 weeks for regression models varied between 22.4% and 25.9%, with baseline KOOS-ADL scores accounting for most of the variance (19.9%).

There were no violations of statistical assumptions requiring corrective action for multiple linear regression analysis, and no influential outlier was found (Cook's Distance values <1). In addition, multicollinearity did not occur; tolerance values were >0.25 (lowest tolerance value was 0.77) and variance inflation factor (VIF) values were <5 (highest VIF value was 1.30) (40).

**Table 6.1.** Baseline participant characteristics (n = 81).

| Variable | Values |
|---|---|
| **Age (y)**, mean (SD) | 61.2 (10.6) |
| **Sex,** n (%) | |
| Males | 30 (37.0) |
| Females | 51 (63.0) |
| **BMI (kg/m²)**, mean (SD) | 31.0 (6.3) |
| **Ethnicity,** n (%) | |
| Caucasian | 62 (76.5) |
| Other | 19 (23.5) |
| **Pain duration (y)**, mean (SD) | 6.0 (8.4) |
| **Highest level of education,** n (%) | |
| Elementary school | 2 (2.5) |
| High school | 13 (16.0) |
| Postsecondary education | 66 (81.5) |
| **Number of comorbidities,** n (%) | |
| 0 | 16 (19.8) |
| 1 | 24 (29.6) |
| 2 | 20 (24.7) |
| 3 | 9 (11.1) |
| 4 | 9 (11.1) |
| 5 or more | 3 (3.7) |
| **Pain-related fear (TSK, 11-44),** mean (SD) | 28.0 (6.8) |
| **Pain catastrophizing (PCS, 0-52),** mean (SD) | 14.8 (10.9) |

Results are based on pooled multiple imputations data, n = 81.

**BMI**: body mass index. **TSK**: Tampa Scale of Kinesiophobia, **PCS**: Pain Catastrophizing Scale.

**Table 6.2.** KOOS-Pain and KOOS-ADL subscale scores at baseline and 8 weeks (n = 81).

| Measure | Values | |
|---|---|---|
| | **Baseline** | **8 Weeks** |
| **KOOS Subscales (0-100)**, mean (SD) | | |
| Pain | 52.0 (15.6) | 62.1 (18.6) |
| Function in daily living | 59.6 (16.5) | 67.9 (19.0) |

Results are based on pooled multiple imputations data, n = 81.

**SD:** standard deviation. **KOOS**: Knee Injury & Osteoarthritis Outcome Score.

**Table 6.3.** Physical task performance and characteristics of SPA-Pain indices at baseline (n = 81)

| Variable | Values | | | | |
|---|---|---|---|---|---|
| | **CST** | **FWT** | **TUG** | **6MWT** | **SCT** |
| Performance on task | 11.5 (5.1) | 29.6 (7.7) | 10.8 (3.7) | 336.7 (158.7) | 112.4 (36.7) |
| SPA-Pain (P2-P1, NRS 0-100) | 6.4 (15.3) | 7.5 (15.0) | 0.6 (8.7) | 16.5 (24.1) | 19.4 (21.3) |
| Pain before task (P1, NRS 0-100) | 12.8 (17.7) | 13.3 (19.3) | 14.5 (20.1) | 14.4 (20.5) | 15.0 (20.1) |
| Pain after task (P2, NRS 0-100) | 19.2 (20.9) | 20.8 (24.4) | 15.1 (21.2) | 30.9 (28.9) | 34.4 (27.1) |
| SPA-Pain ≥MCIC 20/100 NRS, n (%) | 19 (24) | 15 (19) | 3 (4) | 32 (40) | 38 (47) |
| Floor effect: P2 = 0/100, n (%) | 26 (32) | 28 (35) | 40 (49) | 13 (16) | 11 (14) |
| Ceiling effect: P2 = 100/100, n (%) | 0 (0) | 0 (0) | 0 (0) | 1 (1) | 1 (1) |

Means and standard deviations (SD) are provided for continuous variables, unless otherwise noted (number of participants [n] with proportions [%] are provided for categorical variables). Results are based on pooled multiple imputations data, n = 81.

**SPA:** sensitivity to physical activity. **MCIC**: minimally clinically important change. **NRS:** numeric rating scale. **CST**: 30-Second Chair Stand Test (number of repetitions). **FWT**: 40-Meter Fast-Paced Walk Test (time [seconds]). **TUG**: Timed-Up-and-Go Test (time [seconds]). **6MWT**: 6-Minute Walk Test (distance [meters]). **SCT**: Stair Climb Test (time [seconds].

**Table 6.4.** Correlation Matrix (Spearman, n = 81).

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| 1. KOOS-Pain (T1) | - | | | | | | | | |
| 2. KOOS-Pain (T2) | 0.425** | - | | | | | | | |
| 3. KOOS-ADL (T1) | 0.873** | 0.436** | - | | | | | | |
| 4. KOOS-ADL (T2) | 0.374** | 0.865** | 0.458** | - | | | | | |
| 5. SPA-Pain CST | -0.115 | 0.077 | -0.061 | 0.155 | - | | | | |
| 6. SPA-Pain FWT | -0.336** | -0.331** | -0.325** | -0.294* | -0.004 | - | | | |
| 7. SPA-Pain TUG | -0.127 | -0.128 | -0.178 | -0.109 | -0.097 | 0.292* | - | | |
| 8. SPA-Pain 6MWT | -0.230* | -0.184 | -0.263* | -0.085 | 0.132 | 0.210 | 0.257* | - | |
| 9. SPA-Pain SCT | -0.283* | -0.246* | -0.193 | -0.082 | 0.397** | 0.399** | 0.074 | 0.409** | - |

*. Correlation is significant at the $P < 0.05$ level (2-tailed).

**. Correlation is significant at the $P < 0.01$ level (2-tailed).

All correlations are Spearman r values. SPA-Pain measures were those assessed at baseline. Results are based on pooled multiple imputations data, n = 81.

**KOOS**: Knee Injury and Osteoarthritis Outcome Score. **T1**: baseline. **T2**: following 8-week rehabilitation program. **ADL**: Activities of daily living. **SPA**: Sensitivity to physical activity. **CST**: 30-Second Chair Stand Test. **FWT**: 40-Meter Fast-Paced Walk Test. **TUG**: Timed-Up-and-Go Test. **6MWT**: 6-Minute Walk Test. **SCT**: Stair Climb Test.

**Table 6.5.** Unstandardized regression coefficients examining relationships between baseline SPA-Pain indices with pain following an 8-week rehabilitation program (n = 81).

| Dependent Variable | Physical Task | Age B (95% CI) | Sex B (95% CI) | KOOS-Pain (T1) B (95% CI) | SPA-Pain B (95% CI) | $R^2$ |
|---|---|---|---|---|---|---|
| KOOS-Pain (T2) | CST | -0.10 (-0.52, 0.32) | -2.64 (-10.70, 5.43) | **0.58** (0.21, 0.95) | 0.13 (-0.15, 0.42) | 23% |
| | FWT | -0.06 (-0.52, 0.40) | -2.13 (-10.12, 5.86) | **0.51** (0.11, 0.90) | -0.24 (-0.54, 0.54) | 26% |
| | TUG | -0.08 (-0.51, 0.35) | -2.74 (-10.85, 5.38) | **0.57** (0.20, 0.94) | -0.02 (-0.47, 0.43) | 22% |
| | 6MWT | -0.07 (-0.50, 0.36) | -2.59 (-10.62, 5.44) | **0.56** (0.17, 0.95) | -0.03 (-0.20, 0.14) | 22% |
| | SCT | -0.09 (-0.53, 0.35) | -2.43 (-10.24, 5.38) | **0.53** (0.15, 0.91) | -0.12 (-0.33, 0.08) | 24% |

Unstandardized coefficients (B) with 95% confidence intervals (CI), and total explained variance ($R^2$) are provided. Age, sex (0 = females, males = 1), and baseline pain were accounted for in regression analyses. Significant associations are in bold ($P < 0.05$). Results are based on pooled multiple imputations data, n = 81.

**KOOS**: Knee Injury and Osteoarthritis Outcome Score. **T1**: baseline. **T2**: following 8-week rehabilitation program. **SPA**: Sensitivity to physical activity. **CST**: 30-Second Chair Stand Test. **FWT**: 40-Meter Fast-Paced Walk Test. **TUG**: Timed-Up-and-Go Test. **6MWT**: 6-Minute Walk Test. **SCT**: Stair Climb Test.

**Table 6.6.** Unstandardized regression coefficients examining relationships between baseline SPA-Pain indices with physical function following an 8-week rehabilitation program (n = 81).

| Dependent Variable | Physical Task | Age B (95% CI) | Sex B (95% CI) | KOOS-ADL (T1) B (95% CI) | SPA-Pain B (95% CI) | $R^2$ |
|---|---|---|---|---|---|---|
| KOOS-ADL (T2) | CST | -0.07 (-0.60, 0.46) | -2.12 (-10.19, 5.96) | **0.55** (0.25, 0.85) | 0.24 (-0.06, 0.54) | 26% |
| | FWT | -0.01 (-0.61, 0.59) | -1.69 (-9.94, 6.58) | **0.49** (0.15, 0.82) | -0.21 (-0.52, 0.09) | 25% |
| | TUG | -0.03 (-0.58, 0.52) | -2.79 (-11.32, 5.74) | **0.56** (0.22, 0.90) | 0.16 (-0.39, 0.70) | 23% |
| | 6MWT | -0.07 (-0.63, 0.49) | -2.97 (-11.48, 5.55) | **0.58** (0.25, 0.91) | 0.09 (-0.09, 0.27) | 23% |
| | SCT | -0.03 (-0.59, 0.54) | -2.31 (-10.65, 6.02) | **0.54** (0.23, 0.85) | -0.01 (-0.23, 0.22) | 22% |

Unstandardized coefficients (B) with 95% confidence intervals (CI), and total explained variance ($R^2$) are provided. Age, sex (0 = females, males = 1), and baseline physical function were accounted for in regression analyses. Significant associations are in bold ($P < 0.05$). Results are based on pooled multiple imputations data, n = 81.

**KOOS**: Knee Injury and Osteoarthritis Outcome Score. **T1**: baseline. **T2**: following 8-week rehabilitation program. **ADL**: Activities of daily living. **SPA**: Sensitivity to physical activity. **CST**: 30-Second Chair Stand Test. **FWT**: 40-Meter Fast-Paced Walk Test. **TUG**: Timed-Up-and-Go Test. **6MWT**: 6-Minute Walk Test. **SCT**: Stair Climb Test.

## 6.5 Discussion

This study adds to the growing body of research exploring activity-related pain in patients with knee OA. Our study extends past work (9, 10) by shedding light on the potential value of different SPA measurement strategies and their respective merits and limitations in patients with knee OA. More specifically, our findings suggest that evoked pain responses differ depending on the standardized physical task used to assess SPA in patients with knee OA. However, the prognostic value of SPA-Pain indices for OA-related pain and physical function following an 8-week rehabilitation program in patients with knee OA remains unclear.

For SPA-Pain measures, all physical tasks except for the Timed-Up-and-Go evoked statistically significant increases in pain. Consistent with our hypothesis, the 6-Minute Walk Test (16.5-point increase on a 100-point NRS) and the Stair Climb Test (19.4-point increase on a 100-point NRS) were the most evocative physical tasks. Both tasks also had the greatest proportion of participants who experienced a clinically important increase in pain, with the lowest floor effects. Taken together, these findings would suggest that the 6-Minute Walk Test and the Stair Climb Test may be most appropriate for assessing activity-related pain in patients with knee OA.

The magnitude of evoked pain responses observed in our sample were also broadly consistent with past research (10, 17). For instance, Harden et al. (17) found that patients with knee OA experienced a mean increase in knee pain of 2 points (11-point NRS) after climbing a flight of stairs. Wideman et al. (10) found that patients with knee OA experienced a mean increase in knee discomfort of 15 points (0-100 verbal rating scale) following the 6-Minute Walk Test. Although the mechanisms underlying movement-evoked pain are not fully understood, temporal summation of pain (i.e., clinical indicator of central sensitization) has been identified as a potential underlying mechanism of SPA due to the repetitive mechanical demands of physical tasks (i.e.,

walking, stair climbing), resulting in "wind-up" of nociception at the dorsal horn of the spinal cord (10, 12, 13).

Our findings also suggest that cross-sectional associations between SPA-Pain indices and OA-related pain and physical function are dependent on the physical task used to assess SPA. For instance, only greater baseline SPA-Pain indices for the 40-Meter Fast-Paced Walk Test, 6-Minute Walk Test and Stair Climb Test were significantly correlated with worse baseline OA-related pain (KOOS-Pain). Additionally, only greater baseline SPA-Pain Indices for the 40-Meter Fast-Paced Walk Test and 6-Minute Walk Test were significantly correlated with worse baseline OA-related physical function (KOOS-ADL). This is consistent with previous work demonstrating that greater SPA-Pain assessed using the 6-Minute Walk Test is significantly correlated with worse OA-related pain and physical function (10, 41). Collectively, these findings align with the notion that movement-evoked pain represents an important dimension of the pain experience that has a significant impact on physical function and disability (7, 8). This further emphasizes the importance of assessing movement-evoked pain, among other pain-related outcomes, in clinical practice and research settings (7, 8).

Prospectively, greater baseline SPA-Pain indices were significantly correlated with worse OA-related pain at 8 weeks (40-Meter Fast-Paced Walk Test, Stair Climb Test) and physical function at 8 weeks (40-Meter Fast-Paced Walk Test). However, contrary to our hypothesis, the corresponding prospective relationships were no longer statistically significant in regression analyses after accounting for age, sex and baseline OA-related pain or physical function. Only one other longitudinal study (follow-up at two and nine weeks) was identified that examined the potential prognostic value of the SPA-Pain index for predicting future pain and physical function, among other outcomes, in eighty-six patients with knee OA (41). Contrary to what we observed,

baseline SPA-Pain indices assessed using the 6-Minute Walk Test were predictive of OA-related pain (KOOS-Pain, $\beta = -0.19$, $P < 0.01$) and physical function (KOOS-ADL, $\beta = -0.18$, $P = 0.003$) at 9 weeks in patients with knee OA, after accounting for age, sex, BMI, symptom duration, socioeconomic status and baseline pain intensity (not accounted for in multivariate models where pain was the dependent variable) (41). There are several key between-study differences that could potentially explain the discrepancy in findings. For instance, baseline KOOS subscale scores were accounted for in our study, but not in the study by Overton et al. (41). As a result, it is possible that baseline SPA-Pain indices may explain unique variance in OA-related pain prospectively, but not beyond baseline OA-related pain and physical function scores. Second, the follow-up assessment in our study occurred after participants underwent an 8-week activity-based rehabilitation program. Participants also experienced a clinically important improvement (8-10 point change for KOOS subscale scores (24)) in OA-related pain (Mean change in KOOS-Pain scores: 10.1) and physical function (Mean change in KOOS-ADL scores: 8.3) following the rehabilitation program. This may have, in turn, influenced the prospective relationships between baseline SPA-Pain indices and OA-related pain and physical function at 8 weeks in our study. Therefore, it is possible that greater baseline activity-related pain in patients with knee OA is predictive of worse future OA-related pain and physical function (as demonstrated by Overton et al. (41)), but not worse pain-related outcomes following an 8-week activity-based rehabilitation program. Further prospective studies with larger sample sizes are needed to determine the potential added prognostic value of SPA-Pain indices, after accounting for established prognostic factors in regression analyses.

Several limitations should be considered when interpreting these findings. First, floor effects (>15% of participants) were present for all physical tasks except the Stair Climb Test,

suggesting that most physical tasks may not have been adequate in evoking sufficient activity-related pain. One potential solution to help mitigate floor effects would be to tailor the intensity of the physical task to individual pain levels (11, 12). Second, our study sample consisted of patients with knee OA with moderate self-reported pain and functional impairment, and relatively low scores on psychosocial questionnaires (i.e., PCS, TSK-11). This may limit generalizability of our findings to other samples. It is also possible that patients with knee OA who report more severe symptoms and/or higher scores on psychosocial measures would have demonstrated greater levels of SPA, potentially influencing prospective relationships with OA-related pain and physical function. Third, the time between baseline and 8-week follow-up testing sessions varied across participants (mean: 78 days, SD: 18 days). This could have also influenced our findings at the 8-week follow-up session. Lastly the sample size in our study did not allow for us to account for other relevant factors in regression analyses that may have also affected clinical outcomes in patients with knee OA, such as lifestyle factors (i.e., comorbidity burden) (42) and psychosocial measures (i.e., pain-related fear, pain catastrophizing) (43, 44). Furthermore, baseline pain at rest using a 0-10 NRS was not accounted for in regression analyses because KOOS pain was already entered into the model, and this may have caused multicollinearity to occur.

## 6.6 Conclusions

The results of this study would suggest that the 6-Minute Walk Test and Stair Climb Test may be the most appropriate physical tasks for assessing SPA in patients with knee OA. Future research should explore how SPA assessment can be further optimized, such as tailoring the intensity of physical tasks to individual pain levels to help mitigate floor and ceiling effects. In addition, this study did not support the prognostic value of baseline task-specific SPA-Pain indices for OA-related pain and physical function following an 8-week rehabilitation program in patients

with knee OA. Consistent with a biopsychosocial approach, future clinical research should continue to explore the potential value of SPA-Pain indices, as well as other SPA measures (i.e., SPA-Psych, SPA-Sensory) in patients with knee OA.

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**Declaration of Competing Interest**

Mr. Teoli provides continuing education courses on knee osteoarthritis best practice for rehabilitation professionals. All remaining authors have no conflicts of interest to disclose.

## 6.7 Chapter 6 References


1. Badley EM, Wilfong JM, Zahid S, Perruccio AV. Special Report: The Burden of Osteoarthritis in Canada. Arthritis Society; 2021.
2. Long H, Liu Q, Yin H, Wang K, Diao N, Zhang Y, et al. Prevalence trends of site-specific osteoarthritis from 1990 to 2019: findings from the Global Burden of Disease Study 2019. Arthritis & Rheumatology. 2022;74(7):1172-83.
3. Hawker GA. Experiencing painful osteoarthritis: what have we learned from listening? Current Opinion in Rheumatology. 2009;21(5):507-12.
4. Holden MA, Nicholls EE, Young J, Hay EM, Foster NE. Role of exercise for knee pain: what do older adults in the community think? Arthritis Care & Research. 2012;64(10):1554-64.
5. Kanavaki AM, Rushton A, Efstathiou N, Alrushud A, Klocke R, Abhishek A, et al. Barriers and facilitators of physical activity in knee and hip osteoarthritis: a systematic review of qualitative evidence. BMJ Open. 2017;7(12):e017042.
6. Jack K, McLean SM, Moffett JK, Gardiner E. Barriers to treatment adherence in physiotherapy outpatient clinics: a systematic review. Manual Therapy. 2010;15(3):220-8.
7. Corbett DB, Simon CB, Manini TM, George SZ, Riley III JL, Fillingim RB. Movement-evoked pain: transforming the way we understand and measure pain. Pain. 2019;160(4):757.
8. Srikandarajah S, Gilron I. Systematic review of movement-evoked pain versus pain at rest in postsurgical clinical trials and meta-analyses: a fundamental distinction requiring standardized measurement. Pain. 2011;152(8):1734-9.
9. Wideman TH, Edwards RR, Finan PH, Haythornthwaite JA, Smith MT. Comparing the predictive value of task performance and task-specific sensitivity during physical function testing among people with knee osteoarthritis. Journal of Orthopaedic & Sports Physical Therapy. 2016;46(5):346-56.
10. Wideman TH, Finan PH, Edwards RR, Quartana PJ, Buenaver LF, Haythornthwaite JA, et al. Increased sensitivity to physical activity among individuals with knee osteoarthritis: relation to pain outcomes, psychological factors, and responses to quantitative sensory testing. Pain. 2014;155(4):703-11.
11. Woznowski-Vu A, Aternali A, Gervais A, Pavilanis AD, Nijs J, Sullivan MJ, et al. The prospective prognostic value of biopsychosocial indices of sensitivity to physical activity among people with back pain. The Clinical Journal of Pain. 2021;37(10):719-29.
12. Woznowski-Vu A, Uddin Z, Flegg D, Aternali A, Wickens R, Sullivan MJ, et al. Comparing novel and existing measures of sensitivity to physical activity among people with chronic musculoskeletal pain. The Clinical Journal of Pain. 2019;35(8):656-67.
13. Sullivan MJ, Larivière C, Simmonds M. Activity-related summation of pain and functional disability in patients with whiplash injuries. Pain. 2010;151(2):440-6.
14. Lambin DI, Thibault P, Simmonds M, Lariviere C, Sullivan MJ. Repetition-induced activity-related summation of pain in patients with fibromyalgia. Pain. 2011;152(6):1424-30.
15. Trolle N, Maribo T, Jensen LD, Christiansen DH. Task-specific sensitivity in physical function testing predicts outcome in patients with low back pain. Journal of Orthopaedic & Sports Physical Therapy. 2020;50(4):206-13.
16. Cruz-Almeida Y, Cardoso J, Riley III JL, Goodin B, King CD, Petrov M, et al. Physical performance and movement-evoked pain profiles in community-dwelling individuals at risk for knee osteoarthritis. Experimental Gerontology. 2017;98:186-91.

17. Harden RN, Wallach G, Gagnon CM, Zereshki A, Mukai A, Saracoglu M, et al. The osteoarthritis knee model: psychophysical characteristics and putative outcomes. The Journal of Pain. 2013;14(3):281-9.
18. Reid M. Sensitivity to Physical Activity: Identifying Important Predictors and Outcomes in Pain-Free Older Adults Using a Simple Activity-Related Measure. Pain Medicine. 2018;19(8):1512-3.
19. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. The Lancet. 2007;370(9596):1453-7.
20. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis & Rheumatism. 1986;29(8):1039-49.
21. Bannuru RR, Osani M, Vaysbrot E, Arden N, Bennell K, Bierma-Zeinstra S, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis and Cartilage. 2019;27(11):1578-89.
22. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis & Rheumatology. 2020;72(2):220-33.
23. Deyle GD, Allison SC, Matekel RL, Ryder MG, Stang JM, Gohdes DD, et al. Physical therapy treatment effectiveness for osteoarthritis of the knee: a randomized comparison of supervised clinical exercise and manual therapy procedures versus a home exercise program. Physical Therapy. 2005;85(12):1301-17.
24. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health and Quality of Life Outcomes. 2003;1(1):1-8.
25. Collins N, Prinsen C, Christensen R, Bartels E, Terwee C, Roos E. Knee Injury and Osteoarthritis Outcome Score (KOOS): systematic review and meta-analysis of measurement properties. Osteoarthritis and Cartilage. 2016;24(8):1317-29.
26. Sullivan MJ, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. Psychological Assessment. 1995;7(4):524.
27. Ong WJ, Kwan YH, Lim ZY, Thumboo J, Yeo SJ, Yeo W, et al. Measurement properties of Pain Catastrophizing Scale in patients with knee osteoarthritis. Clinical Rheumatology. 2021;40:295-301.
28. Hapidou EG, O'Brien MA, Pierrynowski MR, de Las Heras E, Patel M, Patla T. Fear and avoidance of movement in people with chronic pain: psychometric properties of the 11-Item Tampa Scale for Kinesiophobia (TSK-11). Physiotherapy Canada. 2012;64(3):235-41.
29. Tkachuk GA, Harris CA. Psychometric properties of the Tampa Scale for Kinesiophobia-11 (TSK-11). The Journal of Pain. 2012;13(10):970-7.
30. Dobson F, Hinman RS, Roos EM, Abbott JH, Stratford P, Davis AM, et al. OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. Osteoarthritis and Cartilage. 2013;21(8):1042-52.
31. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. British Medical Journal. 2009;338.
32. Van Buuren S. Flexible imputation of missing data: CRC press; 2018.
33. McHorney CA, Tarlov AR. Individual-patient monitoring in clinical practice: are available health status surveys adequate? Quality of Life Research. 1995;4(4):293-307.

34. Bishara AJ, Hittner JB. Testing the significance of a correlation with nonnormal data: comparison of Pearson, Spearman, transformation, and resampling approaches. Psychological Methods. 2012;17(3):399.
35. Paradowski PT, Bergman S, Sundén-Lundius A, Lohmander LS, Roos EM. Knee complaints vary with age and gender in the adult population. Population-based reference data for the Knee injury and Osteoarthritis Outcome Score (KOOS). BMC Musculoskeletal Disorders. 2006;7:1-8.
36. Tschon M, Contartese D, Pagani S, Borsari V, Fini M. Gender and sex are key determinants in osteoarthritis not only confounding variables. A systematic review of clinical data. Journal of Clinical Medicine. 2021;10(14):3178.
37. Dekker J, van Dijk GM, Veenhof C. Risk factors for functional decline in osteoarthritis of the hip or knee. Current Opinion in Rheumatology. 2009;21(5):520-4.
38. Lee KJ, Carlin JB. Multiple imputation in the presence of non-normal data. Statistics in Medicine. 2017;36(4):606-17.
39. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. Statistics in Medicine. 2011;30(4):377-99.
40. Field A. Discovering statistics using IBM SPSS statistics: Sage; 2017.
41. Overton M, Swain N, Falling C, Gwynne-Jones D, Fillingim R, Mani R. Activity-related pain predicts pain and functional outcomes in people with knee osteoarthritis: A longitudinal study. Frontiers in Pain Research. 2022;3.
42. Calders P, Van Ginckel A. Presence of comorbidities and prognosis of clinical symptoms in knee and/or hip osteoarthritis: a systematic review and meta-analysis. Seminars in Arthritis and Rheumatism. 2018;47(6):805-13.
43. Quartana PJ, Campbell CM, Edwards RR. Pain catastrophizing: a critical review. Expert Review of Neurotherapeutics. 2009;9(5):745-58.
44. Vlaeyen JW, Linton SJ. Fear-avoidance model of chronic musculoskeletal pain: 12 years on. Pain. 2012;153(6):1144-7.

# Chapter 7: General discussion

## 7.1 General discussion

### 7.1.1 Integration of findings

Obesity, quadriceps muscle weakness and joint injury play a role in knee OA pathogenesis, in part, through the creation of an abnormal loading environment at the knee (1). Our findings from chapters 3 and 4 reinforced the notion of knee OA as a complex, multifactorial condition, and shed light on the importance of considering modifiable and non-modifiable systemic (e.g., age, obesity, sex) and mechanical (e.g., obesity, joint injury, joint loading, muscle weakness) risk factors when exploring relationships with knee OA status.

More specifically, Chapter 3 helped to better understand cross-sectional relationships between knee joint loading during walking with regional tibiofemoral cartilage thickness in patients with knee OA. In Chapter 3, a higher KAM impulse was associated with a lower medial-to-lateral cartilage thickness ratio in patients with non-traumatic and post-traumatic knee OA. In addition, a higher late stance KEM was associated with greater medial femoral condyle cartilage thickness and medial-to-lateral cartilage thickness ratio. These cross-sectional relationships differed between patients with non-traumatic and post-traumatic knee OA, suggesting that the potential influence of mechanical knee joint loading on articular cartilage may also differ between these OA subtypes. This could be explained by the fact that patients with post-traumatic knee OA may continue to demonstrate persistent alterations in lower extremity neuromuscular function and movement patterns following their ACL injury or reconstruction, ultimately altering walking kinematics and knee joint loading patterns (2, 3). As a result, altered knee joint loading in patients with post-traumatic knee OA could cause a shift to occur in the contact location to cartilage regions not normally conditioned to increased loading, increasing the susceptibility of these regions to degenerative changes (4).

Moreover, Chapter 4 explored other potential factors contributing to abnormal knee joint loading patterns (i.e., VM intramuscular fat) in patients with non-traumatic and post-traumatic knee OA. More specifically, greater VM intramuscular fat was associated with higher BMI and lower quadriceps muscle strength, but not with radiographic knee OA severity, in patients with non-traumatic and post-traumatic knee OA. These cross-sectional relationships were not dependent on OA subtype. Quadriceps muscle weakness is a common finding in patients with knee OA, and is a risk factor for the development (5) and progression (6) of knee OA. However, the loss of muscle tissue (i.e., due to age-related processes, disuse, etc.) only partly explains quadriceps muscle weakness in this patient population (7). Alternatively, the inverse relationship between knee extensor muscle torque and VM intramuscular fat could be explained by reduced quadriceps muscle quality and impairment in quadriceps muscular function due to the accumulation of VM intramuscular fat. Although not fully understood, the mechanisms are likely related to the release of pro-inflammatory cytokines by intramuscular adipose tissue may impair normal muscle function (8, 9), leading to abnormal loading patterns and an increased susceptibility to joint damage and failure to repair (4). Overall, our findings support past research demonstrating that VM intramuscular fat may be an important determinant of muscle morphology and function.

Then, Chapter 5 mapped out the scientific literature examining the impact of knee joint loading (via PA and sports participation) on implant integrity and failure following knee arthroplasty. To summarize, none of the included studies demonstrated a significant association between greater levels of PA and sports participation with increased implant wear or failure rates in the short- (<5 years) to mid-term (5-10 years) post UKA, whereas results were mixed following TKA. Although our findings are encouraging, it is also possible that studies with short- to mid-term follow-up periods may not have had sufficient time to observe any potential negative impact

of PA level or sports participation on implant integrity or failure. Considering that the majority of knee arthroplasty implants are expected to last 25 years (10), studies with long-term follow-up (>10 years) are needed. In addition, there was a lack of standardized, objective measures used for the assessment of PA and sports participation in included studies. Thus, very limited information was provided regarding relevant activity-related parameters (i.e., duration, frequency, intensity). Together, these limitations must be addressed by future research to be able to confidently make individualized recommendations regarding participation in high-intensity physical activities and/or high-impact sports following knee arthroplasty.

Lastly, Chapter 6 sought to better understand evoked pain responses (i.e., SPA) in response to knee joint loading (i.e., during standardized physical tasks), and assessed the potential merits and limitations of different SPA measurement strategies, in patients with knee OA. In Chapter 6, the 6-Minute Walk Test and the Stair Climb Test were found to be the most evocative physical tasks in patients with knee OA, suggesting that these physical tasks may be most appropriate for assessing SPA in this patient population. These findings are not surprising, given patients with knee OA tend to commonly report pain with weight-bearing activities such as walking and stair climbing (11). However, regression analyses did not support the prognostic value of baseline task-specific SPA-Pain indices for OA-related pain and physical function following an 8-week rehabilitation program in patients with knee OA. This may, in part, be explained by floor effects (>15% of participants) being present for most physical tasks, suggesting they may not have been adequate in evoking sufficient activity-related pain. We concluded that strategies to further optimize the assessment of SPA are needed in patients with knee OA, such as tailoring the intensity of physical tasks to individual pain levels, which could help mitigate floor effects, and potentially improve their predictive value (12).

### 7.1.2 Limitations of the thesis

Limitations generally consistent across multiple studies will be discussed in this section. Firstly, Chapters 3 and 4 were both cross-sectional studies. As a result, the observed cross-sectional relationships do not allow for the inference of causal relationships. It is also important to acknowledge that the measurement of the primary predictors in Chapter 3 (i.e., external knee joint moments) and Chapter 4 (i.e., VM intramuscular fat) are currently confined to gait laboratories with sophisticated and expensive equipment, or require an MRI machine. Both also tend to require experienced personnel to evaluate and interpret findings. Thus, their accessibility and clinical usefulness is limited. In addition, generalizability of findings from Chapter 3, 4 and 6 were limited by characteristics of the study samples. For instance, findings from Chapter 3 and 4 cannot be generalized to patients with severe knee OA or patients with a history of other traumatic knee injuries (e.g., posterior cruciate ligament tear). Findings from Chapter 6 cannot be generalized to patients with knee OA who report more severe symptoms and/or higher scores on psychosocial measures. Similarly, findings from Chapter 5 were only generalizable up to mid-term follow-up following knee arthroplasty. Finally, given the complex, multifactorial nature of knee OA, the statistical models required to evaluate complex relationships in patients with knee OA require fairly large datasets to power their analyses. Therefore, the smaller sample sizes in Chapters 3 and 4, and to a lesser extent, Chapter 6, may have limited our ability to detect smaller effect size relationships, and did not allow for other potentially relevant variables to be accounted for in regression analyses.

### 7.1.3 Clinical implications and future directions

Knee joint loading during functional activities (e.g., ambulation) has been theorized to be a key risk factor for knee OA onset and progression (4). Our findings from Chapter 3 would suggest that the potential influence of mechanical knee joint loading on articular cartilage may differ between patients with non-traumatic and post-traumatic knee OA. Therefore, different treatment approaches may be warranted depending on the knee OA subtype. For instance, gait retraining (e.g., trunk lean, toe-out gait, etc.) is an intervention that has shown to be effective for reducing the KAM (i.e., proxy for medial tibiofemoral joint load) in patients with knee OA (13). Similarly, high tibial valgus osteotomy is an effective treatment for medial compartment knee OA that reduces the load on the medial compartment by shifting the axial load laterally (14). These interventions may be beneficial for patients with non-traumatic knee OA who tend to exhibit structural changes primarily in the medial tibiofemoral compartment (15). However, interventions that offload the medial tibiofemoral compartment may not provide the same benefit, or may even be detrimental, in patients with post-traumatic knee OA, who tend to exhibit structural changes in both tibiofemoral compartments (15). Future research should explore whether the response (i.e., biomechanics, clinical outcomes) to load-modifying interventions differs between patients with non-traumatic and post-traumatic knee OA. Future research should also examine the longitudinal influence of gait kinematics on indicators of disease progression in both knee OA subtypes.

Furthermore, our findings from Chapter 4 would suggest that greater VM intramuscular fat was associated with reduced quadriceps muscle strength in patients with knee OA. As a result, VM (and quadriceps) intramuscular fat may be a potential target for therapeutic interventions. Interventions such as exercise and weight loss can help reduce VM intramuscular fat and improve muscle quality via hypertrophy, which may in turn help to restore optimal VM (and quadriceps) muscle function, enhance knee joint stability and minimize subsequent knee OA progression (16).

These interventions can also help to improve the systemic metabolic profile (7), and mitigate age-related muscle changes (sarcopenia) in patients with knee OA (17). However, the potential impact of a PA intervention on quadriceps intramuscular fat in people with knee OA remains to be assessed. Moreover, it remains unclear whether greater VM intramuscular fat found in patients with knee OA is a contributing factor to OA progression, or simply a consequence of disuse and age-related muscle changes (sarcopenia). Further longitudinal studies are also needed to clarify whether impairments in muscle strength and power in the knee OA population are due to the accumulation of thigh intramuscular fat, the loss of lean muscle mass, other factors (physical inactivity, pain, joint effusion), or a combination thereof.

Our findings from Chapter 5 also have important clinical implications, which were previously discussed in detail. Following knee arthroplasty, patients desire an increased functional capacity, with evolving expectations towards being able to participate in physical activities or sports (18). Therefore, patients should be made aware of the potential risks of higher PA levels or high-impact sports on long-term implant survival, which are not entirely known. Other factors should also be considered when recommending physical activities or sports following knee arthroplasty, such as knee arthroplasty implant type and design, previous experience with a given PA or sport, and general fitness level, among others (19, 20). Consistent with principles of shared decision making, this would allow for patients to make an informed decision, with guidance from their orthopaedic surgeon and physiotherapist, regarding which physical activities and sports to participate in following their knee arthroplasty. Priorities for future research include: 1) large high-quality, prospective cohort studies with long-term (>10 years) follow-up, 2) the use of objective measures (e.g., pedometer, fitness watch) to improve estimates of activity-related parameters (e.g., duration, intensity, frequency), and 3) examining the impact of PA and sport participation on

implant integrity or failure in different patient sub-groups (e.g., patients that participate in vigorous PA and/or high-impact sports).

Lastly, Chapter 6 provided a better understanding of the potential merits and limitations of different SPA measures in patients with knee OA. This was an essential step in developing SPA as a potential clinical assessment tool and integrating sensitized responses to PA within clinical management. We found that the 6-Minute Walk Test and the Stair Climb Test may be most appropriate for assessing SPA in patients with knee OA. This is clinically relevant, as both physical tasks can be used to assess activity-related pain and can be feasibly performed in typical practice settings. In addition, relying solely on measures of physical performance to guide exercise prescription in patients with knee OA may overlook potential negative responses to PA, resulting in a sub-set of patients experiencing symptom flare-ups and ultimately, poor treatment responses. As a result, the clinical measurement of SPA may flag elevated risk of treatment failure and prompt the use of alternate approaches (e.g., tailored activity-based interventions) (21). Next steps for future research include 1) exploring the cross-sectional interrelationships between the biopsychosocial indices of SPA (SPA-Pain, SPA-Sensory, SPA-Psych), and their underlying psychological and sensory constructs in patients with knee OA, and 2) examining the relative prognostic value of these SPA indices for pain and physical function after controlling for relevant prognostic factors in patients with knee OA.

## 7.2 Chapter 7 References


1. Roos EM, Arden NK. Strategies for the prevention of knee osteoarthritis. Nature Reviews Rheumatology. 2016;12(2):92-101.
2. Gardinier ES, Manal K, Buchanan TS, Snyder-Mackler L. Gait and neuromuscular asymmetries after acute ACL rupture. Medicine and Science in Sports and Exercise. 2012;44(8):1490.
3. Kuenze CM, Hertel J, Weltman A, Diduch D, Saliba SA, Hart JM. Persistent neuromuscular and corticomotor quadriceps asymmetry after anterior cruciate ligament reconstruction. Journal of Athletic Training. 2015;50(3):303-12.
4. Andriacchi TP, Mündermann A, Smith RL, Alexander EJ, Dyrby CO, Koo S. A framework for the in vivo pathomechanics of osteoarthritis at the knee. Annals of Biomedical Engineering. 2004;32(3):447-57.
5. Øiestad BE, Juhl CB, Culvenor AG, Berg B, Thorlund JB. Knee extensor muscle weakness is a risk factor for the development of knee osteoarthritis: an updated systematic review and meta-analysis including 46 819 men and women. British Journal of Sports Medicine. 2022;56(6):349-55.
6. Culvenor AG, Ruhdorfer A, Juhl C, Eckstein F, Øiestad BE. Knee extensor strength and risk of structural, symptomatic, and functional decline in knee osteoarthritis: a systematic review and meta-analysis. Arthritis Care & Research. 2017;69(5):649-58.
7. Kumar D, Karampinos DC, MacLeod TD, Lin W, Nardo L, Li X, et al. Quadriceps intramuscular fat fraction rather than muscle size is associated with knee osteoarthritis. Osteoarthritis and Cartilage. 2014;22(2):226-34.
8. Heilbronn L, Smith S, Ravussin E. Failure of fat cell proliferation, mitochondrial function and fat oxidation results in ectopic fat storage, insulin resistance and type II diabetes mellitus. International Journal of Obesity. 2004;28(4):S12-S21.
9. Meyer DC, Hoppeler H, von Rechenberg B, Gerber C. A pathomechanical concept explains muscle loss and fatty muscular changes following surgical tendon release. Journal of Orthopaedic Research. 2004;22(5):1004-7.
10. Evans JT, Walker RW, Evans JP, Blom AW, Sayers A, Whitehouse MR. How long does a knee replacement last? A systematic review and meta-analysis of case series and national registry reports with more than 15 years of follow-up. The Lancet. 2019;393(10172):655-63.
11. Hawker G, Stewart L, French M, Cibere J, Jordan J, March L, et al. Understanding the pain experience in hip and knee osteoarthritis–an OARSI/OMERACT initiative. Osteoarthritis and Cartilage. 2008;16(4):415-22.
12. Woznowski-Vu A, Uddin Z, Flegg D, Aternali A, Wickens R, Sullivan MJ, et al. Comparing novel and existing measures of sensitivity to physical activity among people with chronic musculoskeletal pain. The Clinical Journal of Pain. 2019;35(8):656-67.
13. Rynne R, Le Tong G, Cheung RT, Constantinou M. Effectiveness of gait retraining interventions in individuals with hip or knee osteoarthritis: A systematic review and meta-analysis. Gait & Posture. 2022.
14. Birmingham TB, Giffin JR, Chesworth BM, Bryant DM, Litchfield RB, Willits K, et al. Medial opening wedge high tibial osteotomy: a prospective cohort study of gait, radiographic, and patient-reported outcomes. Arthritis Care & Research. 2009;61(5):648-57.
15. Swärd P, Kostogiannis I, Neuman P, Von Porat A, Boegård T, Roos H. Differences in the radiological characteristics between post-traumatic and non-traumatic knee osteoarthritis. Scandinavian Journal of Medicine & Science in Sports. 2010;20(5):731-9.

16. Teichtahl AJ, Wluka AE, Wang Y, Wijethilake PN, Strauss BJ, Proietto J, et al. Vastus medialis fat infiltration–a modifiable determinant of knee cartilage loss. Osteoarthritis and Cartilage. 2015;23(12):2150-7.
17. Goodpaster BH, Chomentowski P, Ward BK, Rossi A, Glynn NW, Delmonico MJ, et al. Effects of physical activity on strength and skeletal muscle fat infiltration in older adults: a randomized controlled trial. Journal of Applied Physiology. 2008;105(5):1498-503.
18. Dagneaux L, Bourlez J, Degeorge B, Canovas F. Return to sport after total or unicompartmental knee arthroplasty: an informative guide for residents to patients. EFORT Open Reviews. 2017;2(12):496-501.
19. Kuster MS, Horz S, Spalinger E, Stachowiak GW, Gächter A. The effects of conformity and load in total knee replacement. Clinical Orthopaedics and Related Research. 2000;375:302-12.
20. Kuster MS, Stachowiak GW. Factors affecting polyethylene wear in total knee arthroplasty. Orthopedics. 2002;25(2):S235-S42.
21. Wideman TH, Finan PH, Edwards RR, Quartana PJ, Buenaver LF, Haythornthwaite JA, et al. Increased sensitivity to physical activity among individuals with knee osteoarthritis: relation to pain outcomes, psychological factors, and responses to quantitative sensory testing. Pain. 2014;155(4):703-11.

# Chapter 8: Conclusion and summary

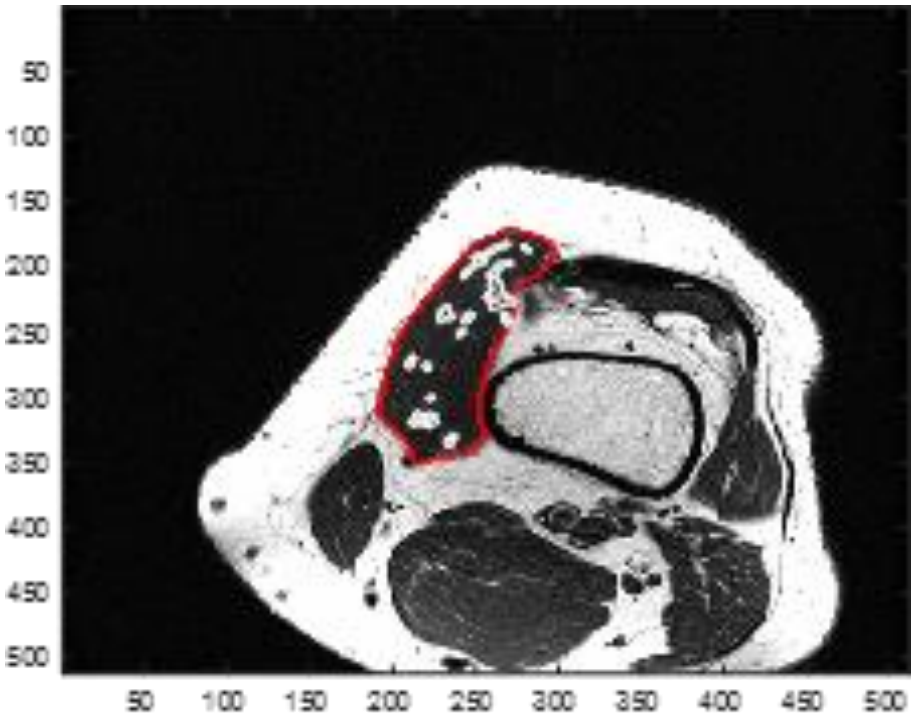
## 8.1 Conclusion and summary

This thesis aimed to better understand the impact of loading and PA measures on outcomes in patients with knee OA, and implant survivorship in patients following knee arthroplasty. First, a cross-sectional study found that relationships between knee joint moments with tibiofemoral cartilage thickness differed between patients with non-traumatic and post-traumatic knee OA. Next, a second cross-sectional study revealed that greater VM intramuscular fat was associated with reduced quadriceps muscle torque, but not OA severity or OA subtype. Then, a scoping review found that none of the included studies demonstrated an association between greater levels of PA and sports participation with increased implant wear or failure rates in the short- to mid-term post UKA, whereas results were mixed following TKA. Lastly, the results of our longitudinal observational study would suggest that the 6-Minute Walk Test and Stair Climb Test may be the most appropriate physical tasks for assessing SPA in patients with knee OA. However, regression analyses did not support the prognostic value of task-specific SPA-Pain indices with respect to recovery trajectories following an 8-week rehabilitation program in patients with knee OA.

Altogether, this work has identified: 1) potential differences in how knee joint loading may impact articular cartilage between patients with non-traumatic and post-traumatic knee OA, 2) the potential role of VM intramuscular fat in impairing quadriceps muscle function in patients with knee OA, 3) the state of the scientific literature regarding the impact of PA level and sports participation on implant integrity and failure following knee arthroplasty, and 4) the potential merits and limitations of different SPA measurement strategies in patients with knee OA. This provides researchers with the necessary foundation to conduct future research on these topics. Additional research is also needed to guide clinical care.

# Appendix

**Appendix 1.1.** An example of vastus medialis muscle segmentation (red contours), along with vastus medialis fat segmentation (white contours).



**Appendix 1.2.** Correlation coefficients for associations between vastus medialis (VM) intramuscular fat (intraMF), body weight normalized knee extensor muscle torque, VM cross-sectional area (CSA), radiographic knee osteoarthritis (OA) severity, sex, age and body mass index (BMI).

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| 1. VM IntraMF | - | | | | | | |
| 2. Knee Extensor Muscle Torque[a] | -0.455** | - | | | | | |
| 3. VM CSA | -0.225 | 0.448** | - | | | | |
| 4. OA Severity[b] | 0.191 | -0.134 | -0.018 | - | | | |
| 5. Sex[c] | -0.319* | 0.427** | 0.691** | 0.068[d] | - | | |
| 6. Age | 0.307 | -0.453** | -0.562** | 0.131 | -0.370* | - | |
| 7. BMI | 0.640** | -0.374* | 0.018 | 0.212 | -0.145 | 0.071 | - |

[a] One participant was missing data for knee extensor muscle torque.

[b] Relationships between radiographic knee OA severity and all other variables (except sex) were examined using Kendall's τ correlations. One participant was missing a KL score.

[c] Relationships between sex and all other variables (except radiographic knee OA severity) were examined using point-biserial correlations.

[d] The relationship between sex and radiographic knee OA severity was examined using a chi-squared test of independence with Cramer's V statistic.

All other relationships were examined using Pearson's correlations.

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

**Appendix 1.3.** Unstandardized regression coefficients examining the relationship between vastus medialis intramuscular fat with osteoarthritis group and radiographic knee osteoarthritis severity – a comparison of the regression results with and without high leverage data points.

| | | Sex<br>B (95% CI) | BMI<br>B (95% CI) | Knee OA Group<br>B (95% CI) | Radiographic Knee OA Severity*<br>B (95% CI) |
|---|---|---|---|---|---|
| With High Leverage Data Points (n = 40) | Vastus Medialis Intramuscular Fat | -1.512<br>(-3.298, 0.274)<br>*P* = 0.095 | **0.321**<br>**(0.173, 0.469)**<br>***P* < 0.001** | -0.167<br>(-2.040, 1.705)<br>*P* = 0.857 | 0.857<br>(-0.902, 2.617)<br>*P* = 0.329 |
| Without High Leverage Data Points (n = 38) | Vastus Medialis Intramuscular Fat | -1.308<br>(-2.723, 0.108)<br>*P* = 0.069 | **0.250**<br>**(0.093, 0.407)**<br>***P* = 0.003** | -0.354<br>(-1.833, 1.126)<br>*P* = 0.630 | 0.318<br>(-1.140, 1.776)<br>*P* = 0.660 |

Unstandardized coefficients (B) with 95% confidence intervals (CI) are provided. Sex (0 = females, males = 1) and body mass index (BMI) were accounted for in the regression model. Significant associations are in bold ($P < 0.05$). Only significant interactions were retained in the model. **OA**: osteoarthritis. Units for VM intramuscular fat are in percent (%) fat. *One participant in the non-traumatic OA group was missing a KL score. **Total explained variance ($R^2$) for the regression model with and without high leverage data points was 48% and 37%, respectively.**

**Appendix 1.4.** Unstandardized regression coefficients examining the between body weight normalized knee extensor muscle torque with vastus medialis intramuscular fat and vastus medialis muscle cross-sectional area – a comparison of the regression results with and without high leverage data points.

| | | Sex<br>B (95% CI) | VM Cross-sectional Area<br>B (95% CI) | VM Intramuscular Fat<br>B (95% CI) |
|---|---|---|---|---|
| With High Leverage Data Points (n = 40) | Knee Extensor Muscle Torque* | 0.086<br>(-0.218, 0.391)<br>*P* = 0.568 | <0.001<br>(0.000, 0.001)<br>*P* = 0.140 | **-0.040**<br>**(-0.072, -0.007)**<br>***P* = 0.018** |
| Without High Leverage Data Points (n = 38) | Knee Extensor Muscle Torque* | 0.041<br>(-0.279, 0.361)<br>*P* = 0.795 | <0.001<br>(0.000, 0.001)<br>*P* = 0.107 | **-0.060**<br>**(-0.109, -0.012)**<br>***P* = 0.016** |

Unstandardized coefficients (B) with 95% confidence intervals (CI) are provided. Sex (0 = females, males = 1) and vastus medialis (VM) muscle cross-sectional area were accounted for in the regression analyses. Significant associations are in bold ( *P* <0.05). Units for VM cross-sectional area and intramuscular fat are in $mm^2$ and percent (%) fat, respectively.*One participant in the non-traumatic OA group was missing data on knee extensor muscle torque. **Total explained variance ($R^2$) for the regression model with and without high leverage data points was 34% and 32%, respectively.**

**Appendix 1.5.** Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR).

| SECTION | ITEM | PRISMA-ScR CHECKLIST ITEM | REPORTED ON PAGE # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a scoping review. | Page 95 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives. | Page 96 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach. | Pages 97-99 |
| Objectives | 4 | Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives. | Pages 98-99 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number. | Page 99 |
| Eligibility criteria | 6 | Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale. | Pages 100-101 Table 5.1 |
| Information sources* | 7 | Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed. | Page 100 |
| Search | 8 | Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated. | Appendix 1.6a to 1.6e |

| SECTION | ITEM | PRISMA-ScR CHECKLIST ITEM | REPORTED ON PAGE # |
|---|---|---|---|
| Selection of sources of evidence† | 9 | State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review. | Pages 101-102 |
| Data charting process‡ | 10 | Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators. | Page 102 |
| Data items | 11 | List and define all variables for which data were sought and any assumptions and simplifications made. | Page 102 |
| Critical appraisal of individual sources of evidence§ | 12 | If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate). | Page 103 |
| Synthesis of results | 13 | Describe the methods of handling and summarizing the data that were charted. | Page 102 |
| **RESULTS** | | | |
| Selection of sources of evidence | 14 | Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram. | Summary on Page 105 Figure 5.1 |
| Characteristics of sources of evidence | 15 | For each source of evidence, present characteristics for which data were charted and provide the citations. | Pages 105-106 Appendix 1.7 |
| Critical appraisal within sources of evidence | 16 | If done, present data on critical appraisal of included sources of evidence (see item 12). | Page 106 Appendix 1.10a and 1.10b |
| Results of individual sources of evidence | 17 | For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives. | Pages 107-109 |
| Synthesis of results | 18 | Summarize and/or present the charting results as they relate to the review questions and objectives. | Tables 5.2 and 5.3, Appendix 1.11 |
| **DISCUSSION** | | | |
| Summary of evidence | 19 | Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review | Pages 113-116 |

| SECTION | ITEM | PRISMA-ScR CHECKLIST ITEM | REPORTED ON PAGE # |
|---|---|---|---|
| | | questions and objectives, and consider the relevance to key groups. | |
| Limitations | 20 | Discuss the limitations of the scoping review process. | Pages 116-117 |
| Conclusions | 21 | Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps. | Page 117 |
| **FUNDING** | | | |
| Funding | 22 | Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review. | Summary on page 106 Appendix 1.9 |

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where sources of evidence (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with information sources (see first footnote).

‡ The frameworks by Arksey and O'Malley and Levac and colleagues and the JBI guidance refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

**Appendix 1.6a. to 1.6e.** Complete search strategies and results for each online database.

**a) Medline (Ovid)**

Database: Medline via OVID, 1946 to Present

No limits

Original Search Date: June 9, 2021. **Results**: 448

Updated Search Date: August 19, 2022. **Results**: 510

**Search Strategy**

| No. | Search Terms | Results June 9, 2021 | Results August 19, 2022 |
|---|---|---|---|
| 1 | knee arthroplasty.mp. or Arthroplasty, Replacement, Knee/ | 34938 | 38846 |
| 2 | knee replacement*.mp. | 10310 | 11136 |
| 3 | Prosthesis Failure/ | 29880 | 31044 |
| 4 | Reoperation/ | 89928 | 93734 |
| 5 | (survivorship or reoperation or revision or durability or wear or adverse or complication* or failure*).tw,kf. | 2309261 | 2514355 |
| 6 | exp Exercise/ | 210666 | 235021 |
| 7 | exp Physical Fitness/ | 32430 | 35227 |
| 8 | (activity level* or exercise or physical activity or physical fitness or sport or athlete or athletic).tw,kf. | 441937 | 482434 |
| 9 | 6 or 7 or 8 | 529333 | 577287 |
| 10 | 3 or 4 or 5 | 2355318 | 2561273 |
| 11 | 1 or 2 | 38380 | 42424 |
| **12** | **9 and 10 and 11** | **448** | **510** |

**b) Search Strategy for Embase+Embase Classic**

Database: OVID, 1947 to Present

No limits

Original Search Date: June 9, 2021. **Results**: 621

Updated Search Date: August 19, 2022. **Results**: 702

**Search Strategy**

| No. | Search Terms | Results June 9, 2021 | Results August 19, 2022 |
|---|---|---|---|
| 1 | knee arthroplasty.mp. or knee arthroplasty/ | 43010 | 47114 |
| 2 | knee replacement*.mp. or knee replacement/ | 30549 | 32183 |
| 3 | prosthesis complication/ | 2186 | 2853 |
| 4 | reoperation/ | 90704 | 98134 |
| 5 | (survivorship or reoperation or revision or durability or wear or adverse or complication* or failure*).tw,kw. | 3441514 | 3649398 |
| 6 | exp exercise/ | 392087 | 425258 |
| 7 | exp fitness/ | 41819 | 43800 |
| 8 | (activity level* or exercise or physical activity or physical fitness or sport or athlete or athletic).tw,kw. | 606621 | 648074 |
| 9 | 6 or 7 or 8 | 53815 | 58386 |
| 10 | 3 or 4 or 5 | 3469992 | 3680039 |
| 11 | 1 or 2 | 740123 | 794565 |
| **12** | **9 and 10 and 11** | **621** | **702** |

**c) Search Strategy for SCOPUS**

Database: SCOPUS

No limits

Original Search Date: June 9, 2021. **Results:** 208

Updated Search Date: August 19, 2022. **Results:** 233

**Search Strategy**

(TITLE-ABS-KEY(knee arthroplasty OR knee replacement*))

AND (TITLE-ABS-KEY(prosthesis failure OR reoperation OR revision OR survivorship OR durability OR wear OR adverse OR complication* OR failure*))

AND (TITLE-ABS-KEY(exercise OR physical fitness OR activity level* OR exercise OR physical activity OR sport OR athlete OR athletic))

**d) Search Strategy for CINAHL Plus with Full Text**

Database: EBSCO

Search Mode: Boolean/Phrase

No limits

Original Search Date: June 9, 2021. **Results**: 197

Updated Search Date: August 19, 2022. **Results**: 242

**Search Strategy**

| No. | Search Terms | Results June 9, 2021 | Results August 19, 2022 |
|---|---|---|---|
| 1 | (MH "Arthroplasty, Replacement, Knee") | 17,337 | 19,508 |
| 2 | (MH "Prosthesis Failure") | 10,100 | 10,887 |
| 3 | (MH "Reoperation") | 19,073 | 21,062 |
| 4 | TI ( (survivorship or reoperation or revision or durability or wear or adverse or complication* or failure*) ) OR AB ( (survivorship or reoperation or revision or durability or wear or adverse or complication* or failure*) ) | 522,815 | 589,458 |
| 5 | (MH "Exercise+") | 119,216 | 127,372 |
| 6 | (MH "Physical Fitness+") | 19,399 | 20,410 |
| 7 | TI ( (activity level* or exercise or physical activity or physical fitness or sport or athlete or athletic) ) OR AB ( (activity level* or exercise or physical activity or physical fitness or sport or athlete or athletic) ) | 234,768 | 257,455 |
| 8 | (S2 or S3 or S4) | 532,792 | 599,488 |
| 9 | (S2 or S3 or S4) and (S5 or S6 or S7) | 20,950 | 23,618 |
| **10** | **((S2 or S3 or S4) and (S5 or S6 or S7)) and (S1 and S8 and S9)** | **197** | **242** |

**e) ProQuest Theses & Dissertations**

Database: ProQuest

Search Mode: Boolean/Phrase

Limits: full text available

Original Search Date: June 9, 2021. **Results:** 14

Updated Search Date: August 19, 2022. **Results:** 17

**Search Strategy**

noft(("knee arthroplasty" OR "knee replacement") AND ("prosthesis failure" OR reoperation OR survivorship OR revision OR durability OR wear OR adverse OR complication* OR failure*) AND (exercise OR "physical activity" OR "physical fitness" OR ("activity level" OR "activity levels") OR sport OR athlete OR athletic))

**Appendix 1.7.** Study characteristics & participant baseline demographic information.

| Author & Year | Country | Surgical Procedure | Study Design | Mean Follow-Up | Number of participants (% female) | Primary Diagnosis n (%) | Mean age (range) |
|---|---|---|---|---|---|---|---|
| Ali et al., 2016[a] | United Kingdom | UKA | Prospective cohort study | 6.1 years (range: 1-14) | 818 (52) | OA: 977 knees (98%)<br>Osteonecrosis: 23 knees (2%) | 66 years (range: 32-88) |
| Crawford et al., 2019 | USA | UKA | Retrospective cohort study | 9 years (range: 4-13.1) | 487 (59) | OA: 576 knees (100%)[b] | 62.3 years<br>58.9 years |
| Hamilton et al., 2017[a] | United Kingdom | UKA | Prospective cohort study | 10.3 years (range: 5.3-16.6) | 818 (52) | Knee OA 977 (98%)<br>Osteonecrosis 23 knees (2%) | 66 years (range: 32-88) |
| Pietschmann et al., 2013 | Germany | UKA | Retrospective cohort study | 4.2 years (range: 1-10) | 131 (56) | OA: 131 knees (100%) | 65.3 years (range 44–90) |
| Presti et al., 2019 | Italy | UKA | Prospective case series | 4 years (range: 2-6) | 53 (72) | OA: 53 knees (100%)[b] | 59.7 years (range 46–66) |
| Schai et al., 1998 | USA | UKA | Prospective cohort study | 3.33 years (range: 2-6) | 28 (61) | OA: 24 knees (86%)<br>Osteonecrosis: 2 knees (7%)<br>Post-traumatic arthritis: 2 knees (7%) | 52 (range: 37-60) |
| Argenson et al., 2013 | France | TKA | Retrospective cohort study | Minimum of 10 years | 828 (67) | OA: 753 knees (89%)<br>RA: 69 knees (8%)<br>Osteonecrosis: 24 knees (3%) | 71 years (range: 41-93) |
| Bauman et al., 2007 | Canada | TKA | Cross-sectional survey | 3.1 years | 184 (59) | OA: 184 knees (100%)[b] | 68.9 years (SD: 9.5 years, range: 41-88) |
| Bercovy et al., 2015 | France | TKA | Prospective cohort study | 7.5 years (range: 5-13) | 482 (66) | OA: 536 knees (91%)<br>Osteonecrosis: 17 knees (2.9%)<br>RA: 16 knees (2.7%)<br>Post-traumatic arthritis: 15 knees (2.6%) | 70.6 (range: 40.1–91.2) |
| Bradbury et al., 1998 | United Kingdom | TKA | Retrospective cohort study | 5 years (range: 3-7) | 160 (55) | OA: 142 patients (89%)<br>Osteonecrosis: 7 patients (4%) | 68 years (range: 27-87) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | RA: 7 patients (4%)<br>Chondrocalcinosis: 3 patients (2%) | |
| Crawford et al., 2020 | USA | TKA | Retrospective cohort study | 11.4 years (SD: 1.5, range: 4-13.1) | 1611 (65) | OA: 2038 knees (100%)[b] | 64.9, 62.3 |
| Heck et al., 1992 | USA | TKA | Matched case-control study | 6 years (range: 0.8-9.6) | 9 (44) | OA: 10 knees (83.3%)<br>RA: 1 knee (8.3%)<br>Gout: 1 knee (8.3%) | 67.4 years (range: 60-85 years) |
| Jones et al., 2004 | USA | TKA | Matched case-control study | 6.4 years (SD: 2.3, range: 2-11) | 52 (65) | OA: 76 knees (100%) | 70.5 (SD: 8.9, range: 47-85) |
| Lavernia et al., 2001 | USA | TKA | Retrospective cohort study | 6.2 years (range: 2.3-11.3) | 22 (68) | OA: 15 patients (65%)<br>RA: 6 patients (26%)<br>Osteonecrosis: 1 patient (4.3%) | 68 years (SD: 14.0) |
| Luetzner et al., 2007 | Germany | TKA | Prospective cohort study | Unilateral TKA: 5.5 years (range: 4.9-7.2)<br>Bilateral TKA: 6.3 years (range: 4.8-10.2) | 41 (63) | OA: 64 knees (100%)[b] | 74 years (range: 67–79) |
| Mayr et al., 2015 | Germany | TKA | Retrospective cohort study | 6.4 ± 0.9 years | 81 (53) | Grade IV knee OA: 81 knees (100%) | 71.8 (SD: 5.4 years) |
| Mont et al., 2007 | USA | TKA | Retrospective cohort study | 7 years (range: 4-14) | 114 (61) | OA: 141 knees (98%)<br>RA: 1 knee (0.7%)<br>Osteonecrosis: 2 knees (1.3%) | 70 years (range: 41–86) |
| Ponzio et al., 2018 | USA | TKA | Retrospective cohort study | Last follow-up: 5-10 years | 2016 (43) | OA: 2016 knees (100%) | 66.3 years |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Reiner et al., 2020 | Germany | TKA | Prospective cohort study | Last follow-up: 1 year | 25 (48) | OA: 25 patients (100%)<br>Primary OA: 22 patients (88%)<br>Secondary OA: 3 patients (12%) | 64.7 years (range: 42–81) |

[a]Ali et al. 2016 & Hamilton et al. 2017 reported on the same dataset with different follow-up periods and were counted as one study for the purpose of this scoping review.

[b]Study authors were contacted to confirm the primary diagnosis in patients undergoing a knee arthroplasty.

**UKA**: unicompartmental knee arthroplasty, **TKA**: total knee arthroplasty, **OA**: osteoarthritis, **SD**: standard deviation.

**Appendix 1.8.** Implant-related information in included studies.

| Author & Year | Surgical Procedure | Company & Design | Type of Bearing | Type of Fixation |
|---|---|---|---|---|
| Ali et al., 2016[a] | UKA | Phase 3 - Oxford (Zimmer Biomet) | Mobile | Cemented |
| Crawford et al., 2019 | UKA | Oxford (Zimmer Biomet) | Mobile | Not specified |
| Hamilton et al., 2017[a] | UKA | Oxford (Zimmer Biomet) | Mobile | Cemented |
| Pietschmann et al., 2013 | UKA | Phase 3 - Oxford (Zimmer Biomet) | Not specified | Not specified |
| Presti et al., 2019 | UKA | Uni Preservation prosthesis (DePuy International Ltd) | Not specified | Cemented tibial component |
| Schai et al., 1998 | UKA | PFC System (Johnson & Johnson) | Not specified | Not specified |
| Argenson et al., 2013 | TKA | Posterior-stabilized (56%)<br>Ultra-congruent (37%)<br>Posterior cruciate retaining (17%) | Fixed (39%)<br>Mobile (61%) | Cemented (83%)<br>Cementless (12%)<br>Hybrid fixation (5%) |
| Bauman et al., 2007 | TKA | Not specified | Not specified | Not specified |
| Bercovy et al., 2015 | TKA | Rotating Concave-Convex (ROCC, Biomed) | Mobile | Femoral components were either cementless with hydroxyapatite coating (93.4%) or cemented (6.6%). Tibial components were either cemented (66.9%) or cementless (33.1%). |
| Bradbury et al., 1998 | TKA | Tricon (1%, Smith and Nephew Richards), Geomedic (2%), Kinematic (2%, Howmedica), Miller Galante 1 (7%, Zimmer), Miller Galante 2 (59%, Zimmer), Motus (28%, Osteo). | Not specified | Geomedic, Kinematic (Cemented) Miller Galante, Miller Galante 2, Motus, Tricon (Not cemented) |
| Crawford et al., 2020 | TKA | Vanguard complete knee system (Zimmer Biomet) | Not specified | Cemented |

| | | | | |
|---|---|---|---|---|
| Heck et al., 1992 | TKA | RAM Gustilo (17%, Dow Corning Wright Inc), Variable Axis (50%, Howmedica Inc), Geomedic (8%), PCA Button (8%), Duopatella (8%), Guepar (8%) | Not specified | Not specified |
| Jones et al., 2004 | TKA | PCL-retaining: 80% cases, 52% controls<br>PCL-sacrificing: 4% cases, 0% controls<br>PCL-substitution: 16% cases, 36% controls<br>Constrained: 0% cases, 12% controls | Not specified | Cemented component:<br>Femoral: 23% cases, 69% controls<br>Tibial: 58% cases, 100% controls<br>Patellar: 73% cases, 100% controls |
| Lavernia et al., 2001 | TKA | PCA prosthesis with a non-conforming flat on flat design | Not specified | Cemented (21%)<br>Biologically fixed (79%) |
| Luetzner et al., 2007 | TKA | Foundation Knee System (Plus Orthopedics GmbH) | Unconstrained | Cemented |
| Mayr et al., 2015 | TKA | Cruciate-retaining TKA with rotating platform (LCS) | Rotating platform | Cemented |
| Mont et al., 2007 | TKA | PCL-retaining Duracon Total Knee System (Stryker Orthopaedics) | Not specified | Not specified |
| Ponzio et al., 2018 | TKA | Not specified | Not specified | Not specified |
| Reiner et al., 2020 | TKA | PFC SIGMA Total Knee System (92%, DePuy Orthopedics Inc)<br>PFC ® SIGMA TC3 Knee System (8%), DePuy Orthopedics Inc) | Fixed | Cemented all-polyethylene resurfacing of the patella (24%) |

[a]Ali et al. 2016 & Hamilton et al. 2017 reported on the same dataset with different follow-up periods and were counted as one study for the purpose of this scoping review.

UKA: unicompartmental knee arthroplasty, TKA: total knee arthroplasty, PCL: posterior cruciate ligament, PCA: porous coated anatomic

**Appendix 1.9.** Funding sources and disclosures of interest in included studies.

| Author & Year | Surgical Procedure | Funding Source | Role of Funding Source | Disclosures of Interest[b] |
|---|---|---|---|---|
| Ali et al., 2016[a] | UKA | Did not specify | Did not specify | One or more authors received benefits for personal or professional use from a commercial party. |
| Crawford et al., 2019 | UKA | Institutional research funding in direct support of this study was received from Zimmer Biomet. | Did not specify | One or more authors disclosed potential conflicts of interest, including receipt of payment from a commercial party. |
| Hamilton et al., 2017[a] | UKA | Study funded by the National Institute for Health Research (NIHR) Biomedical Research Center. Financial support was received from Zimmer Biomet. | Did not specify | One or more authors disclosed potential conflicts of interest, including receipt of payment from a commercial party |
| Pietschmann et al., 2013 | UKA | Did not specify | Did not specify | Did not specify |
| Presti et al., 2019 | UKA | Did not specify | Did not specify | None declared |
| Schai et al., 1998 | UKA | Did not specify | Did not specify | Did not specify |
| Argenson et al., 2013 | TKA | Did not specify | Did not specify | Several authors are consultants for and/or receive royalties from commercial parties. |
| Bauman et al., 2007 | TKA | Did not specify | Did not specify | Did not specify |
| Bercovy et al., 2015 | TKA | No external funding was received. | Not applicable | One or more authors disclosed potential conflicts of interest, including receipt of payment from a commercial party. |
| Bradbury et al., 1998 | TKA | Did not specify | Did not specify | None declared |
| Crawford et al., 2020 | TKA | Did not specify | Did not specify | One or more authors disclosed potential conflicts of interest, including receipt of payment from a commercial party. |

| | | | | |
|---|---|---|---|---|
| Heck et al., 1992 | TKA | Did not specify | Did not specify | Did not specify |
| Jones et al., 2004 | TKA | Study supported by the Arthritis Foundation and the Foundation for Physical Therapy. | Did not specify | Did not specify |
| Lavernia et al., 2001 | TKA | Study supported by a grant from the Arthritis Surgery Research Foundation. | Did not specify | Did not specify |
| Luetzner et al., 2007 | TKA | Did not specify | Did not specify | One or more of the authors received funding from a commercial party. |
| Mayr et al., 2015 | TKA | Study supported by the Alwin Jaeger foundation (AJS). | Did not specify | One or more authors disclosed potential conflicts of interest, including receipt of payment from a commercial party. |
| Mont et al., 2007 | TKA | Did not specify | Did not specify | One or more of the authors received funding from Stryker Orthopaedics. The institutions of the authors have also received funding from Stryker Orthopaedics. |
| Ponzio et al., 2018 | TKA | No external funding was received | Not applicable | None declared |
| Reiner et al., 2020 | TKA | Did not specify | Did not specify | Did not specify |

[a]Ali et al. 2016 & Hamilton et al. 2017 reported on the same dataset with different follow-up periods and were counted as one study for the purpose of this scoping review.

[b]Examples of receipt of payment from a commercial party include, but are not limited to, royalties, paid presentations and paid consulting.

UKA: unicompartmental knee arthroplasty, TKA: total knee arthroplasty

**Appendix 1.10a.** Risk of bias assessment using the NIH Study Quality Assessment Tool for Observational Cohort & Cross-Sectional Studies.

| Author & Year | Surgery | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | Risk of Bias |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ali et al., 2016 | UKA | N | N | Y | CD | N | Y | Y | Y | Y | Y | Y | NR | Y | N | Moderate |
| Crawford et al., 2019 | UKA | Y | Y | Y | Y | N | Y | Y | Y | Y | N | Y | NR | NR | N | Moderate |
| Hamilton et al., 2017 | UKA | Y | N | Y | CD | N | Y | Y | Y | Y | Y | Y | NR | Y | N | Moderate |
| Pietschmann et al., 2013 | UKA | Y | N | Y | Y | N | Y | N | Y | Y | Y | Y | NR | N | N | Moderate |
| Presti et al., 2019 | UKA | Y | N | Y | CD | N | Y | N | Y | N | Y | Y | NR | Y | NA | Moderate |
| Schai et al., 1998 | UKA | N | Y | Y | Y | N | Y | N | N | Y | Y | Y | NR | Y | N | Moderate |
| Argenson et al., 2013 | TKA | N | N | CD | CD | N | CD | Y | Y | N | N | Y | NR | Y | N | High |
| Bradbury et al., 1998 | TKA | N | N | CD | CD | N | Y | Y | Y | N | Y | Y | NR | Y | N | High |
| Bauman et al., 2007 | TKA | Y | Y | Y | Y | N | N | N | Y | Y | N | Y | NR | NA | NA | Moderate |
| Bercovy et al., 2015 | TKA | Y | N | Y | CD | N | Y | Y | Y | Y | Y | Y | NR | Y | N | Moderate |
| Crawford et al., 2020 | TKA | Y | Y | Y | Y | N | Y | Y | Y | Y | N | Y | NR | Y | Y | Low |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lavernia et al., 2001 | TKA | N | N | CD | CD | N | Y | Y | Y | Y | Y | Y | NR | NA | CD | High |
| Luetzner et al., 2007 | TKA | Y | N | CD | CD | Y | N | Y | N | Y | N | Y | NR | NA | CD | High |
| Mayr et al., 2015 | TKA | N | N | Y | Y | Y | N | Y | Y | N | N | Y | NR | NA | NA | High |
| Mont et al., 2007 | TKA | Y | N | N | CD | Y | N | Y | Y | Y | N | Y | NR | NA | NA | High |
| Ponzio et al., 2018 | TKA | Y | Y | N | Y | N | Y | Y | Y | Y | Y | Y | NR | Y | Y | Low |
| Reiner et al., 2020 | TKA | Y | Y | Y | Y | N | Y | N | N | Y | N | Y | NR | Y | Y | Moderate |

**Risk of bias was assessed using the National Institutes of Health (NIH) Study Quality Assessment Tool for Observational Cohort & Cross-Sectional Studies** (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). **1.** Was the research question or objective in this paper clearly stated? **2.** Was the study population clearly specified and defined? **3.** Was the participation rate of eligible persons at least 50%? **4.** Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? **5.** Was a sample size justification, power description, or variance and effect estimates provided? **6.** For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? **7.** Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? **8.** For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? **9.** Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? **10.** Was the exposure(s) assessed more than once over time? 11**.** Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? **12.** Were the outcome assessors blinded to the exposure status of participants? 13. Was loss to follow-up after baseline 20% or less? **14.** Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? **UKA:** unicompartmental knee arthroplasty, **TKA:** total knee arthroplasty**, CD:** cannot be determined, **NA:** not applicable, **NR:** not reported, **N:** no**, Y:** yes**.**

**Appendix 1.10b.** Risk of bias assessment using the NIH Study Quality Assessment Tool for Case-Control Studies.

| Author & Year | Surgery | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | Risk of Bias |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Heck et al., 1992 | TKA | N | N | N | CD | CD | Y | CD | N | Y | CD | NR | N | High |
| Jones et al., 2004 | TKA | Y | Y | N | Y | Y | Y | CD | N | Y | Y | Y | Y | Low |

**Risk of bias was assessed using the National Institutes of Health (NIH) Study Quality Assessment tool for Case-Control Studies** (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools)**. 1.** Was the research question or objective in this paper clearly stated and appropriate? **2.** Was the study population clearly specified and defined? **3.** Did the authors include a sample size justification? **4.** Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)? **5.** Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants? **6.** Were the cases clearly defined and differentiated from controls? **7.** If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible? **8.** Was there use of concurrent controls? **9.** Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case? **10.** Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants? **11.** Were the assessors of exposure/risk blinded to the case or control status of participants? **12.** Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis? **TKA:** total knee arthroplasty, **CD**: cannot be determined, **NA**: not applicable, **NR**: not reported, **N**: no, **Y**: yes.

**Appendix 1.11.** Key constructs and study findings.

| Author & Year | Surgery | Physical Activity | Sports Participation | Implant Failure | Implant Integrity | Key Study Findings |
|---|---|---|---|---|---|---|
| Ali et al., 2016[a] | UKA | ✓ | | ✓ | | Increasing activity associated with superior survival ($P$ = 0.025). In the high activity group, 2.6% were revised and the 12-year implant survival was 97.3% (95% CI: 92.0-99.1%). In the low activity group, 4.3% were revised and the 12-year implant survival was 94.0% (95% CI: 91.4-95.8%). The difference between groups was not significant ($P$ = 0.44). |
| Crawford et al., 2019 | UKA | ✓ | | ✓ | ✓ | Implant revisions were performed in 8.4% of the low activity group and 6.2% of the high-activity group ($P$ = 0.43). At the mean 9-year follow-up, survival to endpoint of revision for any cause for the high activity group was 94.0% (95% CI: 90.9-97.1%) and 92.1% (95% CI: 90.7-93.5%) for the low activity group ($P$ = 0.60). There was also no difference in mean meniscal bearing thickness between groups ($P$ = 0.65). |
| Hamilton et al., 2017[a] | UKA | ✓ | | ✓ | | The 15-year implant survival was 90.1% (95% CI: (72.1-100%) in the high activity group and 92.5 (95% CI: 86.7-98.4%). The difference between groups was not significant ($P$ = 0.51). |
| Pietschmann et al., 2013 | UKA | ✓ | | ✓ | ✓ | No significant correlation between implant position with sports activity ($P$ > 0.05) at a mean follow-up of 4.2 years. No difference in revision rate between active and inactive groups (2 per group). |
| Presti et al., 2019 | UKA | | ✓ | ✓ | | There were no implant failures or revisions at a mean follow-up of 4 years, regardless of sport (low-impact sport vs. high-impact sport). |
| Schai et al., 1998 | UKA | ✓ | | | ✓ | No significant correlation between activity level and the presence of tibial radiolucent lines ($P$ = 0.08) at a mean follow-up of 3.3 years. |
| **Argenson et al., 2013** | TKA | ✓ | | ✓ | | At a minimum of 10 years follow-up, there was a significant correlation between revision rate with activity level assessed using the Devane classification ($P$ = 0.03), whereby risk of TKA implant mechanical complications (i.e., implant loosening) increased with greater activity. |
| Bauman et al., 2007 | TKA | ✓ | | ✓ | ✓ | There were no documented implant revisions, evidence of osteolysis, implant loosening, or signs of implant wear, regardless of UCLA score at a mean follow-up of 3.1 years. |

| | | | | | | |
|---|---|---|---|---|---|---|
| Bercovy et al., 2015 | TKA | ✓ | | ✓ | ✓ | There were no significant correlations between UCLA activity score and radiolucent lines at the tibial or femoral interface ($P = 0.2$) at a mean follow-up of 7.5 years. None of the UCLA ≥ 8 patients had reoperation, revision or modification of the implant interfaces, and Kaplan–Meier survivorship in this group was 100%. |
| Bradbury et al., 1998 | TKA | | ✓ | ✓ | | Similar revision rate in patients who returned to sports (9.8%) vs. patients who did not (9.2%) at a mean follow-up of 5 years. |
| Crawford et al., 2020 | TKA | ✓ | | ✓ | ✓ | The all-cause 12-year survivorship was greater in the high activity group (98%, 95% CI: 97.4-98.6%) compared to the low activity group ($P = 0.003$). In patients who did not have a revision, radiographic radiolucencies and/or polyethylene wear were documented in 5 knees (0.4%) in the low-activity group and 7 knees (0.9%) in the high-activity group ($P = 0.23$). |
| **Heck et al., 1992** | TKA | ✓ | | ✓ | | At a mean follow-up of 6 years, the revision group (cases, n = 12 knees) had higher activity levels compared to the control group ($P = 0.02$) |
| Jones et al., 2004 | TKA | ✓ | ✓ | ✓ | | No association between leisure activity, occupational activity or total physical activity with the risk of revision arthroplasty at a mean follow-up of 8 years ($P > 0.05$). |
| **Lavernia et al., 2001** | TKA | ✓ | | | ✓ | Patients with UCLA activity score of 5-6 (moderate activity) demonstrated greater extent ($P = 0.001$) and severity ($P < 0.001$) of polyethylene insert creep or deformation compared to less active patients at a mean follow-up of 6.2 years. Stepwise multiple regression analysis demonstrated that UCLA score was the most important predictor of extent (%) of involvement of deformation (Coefficient: 1.841 ± 0.835 SE, $P = 0.039$). |
| Luetzner et al., 2007 | TKA | ✓ | | | ✓ | No influence of activity level on measured blood serum metal ion concentrations at a mean follow-up of 5.5 years. |
| Mayr et al., 2015 | TKA | ✓ | ✓ | | ✓ | At a mean follow-up of 6.4 years, there was no evidence of tibial inlay wear, assessed via the height of the tibial inlay, or evidence of implant loosening, regardless of sport or activity (low-, medium- or high-impact). |
| Mont et al., 2007 | TKA | ✓ | ✓ | ✓ | ✓ | No revisions, progressive radiolucencies or osteolysis observed in either the low-activity or high-activity group at a mean follow-up of 7 years. |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Ponzio et al., 2018** | TKA | ✓ | | ✓ | ✓ | At 5 to 10 years post TKA, revision rates were significantly greater in active patients (n = 32, 3.2%) vs. inactive patients (n = 16, 1.6%) (*P* = 0.019). However, activity level was shown not to be a risk factor for revision TKA, after controlling for relevant variables (i.e., age, sex, BMI, among others). Osteolysis and wear (9.4% in the active group compared with 0% in the inactive group) were more frequent in the active group, but the difference did not reach significance. |
| Reiner et al., 2020 | TKA | ✓ | | | ✓ | At 1 year follow-up, there was no correlation between blood cobalt ion concentrations and number of walking cycles (β = 0.08, *P* = 0.788). No signs of osteolysis or implant loosening were detected at 1-year follow-up. |

[a]Ali et al. 2016 & Hamilton et al. 2017 reported on the same dataset with different follow-up periods and were counted as one study for the purpose of this scoping review.

Studies demonstrating a potentially deleterious effect of physical activity or sports participation on implant integrity and/or failure are in bold.

**UKA**: unicompartmental knee arthroplasty, **TKA**: total knee arthroplasty, **UCLA**: University of California at Los Angeles, **CI**: confidence interval, **BMI**: body mass index.

**Appendix 1.12.** Detailed summary of the 8-week rehabilitation program (10 sessions).

| Session Number | Plan for each session |
|---|---|
| 1 (Week 1) | Explanation of program<br>Initial clinical assessment*<br>Information/Education regarding OA<br>• Nature of OA: consequences + prognosis<br>Link patient education back to answers from assessment<br>• ADL<br>• Participation in activities<br>• Health education needs, beliefs, motivation to self-manage<br>Consideration of walking aids and assistive technology when appropriate<br>Individualized exercise program with maximum 3 exercises<br>Pain-relieving therapy either manual therapy or modality |
| 2 (Week 1) | Review patient questions regarding initial assessment/OA program<br>Manual therapy to address range of motion and pain<br>Review/correct exercises, add aerobic exercise to plan (stationary bike/treadmill)<br>Education:<br>• Address weight loss if appropriate<br>➢ Weekly self-monitoring<br>➢ Increase physical activity gradually to 30 minutes/day<br>➢ Specific weight loss goals<br>➢ Team approach with dietician<br>• Review footwear/need for adaptive changes |
| 3 (Week 2) | Manual therapy to address range of motion limitations and pain<br>Daily exercise plan should now include:<br>• Strengthening exercises for both legs<br>• Aerobic activity<br>• Range of motion/stretching exercises<br>Education:<br>• Pacing strategies to prevent flare-ups |
| 4 (Week 3) | Manual therapy to address range of motion limitations and pain<br>Progress Daily exercise plan:<br>• Strengthening in weight-bearing and functional (if possible)<br>• Aerobic activity- increase by 10%/week<br>• Range of motion/stretching exercises - from non weight-bearing to weight-bearing if possible<br>Education:<br>• Linking exercise regimen to activities of daily living |
| 5 (Week 4) | Second clinical assessment*<br>Redefine/restructure/set new patient-specific goals for the following 4 weeks<br>Subjective: patient reports on progress relative to function/pain levels and satisfaction with program<br>Summarize progress |

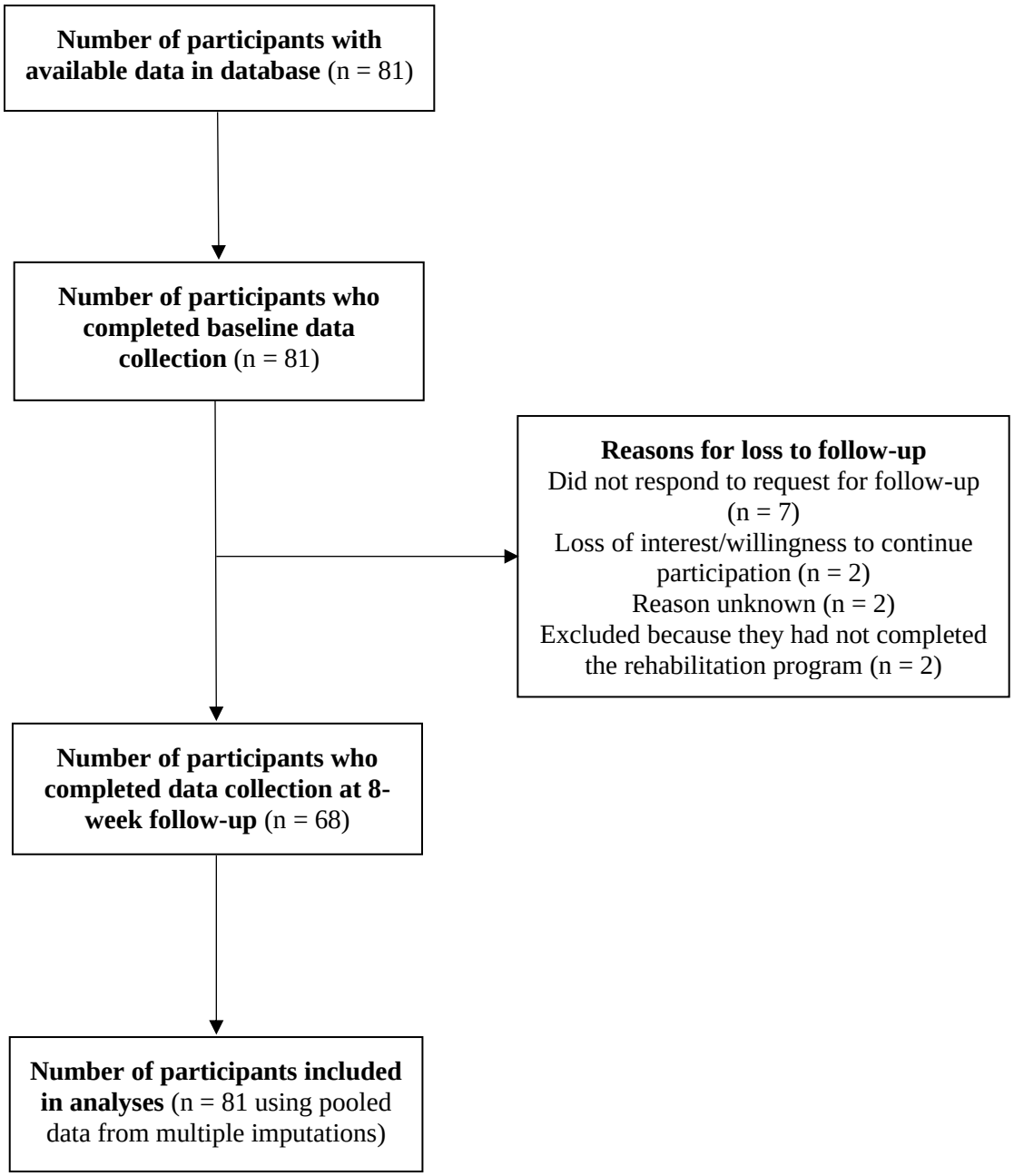
| | |
|---|---|
| | Pain relieving manual therapy/modality<br>Education:<br>• Goal setting<br>• Activity journal |
| 6 (Week 4) | Manual therapy to address range of motion limitations and pain<br>Progress daily exercise plan:<br>• Strengthening exercises in weight-bearing and functional<br>Aerobic activity- increase by 10%/week<br>Range of motion/stretching exercises in weight-bearing (if possible) and prolonged stretching as tolerated<br>Education:<br>• Linking exercise regimen to activities of daily living<br>• Increasing exercise dosage over following months |
| 7 (Week 5) | Manual therapy to address range of motion limitations and pain<br>Progress daily exercise plan:<br>• Strengthening exercises in weight-bearing and functional<br>Aerobic activity- increase by 10%/week<br>Range of motion/stretching exercises in weight-bearing (if possible) and prolonged stretching as tolerated<br>Education:<br>• Linking exercise regimen to activities of daily living<br>• Increasing exercise dosage over following months |
| 8 (Week 6) | Manual therapy to address range of motion limitations and pain<br>Progress daily exercise plan:<br>• Strengthening exercises in weight-bearing and functional<br>Aerobic activity- increase by 10%/week<br>Range of motion/stretching exercises in weight-bearing (if possible) and prolonged stretching as tolerated<br>Education:<br>• Linking exercise regimen to activities of daily living<br>• Increasing exercise dosage over following months |
| 9 (Week 7) | Manual therapy to address range of motion limitations and pain<br>Progress daily exercise plan:<br>• Strengthening exercises in weight-bearing and functional<br>Aerobic activity- increase by 10%/week<br>Range of motion/stretching exercises in weight-bearing (if possible) and prolonged stretching as tolerated<br>Education:<br>• Linking exercise regimen to activities of daily living<br>• Increasing exercise dosage over following months |
| 10 (Week 8) | Final clinical assessment*<br>Subjective: patient reports on progress relative to function/pain levels and satisfaction with program<br>Summarize progress<br>Pain relieving manual therapy |

| | |
|---|---|
| | Review of exercise program<br>Education:<br>• Goal setting: activity/weight loss<br>• Activity journal |

***Clinical assessments were conducted by treating physiotherapists to gather additional information and to track patient progress. Clinical assessments were conducted during Session 1, Session 6 (week 4) and Session 10 (week 8), and were conducted separately from the data collected by research personnel as presented in this study.**

- ✓ Standardized questionnaire: activities of daily living (ADLs)
- ✓ Biopsychosocial questions: participation (work/leisure/social), mood, health education needs/health beliefs
- ✓ Timed-Up-and-Go or 6-Minute Walk Test
- ✓ Functional tests sit-to-stand, walk backward, stair ascent/descent, and single-leg standing balance)
- ✓ Gait observation
- ✓ Musculoskeletal exam
    - Palpation
    - Range of motion/flexibility testing of lower extremity
    - Strength testing lower extremity
    - Lumbar scan

**Appendix 1.13.** Participant flow chart.



**Appendix 1.14.** Unstandardized regression coefficients examining relationships between baseline SPA-Pain indices with pain following an 8-week rehabilitation program (complete case analysis, n = 58 to 64 depending on the analysis).

| Dependent Variable | Physical Task | Age B (95% CI) | Sex B (95% CI) | KOOS-Pain (T1) B (95% CI) | SPA-Pain B (95% CI) | $R^2$ |
|---|---|---|---|---|---|---|
| KOOS-Pain (T2) | 30-s CST | -0.04 (-0.52, 0.44) | -4.17 (-12.60, 4.25) | **0.60** (0.34, 0.87) | 0.28 (-0.01, 0.56) | 31% |
| | 40-m FWT | 0.06 (-0.46, 0.57) | -2.98 (-11.74, 5.78) | **0.53** (0.25, 0.81) | -0.19 (-0.52, 0.13) | 28% |
| | TUG | 0.02 (-0.46, 0.51) | -4.18 (-13.05, 4.69) | **0.59** (0.32, 0.86) | 0.04 (-0.43, 0.51) | 27% |
| | 6MWT | -0.05 (-0.57, 0.48) | -5.13 (-14.53, 4.26) | **0.57** (0.27, 0.88) | 0.00 (-0.19, 0.20) | 24% |
| | SCT | 0.05 (-0.48, 0.59) | -2.11 (-11.45, 7.24) | **0.60** (0.31, 0.90) | -0.08 (-0.30, 0.14) | 29% |

Unstandardized coefficients (B) with 95% confidence intervals (CI), and total explained variance ($R^2$) are provided. Age, sex (0 = females, males = 1), and baseline pain were accounted for in regression analyses. Significant associations are in bold ($P < 0.05$). Results are based on available data (complete case analysis according to analysis-by-analysis).

**KOOS**: Knee Injury and Osteoarthritis Outcome Score. **T1**: baseline. **T2**: following 8-week rehabilitation program. **SPA**: Sensitivity to physical activity. **CST**: 30-Second Chair Stand Test. **FWT**: 40-Meter Fast-Paced Walk Test. **TUG**: Timed-Up-and-Go Test. **6MWT**: 6-Minute Walk Test. **SCT**: Stair Climb Test.

**Appendix 1.15.** Unstandardized regression coefficients examining relationships between baseline SPA-Pain indices with physical function following an 8-week rehabilitation program (complete case analysis, n = 58 to 64 depending on the analysis).

| Dependent Variable | n | Physical Task | Age B (95% CI) | Sex B (95% CI) | KOOS-ADL (T1) B (95% CI) | SPA-Pain B (95% CI) | $R^2$ |
|---|---|---|---|---|---|---|---|
| KOOS-ADL (T2) | 64 | 30-s CST | -0.07 (-0.57, 0.43) | -4.58 (-13.19, 4.03) | **0.59** (0.33, 0.85) | 0.26 (-0.03, 0.54) | 31% |
| | 63 | 40-m FWT | 0.03 (-0.49, 0.55) | -3.09 (-11.92, 5.74) | **0.55** (0.28, 0.82) | -0.22 (-0.55, 0.10) | 31% |
| | 64 | TUG | 0.03 (-0.46, 0.53) | -5.22 (-14.27, 3.83) | **0.65** (0.37, 0.92) | 0.27 (-0.21, 0.76) | 30% |
| | 58 | 6MWT | -0.15 (-0.69, 0.39) | -6.40 (-15.83, 3.03) | **0.65** (0.35, 0.95) | 0.06 (-0.14, 0.26) | 29% |
| | 59 | SCT | 0.02 (-0.53, 0.57) | -3.04 (-12.53, 6.45) | **0.63** (0.35, 0.92) | -0.04 (-0.26, 0.18) | 30% |

Unstandardized coefficients (B) with 95% confidence intervals (CI), and total explained variance ($R^2$) are provided. Age, sex (0 = females, males = 1), and baseline physical function were accounted for in regression analyses. Significant associations are in bold ($P < 0.05$). Results are based on available data (complete case analysis according to analysis-by-analysis).

**KOOS**: Knee Injury and Osteoarthritis Outcome Score. **T1**: baseline. **T2**: following 8-week rehabilitation program. **ADL**: Activities of daily living. **SPA**: Sensitivity to physical activity. **CST**: 30-Second Chair Stand Test. **FWT**: 40-Meter Fast-Paced Walk Test. **TUG**: Timed-Up-and-Go Test. **6MWT**: 6-Minute Walk Test. **SCT**: Stair Climb Test.

**Appendix 1.16.** Ethics certificate for Chapters 3 & 4.

Hôpital général juif
Jewish General Hospital

**BUREAU D'ÉTHIQUE DE LA RECHERCHE**
**RESEARCH ETHICS OFFICE**

**Dr. Vasiliki Bessy Bitzas, N, PhD, CHPCN(C).**
Chair, Research Ethics Committee
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Email: bbitzas@jgh.mcgill.ca
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February 10, 2015

Dr. John Antoniou (Dr. Shawn Robbins)
Orthopedics
Jewish General Hospital

**SUBJECT**: **Protocol #15-010** entitled "Gait Differences between Patients with Primary and Secondary Knee Osteoarthris and the Impact on Disease Progression"

Dear Dr. Antoniou,

Thank you for submitting the following documents pertaining to the above-mentioned protocol to the Research Ethics Office for review:

- Protocol
- Appendix A: Medical Screening Form
- Appendix B: Recruitment Advertisement
- Appendix C: Demographic Form and Contact Information
- Appendix D: Intermittent and Constant Osteoarthritis Pain Scale
- Appendix E: Knee Injury and Osteoarthritis Outcome Score Function Subscale
- Appendix F: International Physical Activity Questionnaire (IPAQ) Short Version to Measure Physical Activity
- Appendix G: Budget Summary
- Appendix H: Approval Letter from the Appropriate Departments at Montreal General Hospital
- Appendix I: Approval Letters from the Appropriate Departments at St. Mary's Hospital
- Appendix J: Approval Letters from the Appropriate Departments at Jewish General Hospital
- Appendix K: Scientific Review
- English Consent form (October 29, 2014

The Research Ethics Committee of the Jewish General Hospital (Federalwide Assurance Number: 0796) is designated by the province (MSSS) and follows the published guidelines of the TCPS 2 -

Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2010), in compliance with the "Plan d'action ministériel en éthique de la recherche et en intégrité scientifique" (MSSS, 1998), the membership requirements for Research Ethics Boards defined in Part C Division 5 of the Food and Drugs Regulations; acts in conformity with standards set forth in the United States Code of Federal Regulations governing human subjects research, and functions in a manner consistent with internationally accepted principles of good clinical practice.

As this study involves no more than minimal risk in accordance with TCPS 2 article 6.12, this protocol received a delegated research ethics review. We are pleased to inform you that the above-mentioned documents are granted Delegated Approval for the period of one year.

For quality assurance purposes, you must use the approved REO stamped consent form when obtaining consent by making copies of the enclosed one. Please note that a French Consent Form, as required by law, must be forwarded to the Research Ethics Office as soon as possible. For your information, the above-mentioned protocol will be presented for corroborative approval at the next meeting of the Research Ethics Committee to be held on March 13, 2015.

Please note that it is the Investigator's responsibility to ensure that Feasibility approval is granted before the study can be initiated at our site.

| | |
|---|---|
| **Delegated Approval Date:** | **February 5, 2015** |
| **Expiration date of Delegated Approval:** | **February 4, 2016** |

Your "Continuing Review Application" must be received by the Research Ethics Office **one month** before the expiration date above in order to ensure timely review. Otherwise, the study will be terminated.
Respectfully,

Dr. Vasiliki Bessy Bitzas, N, PhD, CHPCN(C)
Chair, Research Ethics Committee

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**Appendix 1.17.** Ethics certificate for Chapter 6.

McGill

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Tél/Tel: (514) 398-3124

## CERTIFICATION OF ETHICAL ACCEPTABILITY FOR RESEARCH INVOLVING HUMAN SUBJECTS

The Faculty of Medicine Institutional Review Board (IRB) is a registered University IRB working under the published guidelines of the Tri-Council Policy Statement, in compliance with the Plan d'action ministériel en éthique de la recherche et en intégrité scientifique (MSSS, 1998), and the Food and Drugs Act (17 June 2001); and acts in accordance with the U.S. Code of Federal Regulations that govern research on human subjects. The IRB working procedures are consistent with internationally accepted principles of Good Clinical Practices.

At a full Board meeting on 12 September 2016, the Faculty of Medicine Institutional Review Board, consisting of:

| | |
|---|---|
| Patricia Dobkin, PhD | Sylvie Lambert, PhD |
| Song Lingqiao, LL.M. | Kathleen Montpetit, M.Sc. |
| Scott Owen, MD | Roberta Palmour, PhD |
| Lucille Panet-Raymond, BA | Margaret Swaine, B.A. |

Sylvia Villeneuve, PhD

Examined the research project **A09-B46-16A** titled: *Exploring the relationship between sensitivity to physical activity and treatment response among people with knee pain*

As proposed by: Dr. Timothy Wideman (Applicant) to _____ (Granting Agency, if any)

And consider the experimental procedures to be acceptable on ethical grounds for research involving human subjects.

11 November 2016 (Date) — Roberta Palmour (Chair, IRB) — (Dean of Faculty)

**Institutional Review Board Assurance Number: FWA 00004545**

**Appendix 1.18.** Copyright approval for Chapter 3.



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