Inter-Limb Asymmetry in Motion: Combining Clinical and Biomechanical Outcomes to Understand its Prevalence and Responsiveness in Knee Osteoarthritis

by

Carson Halliwell

Submitted in partial fulfilment of the requirements
for the degree of Doctor of Philosophy

at

Dalhousie University
Halifax, Nova Scotia
June 2024

Dedicated to Dawn Halliwell,

My guiding light when times are dark,

Feb 1959 – June 2023

Table of Contents

List of Tables

List of Figures

Abstract

Walking is consistently recommended for individuals with knee osteoarthritis; however, many avoid physical activity due to pain. Individuals with knee osteoarthritis may attempt to alleviate this pain by adopting asymmetrical walking patterns, which potentially increases the risk for osteoarthritis progression in their contralateral knee. Unfortunately, inter-limb asymmetry in knee osteoarthritis is understudied and not well understood. The overall aim of this thesis was to investigate inter-limb asymmetry quantified using features of dynamic knee joint loading previously associated with knee osteoarthritis onset and progression, and examine its clinical utility based on its relationships with clinical and structural characteristics of knee osteoarthritis and responsiveness to physical activity.

A comparison between individuals with self-reported versus clinically diagnosed knee osteoarthritis revealed that individuals with self-reported knee osteoarthritis walked with gait patterns associated with more severe knee osteoarthritis compared to individuals who are clinically diagnosed (Chapter 4). Regardless of recruitment method, approximately 50% of individuals with knee osteoarthritis walked with asymmetrical knee loading (Chapter 4). Dichotomizing individuals with knee osteoarthritis with either symmetrical or asymmetrical knee loading revealed that individuals with symmetrical knee loading had worse patient-reported function (Chapter 5). Individuals with symmetrical knee loading walked with contralateral knee biomechanics consistent with knee osteoarthritis and in individuals with asymmetrical knee their contralateral knee biomechanics were consistent with asymptomatic individuals (Chapter 5). Walking 30-minutes was not found to negatively influence objective function in individuals with symmetrical or asymmetrical knee loading (Chapter 6). However, pain increased two-fold in individuals with symmetrical versus asymmetrical knee loading after walking 30-minutes (Chapter 6). Inter-limb symmetry-asymmetry status was consistent following 30-minutes of walking regardless of baseline status (Chapter 6).

These studies suggest that approximately half of individuals with knee osteoarthritis walk with asymmetrical knee loading. Contrary to previous thoughts, symmetrical knee loading may be an indicator for bilateral gait patterns resembling knee osteoarthritis in this population. Despite increases in pain, inter-limb symmetry-asymmetry status was consistent following 30-minutes of walking. Clinically, a symmetry-asymmetry index may hold utility as a screening tool to assess potential knee osteoarthritis severity or monitor responsiveness to interventions; however, further research assessing more clinically applicable tools are warranted.

List of Abbreviations Used

ACL	Anterior Cruciate Ligament
ADL	Activities of Daily Living
BMI	Body Mass Index
BLOKS	Boston-Leeds Osteoarthritis Knee Scoring
CI	Confidence Interval
DALY	Disability Adjusted Life Years
GRF	Ground Reaction Force
Hz	Hertz
ICC	Intraclass Correlation Coefficient
ICF	International Classification of Functioning
ICOAP	Intermittent and Constant Osteoarthritis Pain
ICPF	Initial Contact Peak Flexion
KAM	Knee Adduction Moment
KAMR	First Peak Knee Adduction to Midstance Unloading Range
KFM	Knee Flexion Moment
KEM	Knee Extension Moment
KL	Kellgren-Lawrence
KOOS	Knee Osteoarthritis Outcome Score
KRM	Knee Rotation Moment
MDC	Minimal Detectable Change
mm	Millimeter
MOAKS	MRI Osteoarthritis Knee Score
MOST	Multicenter Osteoarthritis Study
MRI	Magnetic Resonance Imaging
m/s	Meters per Second
MVIC	Maximum Voluntary Isometric Contraction
N	Newton
Nm/kg	Newton-Meter per Kilogram
NPRS	Numeric Pain Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs

NSI	Normalized Symmetry Index
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatology Clinical Trials
QoL	Quality of Life
ROM	Range of Motion
RPE	Rating of Perceived Exertion
SD	Standard Deviation
SI	Symmetry Index
SI_{norm}	Symmetry Index Norm
SPM	Statistical Parametric Mapping
SPM{f}	Analysis of Variance Statistical Parametric Mapping
SPM{t}	T-test Statistical Parametric Mapping
SPROM	Sagittal Plane Knee Moment Range
TJM	Total Joint Moment
TKA	Total Knee Arthroplasty
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Osteoarthritis Index
WORMS	Whole-Organ MRI Score
YLD	Years of Life Lost to Disability

Acknowledgements

I would like to start by thanking my supervisor, Dr. Rebecca Moyer, whose unwavering support, invaluable guidance, and exceptional mentorship have been instrumental throughout my doctoral journey. Dr. Moyer's insights, patience, and encouragement have not only shaped my research but have also fostered my personal and professional growth in profound ways. Her dedication to excellence and commitment to fostering academic rigor have been a constant source of inspiration.

I would also like to thank my supervisory committee members, Dr. Janie Astephen-Wilson and Dr. Derek Rutherford, for their time, expertise, and invaluable feedback. Their insightful perspectives and guidance have broadened my understanding of complex issues and enriched the quality of my research. I am profoundly grateful for their constant support and encouragement, which have been instrumental in navigating the challenges inherent in doctoral studies.

I would also like to express my sincere appreciation to all the members of the Dynamics of Human Motion and Joint Action Research Laboratories for their camaraderie, collaboration, and support throughout this journey. In particular, Aleks Budarick for her support and companionship as we navigated the challenges of our PhDs together. Thank you to Sarah Remedios and Meaghan Hannigan for their help with data collections throughout this thesis.

I extend my heartfelt thanks to all those who have supported and encouraged me along the way, including my friends and family. Their belief in me has been a constant source of strength, and I am grateful for their enduring support. In particular, I am indebted to my partner, Taylor Johnston, whose constant support and understanding have been my rock throughout this journey. Taylor's patience during late nights and tolerance of occasional frustrations have been invaluable, and I am deeply grateful for her presence and love. This journey would not have been possible without her support and encouragement.

Lastly, I would like to thank my mother, Dawn Halliwell. Words cannot express the depth of gratitude I hold for your support and encouragement throughout my life's journey. Your love and guidance have led me through every triumph and challenge. As I embark on the culmination of years of hard work, I carry with me the lessons you've taught me, the values you've instilled, and the strength you've imparted. You are the cornerstone of my success, and I dedicate this moment to you.

Thank you.

Chapter 1: Introduction

1.1 Motivation

In 2017, osteoarthritis (OA) ranked 13th globally in years of life lost due to disability (YLDs) and was ranked the 4th fastest growing condition behind diabetes, Alzheimer's and "other" musculoskeletal conditions[1]. From 2010 to 2017, OA had the highest increase in disability adjusted life years (DALYs) among non-communicable diseases[2], and accounted for 10% of DALY's for all musculoskeletal health conditions[2]. Diarthrodial joints are most affected, with the knee accounting for the majority of cases[3]. Approximately 30% of the Canadian workforce reports some form of difficulty during work due to OA related symptoms[4], such as chronic pain and decreased functional ability, increasing the risk for early retirement in individuals with knee OA[5–8]. The high prevalence and impact of knee OA on the population is taking its toll on the Canadian healthcare system.

Knee OA, is a multifactorial disease with multiple variables contributing to its development, including lack of muscle strength, joint injury, obesity, older age, genetics, and female sex[9]. Despite the known multifactorial nature of knee OA, and the wide range of individuals affected, only 5% of Canadian health studies used nationally representative data to study health outcomes[10], leaving a large gap in our ability to generalize findings to the greater population. Previous research has suggested that a limitation to properly representative data in musculoskeletal health research was limited access to healthcare or a specialist[11]. Le and colleagues (2023)[11] suggested a potential solution to this issue: encouraging researchers to actively engage in community-based recruitment efforts[11]. This proposed method to recruit a more diverse group of individuals aligns well with current

shifts in diagnostic practice moving away from radiographic dependency when diagnosing knee OA. This creates the opportunity of utilizing more self-report-based diagnoses, minimizing the need for individuals to have access to healthcare to participate in knee OA research. This diagnostic shift is well-utilized in the scientific community, with a growing number of studies incorporating recruitment criteria based on self-reported knee OA[12–17]. However, it is not known whether individuals recruited through community based self-reported methodologies present with similar patient-reported outcomes or biomechanical adaptations during walking compared to individuals diagnosed based on the American College of Rheumatology guidelines[18] (clinical diagnosis).

Few functional activities are more ingrained in our daily lives then walking, and it is a consistently recommended as a first line treatment option for knee OA to reduce symptoms and maintain functional independence[19–22]; however, most best practice physical activity guidelines are poorly tailored to individuals with knee OA. Many individuals with knee OA report difficulty with walking, either due to fear of flaring symptoms during physical activity, knee pain during physical activity, or a lack of understanding physical activity guidelines[23,24]. As knee OA progresses, altered joint motions and loading lead to limitations in the knee's functional ability[25–28]. Gait analyses have been utilized to assess movement compensations such as reduced range of motion (ROM) and increased joint loading[25–28], which collectively can contribute to force redistribution within the joint and increased load on the underlying tissues[29]. The knee adduction moment (KAM) is a surrogate measure of the load distribution between the medial and lateral compartments of the knee[30–32]. The first peak KAM and KAM impulse have been associated with cartilage thickness loss[33–36], bone marrow lesions[37,38], radiographic severity[33], and appear to

accelerate disease progression[33]. This elevated KAM, combined with a "stiff-knee" gait pattern highlighted by reduced sagittal plane ROM and less dynamic flexion-extension moments, has previously been used to predict individuals at a higher risk of undergoing total knee arthroplasty (TKA)[39], a marker of clinical knee OA progression.

While the current understanding of unilateral gait adaptions in knee OA suggests consistent and well accepted patterns[33,37,40–42], the relationship between limbs and how the affected knee may influence contralateral limb mechanics is less clear. Symmetrical walking patterns are often described as a sign of physiologically healthy movement[43]. Symmetry analyses can be used to assess the effectiveness of surgical procedures such as anterior cruciate ligament (ACL) reconstruction[44], or as a gait assessment technique in various pathological populations[45–47]; however, there is little evidence that implements well-accepted gait mechanics to inform inter-limb asymmetry and its clinical relevance in knee OA. Recent evidence has suggested that upwards of 25% of individuals who undergo TKA are diagnosed with OA in their contralateral knee within 5 years[48] and up to 62% show knee OA progression after 9 years[49]. Currently, there is a lack of understanding surrounding inter-limb asymmetries in individuals with knee OA, and if the contralateral limb undergoes altered biomechanics that increase its risk for knee OA development. Previous research has produced mixed reports as to whether higher prevalence of asymmetry exists in individuals with bilateral symptomatic disease[50] or unilateral knee pain[51]. Further evidence is required to understand the impact of gait asymmetry on knee OA, and whether assessing symmetry has clinical utility in this population.

Current physical activity guidelines recommend 150-minutes per week or 30-minutes per day of moderate-to-vigorous physical activity[52]; however, research has

reported that only 13% of men and 8% of women with knee OA achieve these guidelines[53], often due to pain, or fear of accelerating/worsening the disease[54]. Individuals with knee pain have observable walking patterns associated with increased knee stiffness[39], decreased knee motion[40] and compensatory movement patterns to redistribute knee load[55], with the cumulative intent of reducing knee pain[41]. Results support that individuals who experience a pain flare (1.5-point increase on an 11-point numeric pain rating scale) during prolonged walking adapt their gait to decrease first and second peak KAM compared to those who do not experience pain[55]. Given the potential link between gait asymmetry and pain, exploring the immediate impacts of extended walking on pain and gait mechanics in individuals with both symmetrical and asymmetrical knee loading requires further examination. This direction of research may help to clarify whether individuals with self-reported knee OA report similar patient reported outcomes, and walk with similar gait biomechanics compared to individuals clinically diagnosed, determine the clinical utility of symmetry analyses, highlight its potential role in disease progression, and inform clinicians on tailored rehabilitation and physical activity prescription for individuals with knee OA, potentially enhancing adherence to guidelines and fostering better health outcomes overall.

1.2 Thesis Aim and Objectives

The overall aim of this thesis was to investigate inter-limb asymmetry quantified using features of dynamic knee joint loading previously associated with knee OA onset and progression, and examine its clinical utility based on its relationships with clinical and biomechanical characteristics of knee OA and responsiveness to a 30-minute continuous

walk. This overall aim was addressed by three specific objectives. The motivation, and approach for each objective are described below.

1.2.1 Thesis Objective 1

1.2.1.1 *Rationale*

Limited healthcare or provider access emerges as a major factor hindering more representative musculoskeletal health research endeavors[11]. The lack of properly representative health research leads to a large gap in our ability to generalize the effectiveness of diagnostic strategies and treatment interventions to the greater population. Community-based recruitment efforts are one proposed solution to address this issue[11]. This proposed community-based recruitment method aligns well with current shifts in diagnostic practice moving away from radiographic dependency when diagnosing knee OA[56–58]. This diagnostic shift is reflected among the growing number of studies incorporating recruitment criteria based on self-reported knee OA[12–17]. However, it is not known whether individuals recruited through community based self-reported methodologies present with similar patient-reported outcomes or biomechanical adaptations during walking compared to individuals clinically diagnosed. This information will help inform whether community based self-reported recruitment methodologies yield individuals who present with clinical symptoms and gait biomechanics consistent with those recruited using a clinical diagnosis, informing Thesis Objective 1.

1.2.1.2 *Specific Objectives:*

Thesis Objective 1 aims to investigate differences in patient-reported outcomes and gait biomechanics between individuals with knee OA who are recruited to participate using

either self-reported knee OA criteria or a conventional definition for clinically diagnosed knee OA.

Objective 1 was achieved through three sub-objectives:

i. Determine whether patient-reported outcomes reflecting pain, function and quality of life differ between individuals with self-reported and clinically diagnosed knee OA.
ii. Evaluate differences in sagittal and frontal plane biomechanics during walking between individuals with self-reported and clinically diagnosed knee OA.
iii. Explore the prevalence and magnitude of inter-limb asymmetry within individuals with self-reported and clinically diagnosed knee OA.

1.2.2 Thesis Objective 2

1.2.2.1 *Rationale*

Individuals with unilateral knee OA are at increased risk for developing knee OA in their contralateral limb within 10-years[49]. Currently, walking and physical activity are recommended among clinical practice guidelines for individuals with knee OA[21,59,60]; however, increased pain during walking may be associated with asymmetrical lower limb movement patterns as a strategy to reduce joint symptoms in the affected knee[50,61,62]. Previous research examining whether individuals with unilateral or bilateral disease walk with inter-limb asymmetries have produced conflicting results[50,51,63]. Symmetrical walking patterns are hypothesized to reflect a physiologically healthy and pain-free gait[43]; however, there is minimal-to-no evidence supporting this for individuals with knee OA[50,51,63].

Examining individuals with knee OA dichotomized as having either symmetrical or asymmetrical knee loading may help better explain what factors are driving these asymmetries, informing Thesis Objective 2.

1.2.2.2 *Specific Objectives*

Thesis Objective 2 looks to assess the association between inter-limb asymmetry using features of dynamic knee joint loading previously associated with knee OA onset and progression, with patient-reported outcomes and gait biomechanics in individuals with knee OA.

Objective 2 was achieved through two sub-objectives:

i. Determine whether patient-reported outcomes reflecting pain, function and quality of life, differ between individuals with knee OA who were dichotomized as having either symmetrical or asymmetrical knee loading.
ii. Examine sagittal and frontal plane biomechanical differences in the affected and contralateral knees between individuals with knee OA who were dichotomized as having either symmetrical or asymmetrical knee loading.

1.2.3 Thesis Objective 3

1.2.3.1 *Rationale*

Walking and physical activity are highlighted management strategies across clinical practice guidelines for individuals with knee OA[21,59,60]. Current physical activity guidelines recommend 150-minutes per week or 30-minutes per day of moderate-to-

vigorous physical activity[52]; however, these guideline recommendations were not developed for clinical populations such as individuals with knee OA and their effects on disease specific characteristics (e.g., joint loading) remain unclear[64]. Evidence strongly supports that individuals with knee OA who engage in more physical activity have better self-reported pain and performance-based measures of function, and disability compared to individuals who are not physically active[65–67]. However, individuals with knee OA often limit their engagement in physical activity due to pain[54], and the pain experience may lead to asymmetrical lower-limb loading patterns potentially putting their contralateral limb at risk for knee OA development. Currently, how inter-limb asymmetry responds to prolonged submaximal walking intervention (i.e., becoming more or less symmetric) isn't well understood. This information may help understand the static and dynamic nature of inter-limb asymmetry during prolonged, submaximal physical activity, informing Thesis Objective 3.

1.2.3.2 *Specific Objectives*

Thesis Objective 3 focuses on evaluating the responsiveness of inter-limb asymmetry over a 30-minute walking intervention, assessing patient-reported and biomechanical responses to 30-minutes of continuous walking in individuals with knee OA who are dichotomized as having either symmetrical or asymmetrical knee loading.

Objective 3 was achieved through three sub-objectives:

i. Examine how knee pain changes during 30-minutes of continuous walking in individuals with knee OA who were dichotomized as having either symmetrical or asymmetrical knee loading.
ii. Determine whether affected and contralateral knee biomechanics respond differently to 30-minutes of continuous walking in individuals with knee OA who were dichotomized as having either symmetrical or asymmetrical knee loading.
iii. Assess the responsiveness of inter-limb asymmetry to 30-minutes of continuous walking between individuals with knee OA who are dichotomized as having either symmetrical or asymmetrical knee loading.

1.3 Thesis Overview

Chapter 1 introduced this thesis by outlining the primary motivation for investigating gait inter-limb asymmetries in knee osteoarthritis. The focus is on examining patient-reported outcomes and gait biomechanical characteristics. The chapter outlined the overarching aim of the thesis along with the three specific objectives, each supported by rationale, sub-objectives, and their respective contributions to the overall thesis.

Chapter 2 provides a review of the relevant literature informing this thesis. The literature review identifies gaps in current research regarding recruitment/diagnostic methodologies in knee osteoarthritis research, and inter-limb asymmetries in individuals with knee osteoarthritis. The literature review provides a summary of the economic and physical burden of knee osteoarthritis, factors contributing to its incidence and progression,

strategies to capture the individuals' experience, and walking as a form of physical activity for individuals with knee osteoarthritis.

Chapter 3 outlines the general methodology employed to achieve the objectives of this thesis. Details are described related to the criteria for selecting participants, their preparation, and the procedures for processing and analyzing data related to the specified outcome variables. Detailed descriptions for overground and treadmill walking protocols are provided, along with justification for the chosen sample size. Furthermore, the chapter offers a broad overview of the statistical analyses conducted, with specific statistical details further outlined in each study chapter.

Chapter 4 is a manuscript-style study chapter addressing Thesis Objective 1. The study is a cross-sectional laboratory-based study titled "Comparing Participant Recruitment Methods in Knee Osteoarthritis: Implications for Community Recruitment and its Effects on Clinical and Biomechanical Outcomes".

Chapter 5 is a manuscript-style study chapter addressing Thesis Objective 2. The study is a cross-sectional laboratory-based study titled "The Association of Inter-Limb Asymmetry with Patient-Reported Outcomes and Gait Biomechanics in Individuals with Knee Osteoarthritis".

Chapter 6 is a manuscript-style study chapter addressing Thesis Objective 3. The study is a cross-sectional laboratory-based study titled "A Response To 30-Minutes of Continuous Walking: Does Inter-Limb Asymmetry Alter Knee Pain and Gait Biomechanics in Individuals with Knee Osteoarthritis?".

Chapter 7 concludes the thesis and presents a summary of study findings, a discussion of the implications and clinical significance of the findings and identifies limitations and future research directions.

Appendix A presents research ethics board approval for the studies presented in Chapters 4-6.

Appendix B provides heatmaps of all individual responses for all non-significant Knee Injury and Osteoarthritis Score and Intermittent and Constant Osteoarthritis Pain subscales.

Appendix C presents the Knee Osteoarthritis Knowledge Scale (OAKS) as a potential patient-reported outcome when engaging in community based self-reported recruitment methodologies.

Chapter 2: Review of Relevant Literature

2.1 What is Osteoarthritis?

Osteoarthritis (OA) is one of the most common progressive musculoskeletal diseases, and leading cause of functional disability around the world[1,68], primarily manifesting in diarthrodial joints such as the knee and hip in the lower extremities[25,69–72]. Previously, OA has been defined as a "wear and tear" disease, where excessive mechanical stress, either acute or chronic, begins to wear down the cartilage of the joint[25,73,74]. The perceived pathogenesis of OA has evolved over decades and is now known that all aspects of the joint are affected by the disease, including subchondral bone, joint capsule, menisci, synovium, articular cartilage, ligaments, and surrounding musculature[25,74]. A more all-encompassing definition of OA was made by the Osteoarthritis Research Society International, that defined OA as:

> "A disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness."[73]

The complicated pathogenesis of OA includes the interplay of mechanical, inflammatory and metabolic factors, which ultimately leads to the decoupling of the equilibrium between the repair and destruction of joint tissues[25]. The break in this dynamic

equilibrium of joint metabolism and catabolism leads to loss of cartilage integrity leaving it more susceptible to damage from mechanical forces[25]. As this happens, elevated inflammatory responses inhibit chondrocyte function and bone turnover is increased, leading to bone marrow lesions, and osteophyte development[25]. There are several factors that can increase an individual's risk of OA development such as low muscle strength, previous joint injury, obesity, older age and female sex[9]. These factors can be categorized as modifiable or non-modifiable, and local or systemic (Figure 2-1).

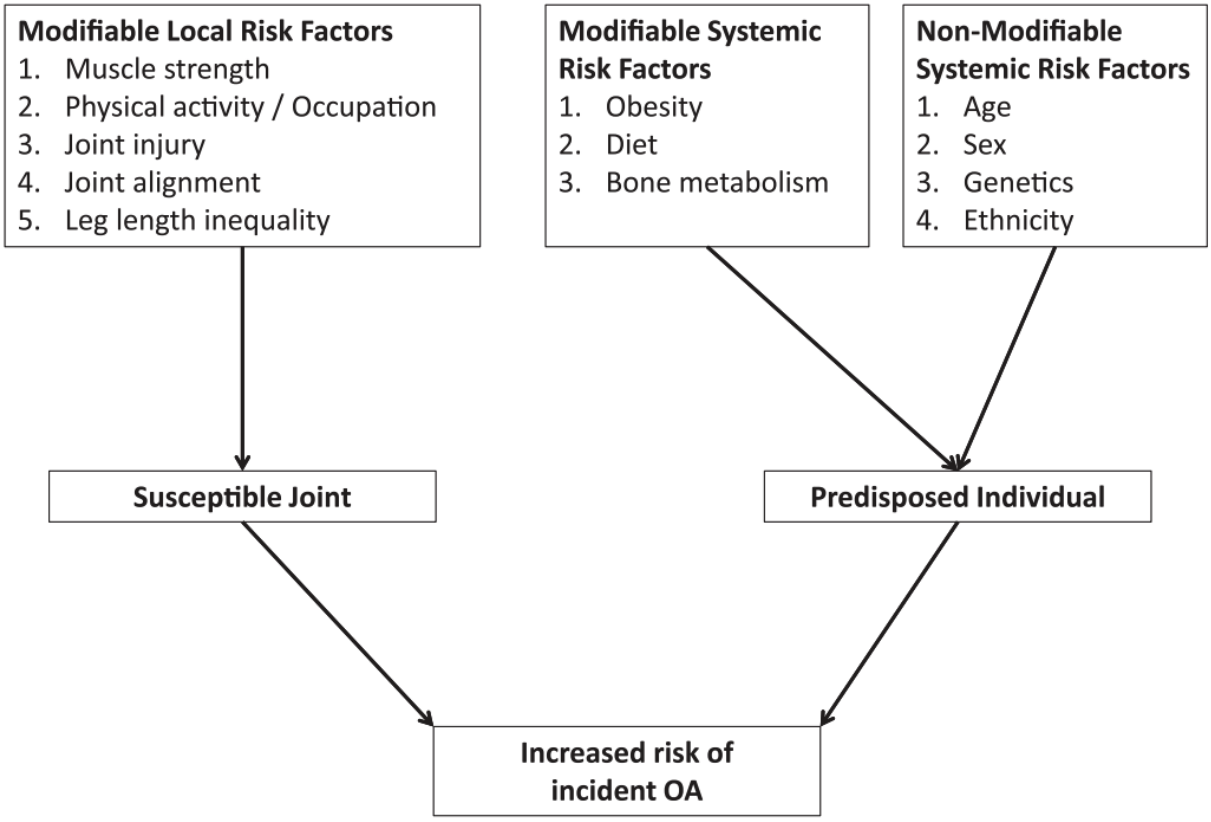


Figure 2-1: Potential risk factors for susceptibility to OA incidence (adapted from Johnson & Hunter 2014)[9].

The impact of OA on an individual can be differentiated as "disease" and "illness" components[73,75]. The disease portion of OA can be thought of as the various molecular, anatomical or physiologic abnormalities occurring at the organ system level, that are common and reoccurring in their presentation[73,75]. Several quantitative measures can be used to assess disease, such as the Kellgren-Lawrence classification[76], joint space narrowing, osteophyte formation, or other imaging biomarkers associated with knee OA[3,77,78]. The illness portion of OA can be thought of as the patient response to the disease or, any experiences felt by the patient because of the disease[73,75]. As such, disease is defined to an organ, while illness is defined to an individual[73,75]. Although the disease and illness components of OA can occur simultaneously, there is often a discordance between them that is particularly notable in the earliest stages of the disease[73]. For example, individuals may present with radiographic OA features but lack clinical symptoms[56,79]. Joint pain is the traditional driving force for individuals with OA to seek health care[80], yet structural changes may present themselves years prior to an individual developing any symptoms (Figure 2-2). Understanding the interplay between OA the disease and OA the illness, can help explain why some individuals reported increased symptoms with low levels of radiographic evidence, while other individuals report low symptoms with high levels of radiographic evidence.

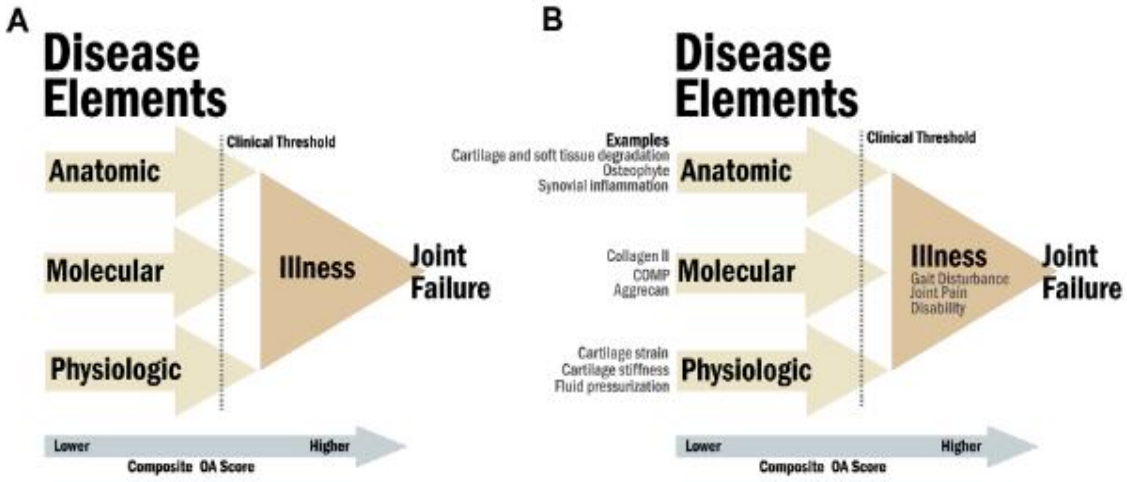


Figure 2-2: Proposed taxonomy of OA based on the standardized nomenclature of disease (made up of molecular, anatomic or physiologic components, domains of disease elements) and illness (adapted from Kraus et al., 2015)[73].

2.1.1 Economic Burden of Osteoarthritis

The economic burden of OA can be broken down into direct costs to the healthcare system and indirect costs to the individual living with OA[70]. Predicted estimates suggest that 10-million Canadians will be diagnosed with OA within the next decade. Due to the extremely high prevalence of OA across Canada[4,70], the associated costs for treating the condition are high, with individuals in the earliest stages of the disease consuming healthcare resources at rates that are approximately two-fold the rate of individuals without OA[81]. As Canada's population continues to age, and rates of obesity continue to escalate, these costs are expected to grow exponentially[82,83] and by 2031, the direct cost of OA is estimated to be approximately 8-billion/year, with the majority of costs resulting from hospitalization and outpatient services[82]. The global COVID-19 pandemic has made a lasting impact on Canada's current health management system, with the percentage of knee replacement surgeries completed within the national 6-month benchmark falling from 72% before the pandemic to 50% across Canada and 38% in Nova Scotia in 2023[84].

Due to the high level of sedentary behaviour seen within OA populations[53,66], it is estimated that up to 87% of individuals with OA have at least one other comorbidity[70,85] such as cardiovascular disease, dementia, and rheumatic disease, leading to an increase in non-OA hospitalizations and further utilization of healthcare resources[70,85]. When examining the economic impact of the individual, there are several factors that need to be considered, including presenteeism (loss of productivity at the workplace) and absenteeism (days off work)[70,86]. Current estimates state that nearly 30% of Canada's labour-force reports some form of difficulty with working due to OA[4]. These difficulties have led to indirect cost estimates for individuals with OA approaching 13.2-billon/year[70,87]. The chronic pain and reduced functional capacity in these individuals likely play a substantial role in the high level of absenteeism. A recent study indicated that knee OA specifically was associated with 2.2x increased likelihood of an early exit from work[5–8].

In 2004, The Arthritis Foundation proposed 14-quality indicators for the management of OA[88], which primarily focused on conservative managements such as physical examinations, education, exercise and weight loss for an individual recently diagnosed with OA[88]. These quality indicators align well with current management strategies, focusing on physical activity education, weight loss and non-steroidal anti-inflammatory drugs (NSAIDs) as first line options for individuals with knee OA[19,59]. Economic evaluations in the literature also support these treatment options. A recent systematic review found that incorporating a regular physical activity program with OA education and diet was found to be cost-effective, beyond that of traditional physician-delivered usual care[89]. Unfortunately, the current quality of nonpharmacological care for OA is quite poor, with only a 22.4% pass rate for quality indicators including advice for

physical activity, advice for weight loss, assessment of ambulatory function, and assessment of non-ambulatory function[90]. Understanding physical activity in individuals with OA could support reductions of both OA and non-OA hospitalizations, and substantially reduce costs associated with the disease.

No cure exists for OA; therefore, the progressive nature of the disease most often leads to debilitating illness, loss of functional capacity, increased pain, and reduced quality of life[70]. These changes result in loss of work and early retirement for individuals with OA[71]. Reducing OA related pain and disability has the potential to improve quality of life, overall health, and reduce both direct and indirect costs associated with the disease.

2.1.2 Burden of Osteoarthritis on Health

The World Health Organization's (WHO) definition of health is "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity". Individuals diagnosed with knee OA are often afflicted by the multifaceted nature of the disease as evidenced by decreased physical function[91], elevated rates of depressive symptoms and deteriorated mental health[92], and increased rates of social isolation[93]. The WHO's International Classification of Functioning Disability and Health (ICF) provides a standardized health status framework that describes the functional, disability and health status at both the individual and population levels[94], allowing for a more holistic picture of the individual's disease and illness experiences (Figure 2-3).

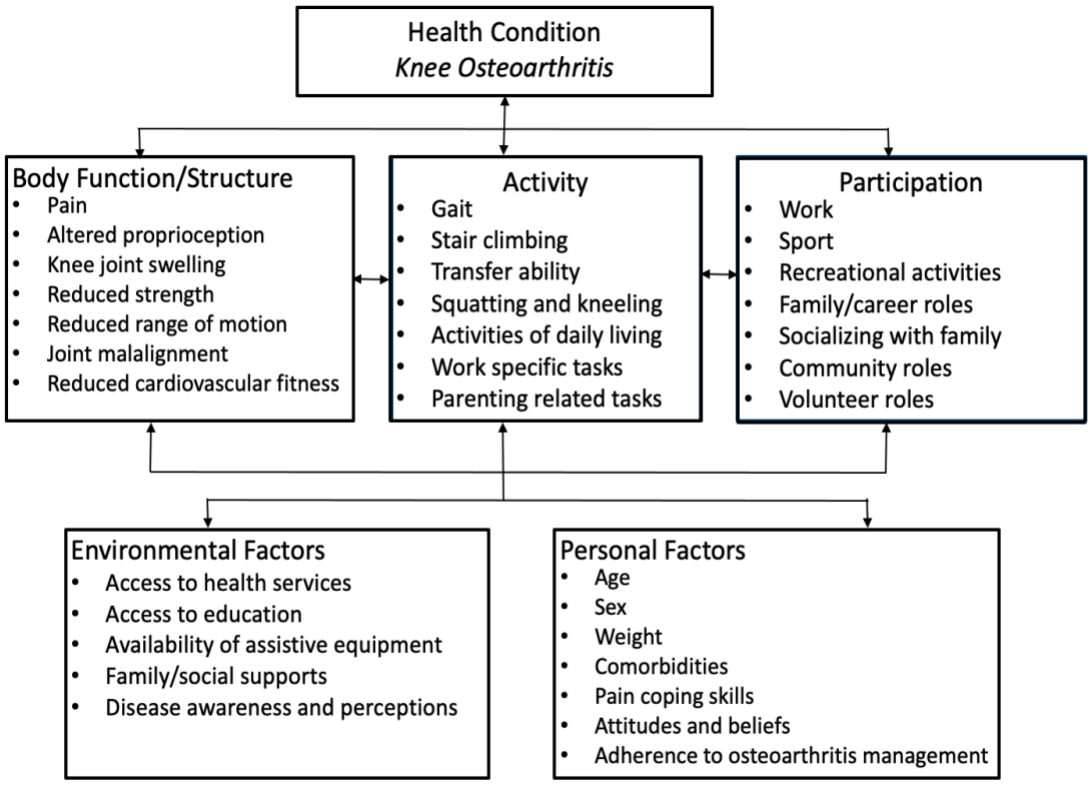


Figure 2-3: International Classification of Functioning model demonstrating impacts of knee osteoarthritis (Adapted from Ackerman et al., 2017)[69].

Globally, OA is ranked 13th in YLDs and ranked the 4th fastest growing condition behind diabetes, Alzheimer's and "other" musculoskeletal conditions[1]. In 2010; OA alone accounted for 10% of DALY's for all musculoskeletal health conditions[2] and showed the highest increase in DALY's from 2010-2017 among non-communicable disease[2], and knee OA makes up approximately 80% of OA diagnoses[95]. The drastic rise in disability observed in individuals with knee OA parallels the increasing population age, obesity, and increases in sedentary behaviours[96,97]. When examining the activity limitations experienced by individuals with knee OA, notable difficulties are observed with walking and stair ambulation[98]. In a cohort study of over 18,000 adults aged 55 and over, 25% reported walking difficulty, and knee OA was the highest predictor of walking difficulty within the

cohort[99]. Gait speed is a highly utilized tool to determine mortality and functional ability, with reports that gait speed of at least 1.2m/s is required for safe community ambulation[100,101], and a gait speed of less than 1.0m/s is highly correlated with an increase in mortality[102]. A systematic review demonstrated that 100% of studies assessing gait speed in individuals with knee OA showed a mean gait speed of <1.2m/s, and 60% demonstrated gait speed <1.0m/s[103]. Examining gait difficulties in individuals with knee OA, and how they respond to continuous submaximal physical activity is an important factor to understand to keep individuals living independently and maintain their overall health.

Walking and physical activity is a highlighted clinical practice guideline recommendation for individuals with knee OA[21,59,60]. Federal best practice physical activity guidelines recommend 150-minutes per week or 30-minutes per day of moderate-to-vigorous physical activity[104]. Currently, these guidelines are not specific to knee OA; however, the evidence consistently suggests the importance of physical activity for maintaining functional ability[105–108]. Despite the widespread recommendation of physical activity for knee OA, <13% of men and <8% of women with knee OA meet current physical activity guidelines[53], often due to patient reported barriers including psychological factors (e.g., fear of pain, lack of motivation), physical factors (e.g., knee pain, asthenia), and mental factors (e.g., depression)[23,24]. Patients also report a lack of understanding surrounding physical activity guidelines, how to differentiate between light and moderate intensities, and the overall benefits of physical activity for knee OA[109]. Further, the impact of differing prescriptions, including duration and intensity, along with type (i.e., walking, cycling, aquatic or strength) on knee OA outcomes is unclear[21]. Currently, our understanding of whether extended bouts of submaximal physical activity (30-minutes of

walking) protect or compromise the joint and prevents OA progression is unclear. Evidence suggests that specific features related to joint loading during walking, can be used to predict individuals whose symptoms and joint damage may progress at an accelerated rate[33,37,110–112]. Biomechanical analyses can be used to assess how extended walking affects these metrics and begin to develop knee OA specific physical activity guidelines.

2.1.3 Diagnosis of Osteoarthritis the Disease

2.1.3.1 Radiography

Radiographic assessment remains one of the most commonly utilized tools for the diagnosis of knee OA, including the Kellgren-Lawrence classification system (KL)[76,113–115]. This classification system ranges from 0-4, with 0 representing no OA presence, and 4 representing severe OA (Figure 2-4)[76]. The scoring system utilizes a combination of osteophyte formation, narrowing of the joint space associated with sclerosis of subchondral bone, sclerosis, and altered shape of the bone ends[76,113]. The KL classification system has shown good to very-good interrater reliability with intraclass correlation coefficients ranging from 0.68-0.85[116,117].

Currently there is inconsistent evidence suggesting a positive correlation between KL grade and the probability of an individual presenting with OA symptoms, more severe pain, depressive symptoms, and worse performance on functional tests[118]. These findings; however, are in stark contrast to studies showing no association between depressive symptoms, pain, or functional performance and radiographic severity[118]. Recent evidence suggests no correlation when all KL grades are treated separately; however, when treated as a group (grades 2-4) were associated with poorer scores in the Western Ontario and

McMaster Universities Osteoarthritis Index (WOMAC), and balance scores[119]. Changes in clinical guidelines have occurred due to discrepancies between symptoms and radiographic definitions of osteoarthritis, leading to a shift away from the traditional reliance on radiographs for diagnosis[56–58].

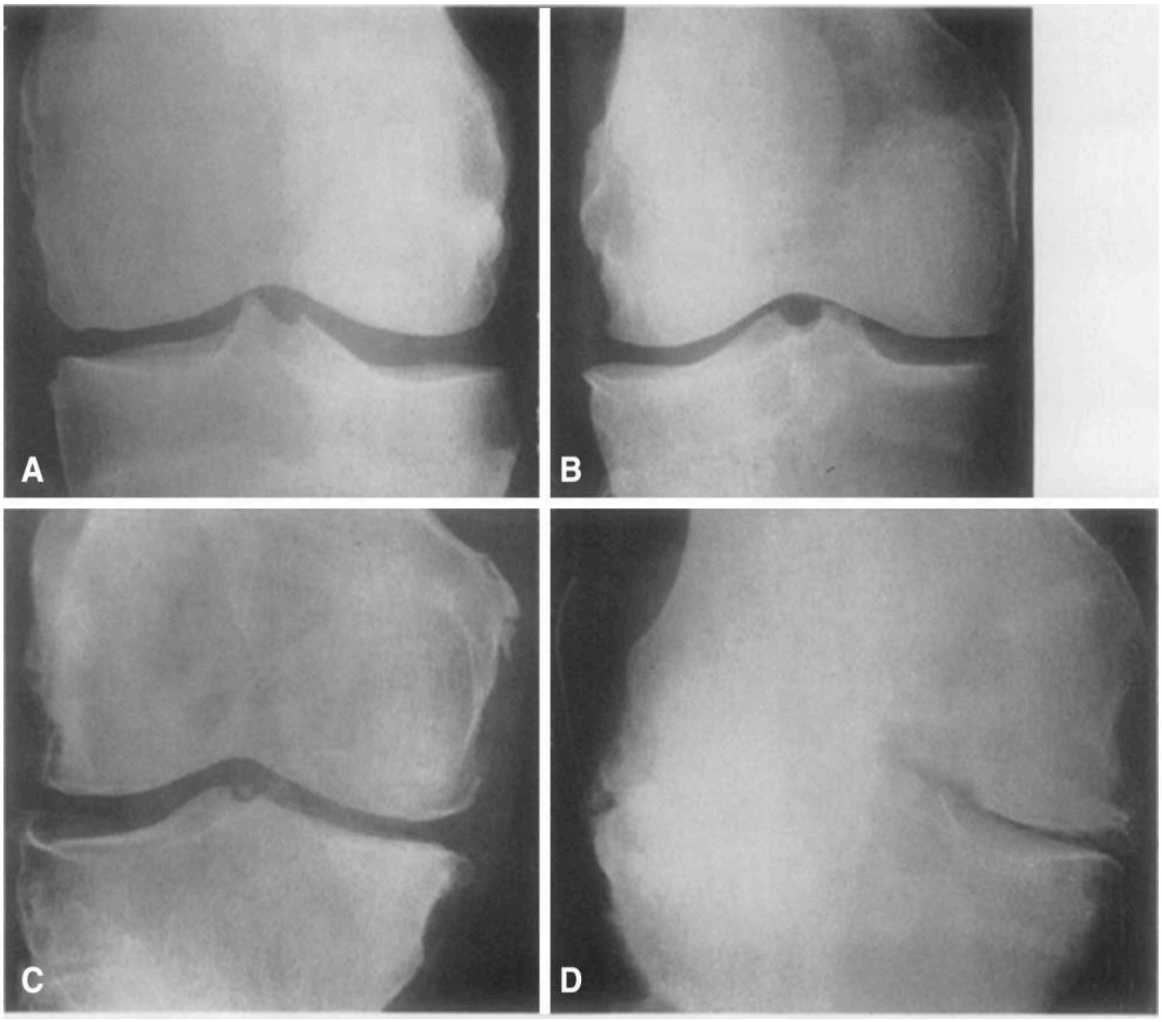


Figure 2-4: (A) Representative knee radiograph of KL classification Grade 1, which demonstrates doubtful narrowing of the joint space with possible osteophyte formation. (B) Representative knee radiograph of KL classification Grade 2, which demonstrates possible narrowing of the joint space with definite osteophyte formation. (C) Representative knee radiograph of KL classification Grade 3, which demonstrates definite narrowing of joint space, moderate osteophyte formation, some sclerosis, and possible deformity of bony ends. (D) Representative knee radiograph of KL classification Grade 4, which demonstrates large osteophyte formation, severe narrowing of the joint space with marked sclerosis, and definite deformity of bone ends (Adapted from Kellgren & Lawrence 1957)[76].

One of the hallmark measures to assess knee OA progression is tracking the joint space width, defined as the minimal distance between the femoral condyle and tibial plateau[120]. Joint space narrowing is a surrogate measure of cartilage thickness, and due to the low cost, and ease of access, this measure is a primary outcome for assessing disease progression[121]. The measure of joint space width is recommended by the Osteoarthritis Research Society International (OARSI) as a radiographic outcome for use in clinical trials tracking structural disease progression[121]. Severe joint space narrowing (bone on bone) is typical in knee replacement surgery[122]. The substantial drawback of joint space width is that it doesn't account for other changes that may be happening within the joint leading to a reduced joint space[123,124]. A common limitation of interpreting joint space narrowing as a measure of cartilage thickness, is that it is affected by meniscal changes[123,124]. Although cartilage and meniscal integrity can degrade together throughout the disease process, radiographs are not able to differentiate between the two when monitoring progression.

2.1.3.2 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is the current gold standard for imaging knee OA and assessing structural progression of the disease[121,125]. Due to the limitations of radiography, MRI has been stated as the most appropriate imaging modality to assess joint status in OA research studies by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) and OARSI[121,125]. The advantage of MRI is its ability to visualize all tissues in the joint simultaneously in three dimensions. With the growing knowledge that knee OA is a whole joint disease[74], MRI allows for the assessment of the subchondral bone, joint capsule, menisci, synovium, articular cartilage, ligaments, and surrounding

musculature[25,74]. While MRI is not the go to imaging modality in clinical settings, it is preferred in research for its higher sensitivity and ability to better assess longitudinal changes to the joint[121,125]. It also lacks the radiation exposure experienced during radiography.

The ability of MRI to directly visualize the articular cartilage allows for parametric mapping techniques to exploit the sensitivity of MRI to the biophysical properties of cartilage[126]. These techniques give the ability to identify cartilage matrix degradation preceding visible cartilage damage[127]. Cartilage T2 mapping reflects interactions among water molecules, and between water molecules and surrounding macromolecules[128,129], making this technique sensitive to cartilage matrix adaptations[128,129]. Increased interactions between water and collagen result in decreased T2 times, making it highly sensitive to changes in hydration and collagen concentration[129,130]. T2 mapping uses water to assess the structural integrity of the extracellular matrix by a combination of water content and collagen fibre arrangement[129,130].

Evidence suggests that T2 mapping can identify sites of early cartilage degeneration, measured as a disruption of the cartilage matrix[129,130]. Increased T2 values are most commonly associated with cartilage damage; however, can be due to excess water content in the cartilage[129,130]. Research has shown that individuals with knee OA present with increased T2 relaxation times compared to healthy controls due to higher water content and worse cartilage integrity[131]. Longitudinal data has linked increased T2 relaxation times to morphologic cartilage abnormalities, with a recent systematic review noting that elevated T2 relaxation times at baseline predicted degeneration of articular cartilage, meniscus and bone marrow lesions over three-years[132].

Additionally, T1rho relaxation time is described as the duration of spin-lattice relaxation in the rotating frame and is similar to T2 relaxation time; however, requires an additional radiofrequency pulse[129]. The interactions between water molecules and their environment can be assessed using T1rho, and is a promising technique for assessing the composition of articular cartilage[129]. Changes in T1rho may be caused by adaptations in the extracellular matrix such as proteoglycan depletion; however, may also be due to collagen fibre orientation and concentration[129,133]. These changes in the cartilage composition lead to elevated T1rho times in diseased vs healthy cartilage, even in mild radiographic knee OA (KL 1-2)[134]. Results suggest that T1rho may be more sensitive than T2 imaging for differentiation between healthy and early-stage diseased cartilage[134]. The main downfall of T1rho is the requirement of special pulse sequences typically restricted to research institutions, and multiple datasets making its use less clinically appealing[129].

Semi-quantitative scoring methods using MRI enable the comprehensive evaluation of multiple aspects of knee OA[135]. These approaches assess various features crucial for understanding the knee's functional health, including articular cartilage morphology, subchondral bone marrow lesions, osteophytes, the menisci, the anterior and posterior cruciate ligaments, collateral ligaments, synovitis and joint effusion, and bone attrition[135]. The first semi-quantitative measure published was the Whole-Organ MRI Score (WORMS)[136]. The WORMS looks to split the knee joint into subregions and assesses aspects of cartilage, subchondral bone and lesions around the knee. The WORMS splits each tibial plateau into three subregions anterior-posteriorly, and each femoral condyle into two subregions (central and posterior), with the patella-femoral joint is split into four subregions[137]. Other commonly utilized semi-quantitative MRI outcome measures used in

clinical trials include the Boston-Leeds OA Knee Scoring (BLOKS)[138] and the MRI Osteoarthritis Knee Score (MOAKS)[135].

2.1.4 Diagnosis of Osteoarthritis the Illness

While the American College of Rheumatology diagnostic guidelines[18] are likely the most commonly utilized diagnostic tool, the Arthritis Society of Canada and Health Quality Ontario have recently stated that radiographic imaging is not needed for a knee OA diagnosis if the patient satisfies a typical presentation of knee OA[56–58]. This statement also demonstrated a level of agreement of 8.7/10 (0 representing no agreement, 10 representing perfect agreement) between the literature evidence and expert opinion[139]. In patient cases where the presentation is atypical, an x-ray may be recommended to rule out a potential alternative diagnoses[139]. Guidelines now state that an individual has knee OA if "they are >40 and have symptoms typical of knee OA, including persistent atraumatic movement related joint pain, aching, stiffness and/or swelling, and morning stiffness lasting less than 30-minutes may or may not be present"[56–58,139]. This diagnostic shift has been well-supported as the prevalence of OA increases in younger age groups, the association between x-ray findings and symptoms is poor, and radiographic features of OA do not require treatment if the person does not have symptoms[56–58]. The newer diagnostic method is also being well-utilized in the scientific community, with a growing number of studies incorporating recruitment criteria based on self-reported knee OA[12–17]. Across these studies, the most common recruitment criteria for a self-reported diagnosis of knee OA included 1) >40 years of age, 2) activity related knee pain on most days in the past month, 3) pain experienced for at least the past three months, 4) pain ranging between 40 to 90 on

a 100-point numeric rating scale, and 5) morning stiffness lasting <30-minutes[12–17]. By adopting this new diagnostic and eligibility criteria, researchers may be better able to target a wider and more inclusive sample of individuals with knee OA from the community and improve generalizability of the findings.

2.2 Patient-Reported Outcomes in Knee Osteoarthritis

Patient-reported outcomes are a key component of understanding the impact of knee OA from the perspective of the individual[140,141] and give consideration to the biopsychosocial model when describing the illness state of knee OA[141]. Patient-reported outcomes serve an important role in knee OA research by aiding in treatment decision making and measuring the effectiveness of interventions. These quantitative evaluations are essential for: 1) delineating the present clinical condition, encompassing pain and functional limitations, as well as the ramifications of knee OA on various aspects of daily life such as fatigue, mood, sleep quality, and the presence or absence of pain sensitization; 2) identifying alterations in clinical status over time, whether indicative of improvement or deterioration; and 3) measuring the effectiveness of interventions and the achievement of desired symptom states[141]. Several different patient-reported outcomes exist including the WOMAC[142], Knee Outcome Survey (KOS)[143] and Oxford Knee Scale (OKS)[144], the Knee Injury and Osteoarthritis Outcome Score (KOOS)[145] and Intermittent and Constant Osteoarthritis Pain (ICOAP)[146] score. In this thesis, the KOOS and ICOAP were chosen for inclusion and will be elaborated upon further. The selection of KOOS over WOMAC, KOS, and OKS was based on its ability to offer a more comprehensive assessment of the patient experience. Unlike the WOMAC and KOS, the KOOS provides insights into knee

related QoL, which is valuable for understanding potential differences in perceptions between individuals with self-reported and clinically diagnosed knee. The OKS, primarily intended for those undergoing TKA, was not chosen as it is uncertain whether individuals with self-reported knee OA had previously sought medical treatment. The ICOAP was selected to better understand different pain experiences that the groups may be reporting.

2.2.1 Knee Injury and Osteoarthritis Outcome Score

The KOOS is a 42-item, self-report questionnaire developed to evaluate individual perceptions about the knee-related problems they experience[145]. The KOOS was developed based on the WOMAC and includes five subscales: symptoms (7 items), pain (9 items), function of daily living (ADL) (17-items), function in sport and recreation (5-items) and knee related quality of life (QoL) (4-items)[145]. The symptoms subscale focuses on the frequency and severity of symptoms such as swelling and stiffness[145]. The pain subscale evaluates the intensity and frequency of knee pain during various activities[145]. The ADL subscale assesses the difficulty experienced when performing daily activities like walking or climbing stairs[145]. The sport subscale gauges limitations in sports and recreational activities due to knee issues[145]. Lastly, the QoL subscale measures the impact of knee problems on overall QoL, including social and emotional aspects[145]. Each subscale contains specific questions tailored to comprehensively evaluate different aspects of knee function and its influence on various aspects of life. Responses to all items are on a 5-point Likert scale ranging from 0-4 and is typically converted to a 0–100-point scale (0 = “worse symptoms”, 100 = “better symptoms”). The KOOS is regularly used to assess effectiveness of treatments such as total knee arthroplasty (TKA)[147], and physical activity

interventions[148]. All subscales of the KOOS have shown excellent tests-retest reliability (ICC = 0.83-0.90), and good to excellent internal consistency (Cronbach's alpha = 0.74-0.92)[149]. The KOOS subscales have minimal clinically important difference (MCID) values of 9 for symptoms, 12 for pain, 10 for ADL, 9 for sports and 16 for QoL 6-months post TKA[150].

2.2.2 Intermittent and Constant Osteoarthritis Pain Score

The ICOAP score is an 11-item self-report questionnaire evaluating the experience of pain over the past week including pain intensity, frequency and impact on sleep, mood, and QoL[141]. The questionnaire is broken down into two subscales: constant pain (5-items) and intermittent pain (6-items)[146]. Responses to all items are on a 5-point Likert scale ranging from 0-4 and is typically converted to a (0–100-point scale 0 = "worse symptoms", 100 = "better symptoms")[146]. The constant pain sub-scale focuses on persistent pain throughout the day, while the intermittent pain sub-scale focuses on pain that comes and goes, evaluating its overall impact on QoL, including effects on sleep, mood, and daily function[146]. The ICOAP has shown moderate-to-high test-retest reliability across its subscales (ICC = 0.57-0.64)[151]. Researchers have observed various pain patterns associated with the frequency of pain experienced by individuals with knee OA[146,152]. According to previous research, pain typically starts as sporadic pain related to activity[146,152] then as the disease progresses, this pain transitions into persistent discomfort, with late-stage disease characterized by constant and often unpredictable intermittent pain[152]. These collective findings indicate that assessing pain patterns, particularly using ICOAP, may offer a more effective means of distinguishing between different levels of knee OA severity.

2.3 Knee Osteoarthritis Biomechanics During Walking

The progression of knee OA is a complex combination of an altered loading environment, structural changes and disruption of biological pathways[25,72]. As knee OA progresses, joint function is impaired accompanied by altered movement patterns and neuromuscular control[25–28]. The anatomical adaptations of the knee and the corresponding abnormal joint loading associated with knee OA, have driven human movement research to identify potential biomechanical adaptations that may accompany or precede the pathology. Gait analyses are considered the gold standard for assessing outcomes of lower extremity joint function. Four main reasons to perform clinical gait analysis have been proposed and these include: 1) diagnosis between disease entities, 2) assessment of the severity of disease or injury, 3) monitoring the progression of the disease in the presence or absence of intervention, and 4) prediction of the outcome of intervention[153,154]. The following section will review joint kinetics, and kinematics in the context of knee OA.

2.3.1 Kinematics

Kinematic analysis is the branch of biomechanics concerned with the description of motion in three-dimensional space without regard for the forces that cause the motion[155]. Kinematic analysis has been used as a tool by clinicians and researchers to quantify movement adaptations observed in individuals with knee OA, with a particular focus on sagittal and frontal plane ROM. The most commonly reported kinematic variables analyzed in knee OA research are in the sagittal plane, including knee flexion at initial contact, early stance ROM, and late stance ROM[23,40,41,156–158]. Individuals with knee OA typically display increased knee flexion at initial contact, and this value increases with knee OA

severity[41,157,159–161]. This alteration in sagittal plane knee flexion angle at initial contact can have deleterious effects on cartilage health due to the high magnitude and rapid accumulation of forces incurred during initial contact and loading response[162]. The increased knee flexion at initial contact may lead to altered loads on the joint, and overload portions of the cartilage not accustomed to the magnitude of forces experienced[41]. Findings reported by Favre and colleagues[41] demonstrated that a greater knee flexion angle at initial contact was positively associated with accelerated cartilage loss in individuals with knee OA[41]. The high amount of quadricep and hamstring activation required during initial contact to stabilize the knee joint may also compound this damaging effect by further increasing compressive forces in the knee[112].

Individuals with knee OA also typically walk with reduced early stance ROM (i.e., initial contact to peak stance knee flexion) and late stance ROM (i.e., peak stance knee flexion to minimum flexion during terminal stance)[23,40,41,156–158] (Figure 2-5). Similar to the findings observed for elevated knee flexion at initial contact, the reduced sagittal plane knee ROM during stance reduces the overall surface area used to distribute loads throughout the joint. This reduced surface area may increase cartilage stress and may not be able to withstand these loads[29,163]. It has been thought that individuals with knee OA may be hesitant to move into positions of greater knee extension due to pain, and as such, limit movement into this position[29]. This finding is supported by the use of NSAIDS leading to an increase in sagittal plane knee ROM[164]. Additionally the lack of sagittal plane knee ROM may cause joint damage and eventually lead to elevated pain[29]. This notion may be supported by Panjabi's model, which suggests that as the passive system of the joint (i.e., cartilage, ligaments, bone) begins to fail, the active system (i.e., muscles and tendons)

must work harder to maintain the stabilizing structure of the joint[165]. Multiple gait studies support that individuals with knee OA walk with elevated and prolonged activation of the major knee extensors and flexors, thought to act as a natural brace for the joint[28,40,166,167]. Sagittal plane knee ROM, like the KFM, appears to adapt with increased knee pain, and reduced ROM is likely a compensatory strategy to increase joint stability and reduce knee pain during walking.

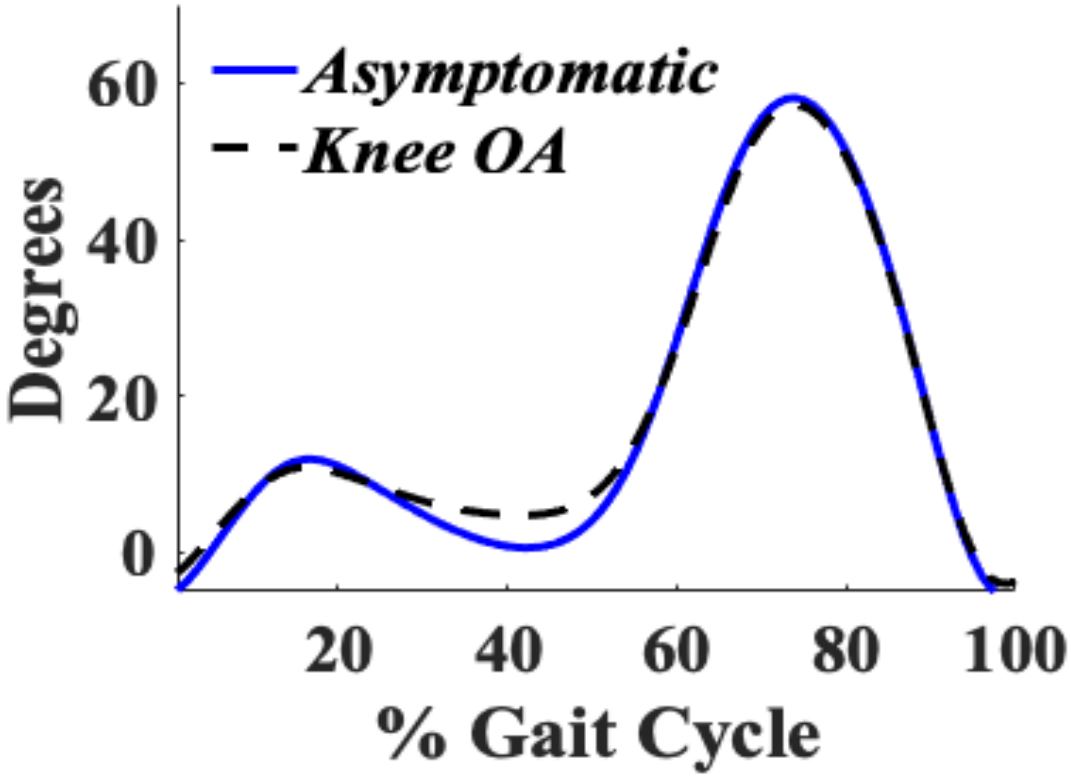


Figure 2-5: Ensemble average waveforms for sagittal plane knee flexion angles during level walking. Each waveform is time normalized to a percentage of the gait cycle. Data are presented for asymptomatic individuals (blue line) and participants with self-reported knee osteoarthritis (Knee OA, dashed line). Waveforms represent preliminary data from Chapter 4 of this thesis.

Although the majority of knee motion occurs in the sagittal plane, the medial compartment prevalence of OA, which is greater than lateral compartment prevalence, has been shown to influence movements of the knee in the frontal plane[168–172]. Individuals with knee OA walk with increased knee adduction during the stance phase of gait[168–172]. This abnormal motion in the frontal plane may be influenced by static joint alignment, most commonly observed in individuals with varus malalignment. A static varus angle may cause individuals with knee OA to walk with an offset toward knee adduction regardless of dynamic frontal plane ROM[173]. This is important due to the high association between varus alignment and elevated KAM values, as well as increased loads in the medial compartment of the joint[174].

Additionally, dynamic varus knee motion throughout stance is also a risk factor for increased load on the medial compartment and knee OA development[175,176]. This dynamic movement toward a varus knee position during initial contact and throughout stance, before returning to neutral alignment during terminal stance, is known as varus thrust[175,176]. The presence of varus thrust may result from dynamic instability in the frontal plane, potentially arising from impaired muscle function and peri-articular stabilization[177]. The presence of varus thrust during gait has been highly correlated with an elevated KAM compared to individuals without varus thrust[175,178,179], and is associated with up to a four-fold increase in the risk of radiographic medial knee OA progression[33,176]. This altered frontal plane knee motion is also significantly correlated with knee joint symptoms and increased pain[180]. The cumulative results suggest that altered frontal plane motions of the knee, specifically that of dynamic varus thrust during walking, may play a role in the elevated loads experienced in the medial compartment of the knee and contribute to accelerated knee OA progression.

2.3.2 Kinetics

Kinetics is the branch of biomechanics examining the forces that cause motion, and in terms of gait analysis, the internal (i.e., muscles) and external (i.e., ground reaction forces) moments that facilitate locomotion[155]. Movement results from the activation of multiple muscles acting across joints, in combination with the bodies interaction with the environment to cause the movement we are measuring[155]. How these forces interact and transmit across the tibiofemoral compartments have a strong influence on the pathogenesis of knee OA[9,25,72]. Typically, these forces are measured via the frontal plane adduction, and sagittal plane flexion-extension moments and calculated using inverse dynamics. Inverse dynamics is a biomechanical technique used to estimate the forces and moments acting within a system, such as the human body, based on observed motion data. In the context of the knee joint, inverse dynamics involves a multi-step process. Firstly, kinematic data, including joint angles, velocities, and accelerations, are collected. Next, employing principles of Newtonian mechanics, inverse dynamics integrate this kinematic data with inertial properties, segmental accelerations, and external forces (e.g., ground reaction forces) to estimate the forces and moments at the joint. The KAM has been proposed as a proxy for the distribution of load between the medial and lateral compartments of the knee[181], and the knee flexion-extension moment has been proposed as a surrogate measure of net muscle contributions to joint load[182]. This subsection will assess the literature of the most common kinetic variables measured in knee OA, and their implications toward knee OA development, progression, and symptoms.

Undoubtedly the KAM has been the most well-studied variable throughout the knee OA literature, which is a surrogate measure of the load distribution between the medial and

lateral compartments of the knee[30,33,183]. As the net external KAM increases, the evidence suggests that there is increased loading on the medial compartment of the joint, and partially justifies the higher prevalence of medial versus lateral compartment knee OA[30,33,183]. The peak KAM has been linked to knee OA development and progression, and is significantly associated with cartilage thickness loss[33–36], bone marrow lesions[37,38], and radiographic severity[33,111]. Not only is the KAM associated with knee OA development, it also appears to accelerate disease progression[110,184], which may be augmented by certain patient characteristics such as obesity (i.e., increased load magnitude) and varus lower limb alignment (i.e., increased aberrant load distribution)[185].

Typical presentation of the KAM in individuals with mild-to-moderate knee OA demonstrates an elevated peak value[33,34,36,37,185], while individuals with severe disease are more characterized by a reduction in mid-stance unloading, resulting in a more unimodal waveform[42,186]. This unimodal pattern demonstrates a reduced unloading of the joint, which can be captured by quantifying the KAM impulse and is calculated as the area under the KAM waveform. The KAM impulse accounts for loading over the entire stance phase rather than investigating a single peak value and therefore may be a more informative metric over peak KAM. Due to the cyclical nature of gait, the prolonged and repetitive loading in the medial compartment associated with a slower walking speed could lead to chronic damage in the joint[33]. Therefore, KAM impulse may be a better measure of overall knee loading, which has utility when examining cumulative joint loading in individuals with knee OA[187,188]. In an attempt to understand the impact of these repetitive loads on knee OA development, authors have begun to use accelerometry data to estimate total daily loads experienced by the joint[187,188]. Results demonstrate that individuals with knee OA

walk with both elevated KAM and cumulative knee joint loading compared to healthy matched controls[187]. These findings may be particularly useful when examining the effects of extended periods of walking on the loading environment of the knee and needs further investigation.

In the sagittal plane, the knee flexion moment (KFM) is also readily studied in knee OA research and referred to as a surrogate measure of overall muscle contributions to load transferred thorough the knee during walking[182]; however, results on its correlation with knee OA development and progression are less consistent than the KAM[33]. Evidence has suggested that individuals with knee OA walk with a reduced overall sagittal plane knee moment range (i.e., the difference between the peak knee flexion moment in early stance and the peak knee extension moment (KEM) in late stance), which has been referenced as a "stiff knee gait pattern" and an adaptive measure to increase stability in the joint[39,110,189]. Along with the KFM range, peak values such as the peak KFM have shown associations with cartilage loss over five years[110]; however, this association was not observed at earlier timepoints (i.e., over two years)[37]. Researchers have noted that individuals without knee OA that had experimentally influenced pain demonstrated similar reductions in the KFM that have typically been observed in individuals with knee OA[159]. This finding may help to understand why the changes in the KFM appear to be more patient specific and less correlated with knee OA progression[26,159]. The findings indicate that while KAM values are better associated with knee OA development and progression, the KFM may be an adaptive response to pain and should be used in conjunction with the KAM to develop a more comprehensive understanding of joint mechanics during walking.

Although the KAM and KFM have been heavily investigated in individuals with knee OA, the total joint moment (TJM) has been proposed as an alternative, multiplanar outcome that captures the total contribution of the KAM, KFM and knee rotation moment (KRM) into a single metric[190]. Investigating the effectiveness of conservative treatments to reduce medial compartment loading in individuals with knee OA has been achieved by primarily targeting the KAM. Treatment options such as valgus knee bracing[191], and gait retaining[192] have shown promise at reducing peak KAM; however, there is little evidence to confirm whether these reductions in KAM are associated with subsequent increases in KFM and KRM. Therefore, reducing peak KAM may not yield decreases in total joint loading. Asay and colleagues (2018)[190] performed a natural progression study to assess how the TJM and its relative external knee moment contributions changed over five-years[190]. At baseline in individuals with mild-to-moderate knee OA, the KAM accounted for ~45%, the KFM accounted for ~54% and the KRM accounting for ~1% of the first peak TJM[190]. Over five-years, the participants progressed to moderate-to-severe knee OA with KAM accounting for ~72%, the KFM accounting for ~27% and the KRM accounting for ~1% of the first peak TJM[190]. Therefore, as the disease progresses the KAM may acquire a more dominant role in the TJM, and the distribution of the KAM, KFM and KRM contributions could potentially be used as an indicator of disease progression. The TJM may also serve as a more broad measure assessing total loading exposure to the joint compared to the KAM or KFM alone[190].

2.4 Walking for Physical Activity in Knee Osteoarthritis

Both physical activity and clinical practice guidelines recommend walking to reduce knee OA pain and improve physical function and QoL[19,64]. Individuals with knee OA who engage in physical activity consistently have better self-reported and performance-based measures of pain, function, and disability compared to individuals with knee OA who are not physically active[65–67]; however, the majority of individuals with knee OA are physically inactive, which may be driven by increases in knee symptoms and/or heightened fears that more frequent walking will worsen joint damage[23,54]. Currently, walking guidelines are lacking for individuals with knee OA and minimal evidence is available to tailor walking interventions for this clinical population. The American College of Rheumatology has published recommendations encouraging researchers to establish a knowledge-base for physical activity prescription for individuals with knee OA[21]. Recommendations called for research to examine differences in activity duration, frequency and intensity, while taking disease severity into consideration[21]. To address these knowledge gaps and target the strong association between physical inactivity and knee OA symptoms and function[65–67], further research is needed to assess the biomechanical implications of prolonged walking on joint health to better inform tailored physical activity recommendations by healthcare providers.

2.4.1 Response to Prolonged Walking in Knee Osteoarthritis

Pain is a key patient-reported barrier to physical activity[23,54]; therefore, examining acute changes in knee pain for individuals with knee OA during physical activity is a necessary research focus. Acute changes in knee pain following walking bouts are typically

assessed using an 11-point numeric pain rating scale (NPRS) ranging from 0 (no pain) to 10 (worst pain imaginable)[193]. Evidence consistently suggests that individuals with knee OA do not report a clinically meaningful worsening in pain following walking bouts of 20-30-minutes[194–196]. However, these studies may be subject to selection bias, where individuals who experience pain or discomfort during walking may not participate in this research for fear of aggravating symptoms[197]. When examining pain responses on an individual level, two subgroups have been shown to emerge. Boyer and colleagues (2019)[55] found that approximately half of individuals with knee OA engaging in a 20-minute walk reported a pain flare (1.5-2-point increase on an 11-point NPRS)[55], while the other half experienced no change or improved pain following 20-minutes of walking[55]. Further, individuals who experienced a pain flare showed decreased peak KAM and KFM compared to individuals who did not experience a pain flare[55]. These results demonstrate that pain responses to continuous walking may be individualized and related to factors such as gait mechanics, which supports additional investigations for evaluating individualized knee pain responses in relation to physical activity.

Biomechanical responses to prolonged walking[55,194–196] further suggest that individuals with knee OA with no increase in pain walked with increased knee flexion angles, first peak KAM, KFM, and peak knee flexion to knee extension moment difference[195,196]. Individuals with knee OA who had a pain flare following prolonged walking demonstrated reductions in first and second peak KAM compared to individuals with no pain flare, and reduced peak KFM compared to asymptomatic individuals[55]. These results highlight that changes in gait mechanics following continuous walking may be more closely linked with pain responses when evaluated at a subgroup level. Individuals with

knee OA who do not report an increase in pain walk with more dynamic gait patterns, and increased joint loading following prolonged walking, signifying a potential functional benefit after the activity[195,196], while individuals who experience a pain flare walk with reduced loading magnitudes, potentially in an attempt to alleviate pain[55]. Whether these gait changes in the affected knee are consistent in the contralateral knee is unclear. Knee pain is proposed to stimulate asymmetric walking patterns in individuals with knee OA[198,199]. Therefore, how individuals with knee OA and symmetrical versus asymmetrical gait characteristics respond to prolonged walking tasks are warranted and may help identify patient specific walking protocols.

2.5 Gait Asymmetry

During movements such as gait humans are assumed to be relatively symmetrical beings, and symmetrical patterns are often described as a sign of physiologically healthy movement[43]. The possibility exists that individuals with knee OA walk with abnormal and asymmetrical movement patterns to compensate for the affected joint, which may expose the contralateral limb to increased risk for disease onset[29]. This relationship may explain why 25% of individuals who have unilateral TKA undergo surgery on their contralateral knee within five years[48], and 62% had OA progression in their contralateral knee after nine years[49]. Symmetry analyses have been utilized for several decades to assess the efficacy of surgical interventions, or risk of injury[45–47]. Although the concept of inter-limb symmetry analysis has good potential for identifying altered movement compensations in pathological gait, there are several different symmetry calculation methods. Currently, there is a lack of knowledge on which method may provide the best assessment of

symmetry with the least amount of measurement variability[43,44,200–202]. This section will compare three of the most utilized symmetry calculations to assess which method may be most appropriate for use during gait analysis walking protocols.

2.5.1 Asymmetry Calculations

One of the earliest and most commonly reported symmetry index (SI) metrics was published in 1987[203], and slightly modified in 1989[201]. The calculation itself is simplistic and lends itself to clinical utility, proving to be sensitive to discrete spatial-temporal variables during gait[204]. The equation itself can be altered to assess symmetry between the affected and contralateral limbs for individuals with knee OA: $((X_A - X_C)/(0.5(X_A + X_C)) * 100)$, where X_A represents the value from the affected limb, and X_C represents the value from the contralateral limb. A value of zero indicates there is no difference between limbs, a positive value indicates that the magnitude is greater in the affected limb, and a negative value indicates that the magnitude is greater in the contralateral limb[201]. The main limitation of this equation is the artificial inflation of SI values when the variables are near zero[43,201]. An example from Herzog and colleagues[201] used the anterior posterior impulse calculation to determine 1.1Ns for the right limb and -1.0Ns for the left limb. Although these differences may appear minimal, they yield a SI of 4200%. This artificial inflation of values near zero also prevents the calculation from being used over the entire gait cycle and only lends itself to discrete metrics with values above zero. For this reason, a more recent adjustment of the above equation was made in 2012.

The SI_{norm} was proposed by Gouwanda in 2012 to develop a symmetry calculation that was less prone to artificial inflation, and in practice, could be used to calculate

symmetry at every instance of the gait cycle[202]. The equation is only slightly different, utilizing minimum-maximum normalized values: $SI_{norm} = \frac{(X_{norm(s)} - X_{norm(c)}}{(0.5(X_{norm(s)} + X_{norm(c)})) * 100)}$ where $X_{norm(n)} = \frac{X_n - X_{min}}{X_{max} - X_{min}} + 1$[202]. This calculation constrains the symmetry value to a maximum of 100%, limiting the artificial inflation seen in the original SI calculation. The most recently proposed SI calculation was presented by Queen and colleagues[200] utilizing a similar normalization technique; however, this calculation used data from multiple trials. In the equation:

$$NSI = \frac{X_{R(trial)} - X_{L(trial)}}{max_{trial=1:n}(max(0, X_{R(trial)}, X_{L(trial)})) - min_{trial=1:n}(min(0, X_{R(trial)}, X_{L(trial)}))} * 100\%$$

the numerator represents the difference between the affected and contralateral limbs for a single trial, and the denominator represents the maximum and minimum values for the metric across three trials (n). If all values are positive, zero will be used as minimum and if all values are negative, zero will be used as maximum.

Recently, Siebers and colleagues[43] compared these three SI calculations for knee ROM during overground walking, stair ascent and stair descent in healthy asymptomatic individuals[43]. The SI[201] yielded mean scores of 6.71%, 6.66% and 8.0% for knee ROM during walking, stair ascent and descent, respectively. The SI_{norm}[202] yielded mean scores of 8.67%, 6.76% and 10.4% for knee range of motion during walking, stair ascent and descent, respectively. Lastly, the NSI[200] yielded mean scores of 13.4%, 11.2%, and 14.8% for knee ROM during walking, stair ascent and descent respectfully[43]. Analysis between calculations showed good agreement between measures as all limits of agreement between symmetry values were within the authors predefined limit of 5%; however, a significant bias was found between most comparisons[43]. The highest asymmetry values were

calculated by the NSI followed by the SI_{norm} and SI; and highest variance was found in the NSI followed by the SI and SI_{norm}[43]. The lowest symmetry and variance values found by the SI calculation, combined with its ease of calculation, may be the optimal symmetry calculation for implementation in knee OA research aimed at establishing clinical utility.

2.5.2 Asymmetries During Gait in Knee Osteoarthritis

Knee OA is associated with altered walking patterns either as a result of disease progression, or in an attempt to alleviate joint symptoms[25]. Most knee OA research focuses on the affected knee, with little evidence evaluating the potential compensations that may be occurring in the contralateral knee. Gait asymmetry has been noted in pathological conditions such as lower limb amputations[205], stroke[45], and anterior cruciate ligament injury[206], and have been used to assess gait asymmetry in healthy individuals[43,200,202], pre-post surgeries or rehabilitative interventions[207], and disease[45,46]. The use of symmetry calculations may advance the knee OA research field on human movement patterns and functional mechanics observed early in the disease process. Innovative strategies to detect, assess and track early biomechanical deterioration and reduced function between the affected and contralateral knees are imperative for investigating treatments to prevent, delay or potentially reverse disease.

By combining Andriacchi[29] and Felson's[208] theories on the role of mechanics in knee OA onset and progression with Shakoor and colleague's[209] theory for the non-random evolution of end-stage OA, a mechanistic theory for the role of symmetry in knee OA onset and progression emerges. Shakoor and colleagues[209] note that individuals with unilateral knee or hip replacements are significantly more likely to show progression of OA in the

contralateral limb, and most commonly, the susceptible contralateral joint is consistent with the original affected knee or hip (i.e., knee to knee)[209]. Further, if the susceptible contralateral joint is not consistent, a joint on the contralateral limb was still 2x more likely to experience OA progression than that of the ipsilateral limb (i.e., knee to hip or hip to knee)[209]. Movement and loading asymmetries appear to be present after TKA, where the non-operated limb demonstrates increased KAM, KAM impulse and dynamic adduction angle[210–212]. All of these outcomes have been linked to knee OA progression in a recent meta-analysis[33], and may begin to explain why there is such a high proportion of contralateral knee OA development post TKA[48,49]. Therefore, there appears to be a link between unilateral knee OA progression and contralateral knee OA development. Symmetry analysis offers a unique opportunity to identify individuals who may experience altered loading between knees and potentially identify individuals more likely to progress to bilateral knee OA.

There have been limited efforts in knee OA research involving the previously described SI calculation, with most studies implementing an asymmetry analysis that tests statistical differences between limbs[44,47,50,51,213,214]. Currently, the literature investigating kinematic and kinetic inter-limb asymmetries in knee OA is inconsistent due to the lack of consensus on a valid and utilized symmetry calculation, and the variables to be investigated. Results suggest that kinematic asymmetries may manifest in the earlier stages of the disease; however, they appear to be driven by symptomatic disease rather than radiographic severity[50,51]. Mills and colleagues[50] reported that knee flexion asymmetries at initial contact were greater in a group of individuals with unilateral symptomatic knee OA compared to both bilateral symptomatic and healthy individuals[50]. The notion that

symptoms may be driving these kinematic and kinetic asymmetries is also supported by Creaby and colleagues[51]. Authors reported that inter-limb asymmetries in the frontal plane varus angle and external flexion moment were present in individuals with unilateral symptoms, while individuals with bilateral severity exhibited symmetrical biomechanics[51]. These findings were found regardless of unilateral or bilateral radiographic diagnosis[51].

Investigations for spatiotemporal asymmetry have previously been reported in individuals with knee OA across three studies[198,199,215]. Results from the Multicenter Osteoarthritis (MOST) Study demonstrated that mild-to-moderate unilateral knee pain was not associated with temporal asymmetry, and elevated SI (i.e., longer time on the contralateral limb) was associated with a decreased odds of contralateral knee pain over two years[198]. Authors did note that the walking assessment used (4.9m walk, completed 4 times) may not have been challenging enough to elicit pain in the affected knee, and may explain why no association was observed between temporal SI and knee pain during walking[198]. Additionally, individuals one week before TKA were found to have asymmetric plantar pressures and weight transfer, which authors attributed to asymmetric step times, where individuals walked with shorter step times on their contralateral limb[215]. These spatial-temporal asymmetries appear to persist following TKA and may have implications toward contralateral TKA. Spatial asymmetry following unilateral TKA has been associated with increased odds of contralateral TKA over 8-years[199]. Kim and colleagues (2023)[199] found that following unilateral TKA, every 1cm increase in step-length asymmetry (i.e., longer step length on the affected knee and shorter step length on the contralateral knee) increased the odds of contralateral TKA two-fold[199]. A longer step length on the affected limb may lead to longer single leg stance on the contralateral limb,

potentially increasing KAM impulse leading to greater loading on the contralateral knee[199]. Investigating inter-limb asymmetries between the affected and contralateral knees in individuals with unilateral knee OA is an important step for understanding early biomechanical adaptations in knee OA populations and identifying biomechanically-driven indices as possible risk factors for bilateral disease onset and progression.

Chapter 3: General Methodology

This chapter outlines the detailed methodology for three studies included in this thesis: (1) Self-Reported Recruitment Methodologies in Knee Osteoarthritis: Community Recruitment Implications, (2) Inter-limb Asymmetry, Patient-Reported Outcomes and Gait Biomechanics in Knee Osteoarthritis, (3) Inter-Limb Asymmetry Responsiveness to 30-Minutes of Walking in Knee Osteoarthritis. The specific methods implemented to address the objectives in each study are described in Chapters 4-6. Study protocols were approved by, and informed consent was obtained from all participants in accordance with, the Dalhousie University Ethics Review Board (REB# 2022-6340). A copy of the ethics approval for this work is provided in (Appendix A).

3.1 Participant Recruitment

3.1.1 Asymptomatic Individuals

Asymptomatic individuals were recruited using convenience sampling from the local Dalhousie and Halifax communities with poster board and social media advertisements. Interested individuals contacted the Dynamics of Human Movement Laboratory and a standardized email outlining study procedures was sent. Interested individuals were contacted by telephone, and a standardized script was used to determine study eligibility. Asymptomatic individuals were recruited based on the following criteria: (i) age >40 years, (ii) no history of lower limb pathology or symptoms within the past year, (iii) no lower limb injury within the past year, (iv) absence of neurological or cardiovascular conditions that would affect their walking ability, (v) able to walk independently without gait aids, (vi) and no lower limb surgery within the past 12-months.

Eligible participants were sent an informed consent form and details of the study visit by email, and a data collection appointment was established.

3.1.2 Participants with Self-Reported Knee Osteoarthritis

Participants with self-reported knee osteoarthritis (OA) were recruited using a sample of convenience from the local Dalhousie and Halifax communities with poster board and social media advertisements. Interested individuals contacted the Dynamics of Human Movement Laboratory and a standardized email outlining study procedures was sent. Using a standardized script, interested individuals were contacted by telephone to determine study eligibility. Individuals with self-reported knee OA were recruited from the community based on the inclusion criteria: >40 years of age, activity-related knee pain on most days in the past month, pain experienced for at least the past three months, pain ranging between 40-to-90 on a 100-point numeric pain rating scale (NPRS) (0 “no pain”, 100 “worst pain imaginable”), and morning stiffness lasting <30-minutes[12,13,15–17]. Participants were excluded if they had bilateral knee pain, bilateral activity related pain, were unable to walk without the use of a gait aid, had a history of lower extremity injury within the past year, presence of cardiovascular, neurological or respiratory impairments, inflammatory arthritis (rheumatoid, psoriatic or gout) in either limb, were unable to jog five meters, walk a city block or climb stairs in a reciprocal fashion. Eligible participants were sent an informed consent form and details of the study visit by email, and a data collection appointment was established.

3.1.3 Participants with Clinically Diagnosed Knee Osteoarthritis

Participants with clinically diagnosed moderate knee OA were diagnosed with knee OA by a health care professional and recruited from a single tertiary care centre specializing in OA assessments. Symptomatic moderate knee OA diagnoses were completed by an orthopaedic surgeon based on clinical signs and symptoms consistent with the American College of Rheumatology Guidelines[18]. The surgeon recruited potentially eligible participants using a standardized research study introduction. Interested participants were asked to consent to transfer contact information to the research team. The research team contacted each participant by telephone to determine study eligibility using a standardized script. Participants were eligible if they were >40-years of age, had unilateral knee pain, no bilateral activity related knee pain, were able to walk without the use of a gait aid, had no history of lower extremity injury within the past year, no presence of cardiovascular, neurological or respiratory impairments, no inflammatory arthritis (rheumatoid, psoriatic or gout) in either limb, were able to jog five meters, walk a city block and climb stairs in a reciprocal fashion[28]. Eligible participants were sent an informed consent form and details of the study visit by email, and a data collection appointment was established. A description of participant demographic characteristics is provided in (Table 3-1).

Table 3-1: Participant demographics and clinical characteristics for asymptomatic individuals and individuals with self-reported or clinically diagnosed knee OA (n=64)

	N	Sex	Age (years)		Mass (kg)		Height (m)		BMI (kg/m^2)		Speed (m/s)	
		F:M	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Asymptomatic	21	13:8	61	10	78.8	15.1	1.67	0.08	28.0	3.70	1.39	0.13
Self-Reported	27	16:12	57	11	85.5	20.2	1.68	0.09	29.7	8.1	1.24	0.17
Clinically Diagnosed	16	7:9	64	5.9	84.5	9.75	1.73	0.08	28.4	3.76	1.29	0.18

3.2 Participant Preparation

Data collection procedures were conducted in the Dynamics of Human Movement Laboratory in the Dentistry Building, Dalhousie University. At the data collection visit, participants were oriented to the space, equipment and study procedures. Prior to obtaining informed consent, a member of the research team gave participants the opportunity to ask any questions, reiterated that the study was completely voluntary and that by signing the informed consent form the participant could withdraw their inclusion to the study at any time. After informed consent was obtained, participants completed a set of self-reported questionnaires including the Knee Injury and Osteoarthritis Outcome Score (KOOS)[145], and Intermittent and Constant Osteoarthritis Pain (ICOAP)[146] scale. Baseline knee pain was collected using an 11-point NPRS (0 “no pain at all”, 10 “worst pain imaginable”) prior to testing. Knee pain using the NPRS was assessed in the self-reported dominant knee for asymptomatic individuals and the affected knee for individuals with knee OA. The KOOS was used to determine individual perspectives about their knee and associated symptoms within the past week. This questionnaire consists of five subscales including symptoms, pain, function, daily living (ADL), function sports and recreational activities (Sport), and quality of life (QoL)[145]. The KOOS has demonstrated moderate-to-excellent

test-retest reliability in individuals with knee OA across all subscales (ICC = 0.61-0.95)[216]. The ICOAP consists of two subscales and was used to quantify the type of pain experience as either intermittent or constant. The ICOAP has shown moderate-to-high test-retest reliability across its subscales (ICC = 0.57-0.64)[151]. All subscales for the KOOS and ICOAP were normalized to a 0–100-point scale (0 = "worse symptoms", 100 = "better symptoms"). The 11-point NPRS has shown excellent test-retest reliability in OA populations (ICC = 0.95)[193].

Participants were then asked to change into form-fitting shorts, a t-shirt and wear their regular walking/running shoes. Anthropometric measurements were collected including height, weight, waist, hip, thigh and shank circumferences, then participants were outfitted with a full-body retroreflective marker set including seven rigid clusters each containing four retroreflective markers placed over the pelvis, and bilaterally over the lateral femurs, lateral shanks and feet, and secured using Velcro straps. Individual retroreflective markers were placed over the seventh cervical vertebrae and bilaterally over the acromion, lateral epicondyles, ulnar styloid processes, greater trochanters, iliac crests, anterior superior iliac spine, medial and lateral tibial and femoral epicondyles, lateral and medial malleoli, first, second and fifth metatarsal heads and posterior heels (Figure 3-1).

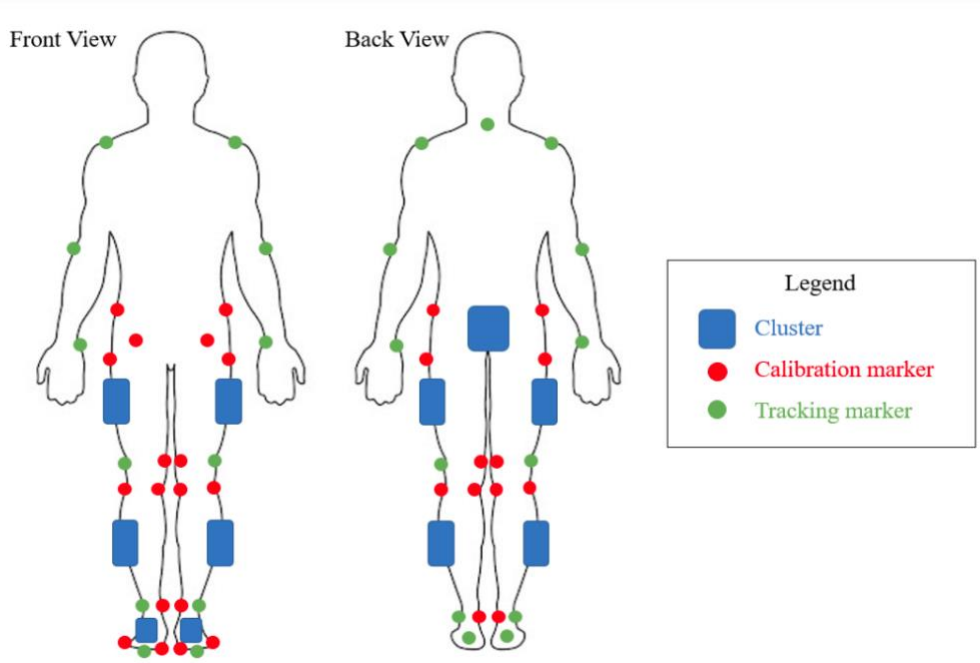


Figure 3-1: A schematic illustrating the whole-body passive reflective marker set. Blue squares represent marker clusters and green spheres represent individual markers. Both marker types remained affixed to the participant for the entirety of the walking protocol. Red spheres were removed after the initial calibration trial.

3.3 Gait Analysis

3.3.1 Calibration

An initial two-second standing calibration trial was collected with the participant standing on the force platform (Advances Medical Technologies Inc, Watertown, MA), their feet shoulder width apart and their knees as straight as possible ensuring all 59 markers were visible. Markers located at the medial femoral and tibial epicondyles, medial malleoli, the first and fifth metatarsal heads, lateral tibial epicondyles, iliac crests, anterior superior iliac spine, and greater trochanters were then removed. A second two-second standing calibration trial was collected with the remaining markers to generate the active

model used to automatically identify the marker template within the motion analysis software (Cortex, version 8.0, Motion Analysis Corporation, California, U.S.A).

3.3.2 Overground Walking Protocol

Participants completed a minimum of five overground walking trials at a self-selected pace across a six-meter walkway. Participants were instructed to walk at a comfortable pace while focusing on a point located on the opposite wall. A successful walking trial was completed when both feet contacted the floor embedded force platforms, which were offset to enable bilateral collection during a single trial (Figure 3-2). Three-dimensional kinematic data were collected at 100Hz using a ten-camera passive motion capture system (Cortex, version 8.0, Motion Analysis Corporation, California, U.S.A). Ground reaction force (GRF) data was collected at 1200Hz synchronized with two floor embedded force platforms (Advances Medical Technologies Inc, Watertown, MA). Participants were not told of the location of the force platforms during the collection to minimize potential changes in gait. Immediately after five successful overground trials were collected, the participants rated their affected knee pain using an 11-point NPRS. Average self-selected walking speed was calculated for each participant using the speed of the four pelvis markers in the anterior-posterior direction of the lab (i.e., aligning with the direction of walking), averaged across five trials. This overground walking protocol was completed before and after a 30-minute treadmill walk.

Figure 3-2: A posterior view of the lower extremity portion of the marker set. Clean bilateral force platform contacts indicate a successful walking trial in the anterior-posterior lab direction.

3.3.3 Treadmill Walking Protocol

After the overground walking trials, participants completed a bout of physical activity implemented as a 30-minute continuous treadmill walk (Figure 3-3), with walking speed set at ± 10% of the individualized average walking speed calculated during their overground trials. The 30-minute walk was completed on a Biodex treadmill (RTM600, Biodex Medical Systems, Inc., New York, U.S.A). During the walk, participants were asked not to use the handrail unless they felt uneasy or were going to lose their balance. An emergency stop clip was attached to the participants which would stop the treadmill if

they travelled too posteriorly. If participants were not able to complete the continuous 30-minute walk, they were allowed a short break before beginning the protocol where they left off. All participants successfully completed the 30-minute walk and only one required a short 2-minute break. For this participant the 30-minute timer was stopped during their break and resumed when they began walking again, the participant walked at the same speed after the break and accumulated a total of 30-minutes of walking. Their data was checked to ensure consistency with other participants. During the walk, participants were asked to rate their knee pain using an 11-point NPRS, and their rating of perceived exertion (RPE) using the Borg scale ranging from 6 "no exertion" to 20 "maximal exertion"[217]. Three-dimensional kinematic data, knee pain and RPE were collected at 10-minute intervals during the treadmill walk (i.e., once treadmill reached full speed, 10-, 20-, and 30-minutes) for a duration of 20-seconds. After completing the treadmill walking protocol, participants immediately repeated the overground walking protocol outlined in Section 3.3.2 Overground Walking Protocol.

Figure 3-3: A sagittal view of the lower extremity portion of the marker set during the treadmill walking protocol.

3.3.4 Maximum Voluntary Isometric Contractions

Retroreflective markers and marker clusters were removed after participants completed the walking protocols and maximum voluntary isometric strength was then collected bilaterally using a Biodex isokinetic dynamometer (Advantage BX Software 5.2, Shirley, NY, U.S.A) normalized to body mass (Nm/kg). Strength was collected after the walking protocols to minimize potential fatigue effects during walking and to ensure participants were warmed up prior to testing maximal effort contractions. Maximum knee flexion and extension strength were collected with the participant seated and their hips flexed to 90^{o}, and the knee flexed to 45^{o} with the lever positioned on the anterior portion of the shank just proximal to the ankle joint[218]. Velcro straps were used to stabilize the

participant for each strength test (Figure 3-4). The dynamometer axis of rotation was aligned with the medial-lateral axis of the knee. A gravity correction value was recorded by weighing the participant's limb prior to each strength trial to adjust for the effect of gravity on limb mass. The correction value was either added (extension) or subtracted (flexion) from the torque values for each trial[218]. A warm-up, practice contraction was performed to familiarize the participant with the test protocol. Each muscle group contraction was held for three-seconds and performed twice with a 60-second break between contractions. Verbal encouragement was given to each participant to maximize effort and contraction consistency[219].

Figure 3-4: Illustration depicting a maximum isometric strength trial for knee flexion and extension.

3.4 Data Processing

3.4.1 Kinematics

All three-dimensional marker data were filtered with a 6Hz lowpass fourth-order recursive Butterworth filter[218] in Visual 3D (v2023.04.2, C-motion Inc., Germantown, MD, U.S.A). Local and technical anatomical bone embedded coordinate systems for the pelvis, thigh, shank and foot were derived from virtual points, marker clusters and retroreflective skin markers. The origin of the thigh coordinate system was set at the hip joint center calculated based on the algorithm provided by Robertson and colleagues[155]. To develop the thigh coordinate system, a distal-proximal unit vector was created along the axis from the midpoint between the femoral epicondyles and the thigh origin (k). A unit vector was then created between the medial and lateral femoral epicondyles (v). The anterior-posterior vector (j) was created by crossing the k and v unit vectors. lastly, the medial-lateral (i) unit vector was created by crossing the k and j vectors[155]. The shank and foot coordinate systems were calculated with the same method using the medial and lateral tibial epicondyle and malleoli markers for the shank, and medial and lateral malleoli, first, second and fifth metatarsal markers for the foot[155].

Joint angles were calculated using standards from the International Society of Biomechanics[220] as the distal segment with respect to the proximal segment (i.e., shank with respect to thigh) using a Cardan/Eular rotational sequence[221] including flexion/extension, adduction/abduction, and internal rotation/external rotation, which is standard for the reporting of joint angles[220]. Flexion, adduction and internal rotation represent positive angles. All kinematic data was time normalized to 100% of the gait cycle (initial contact to ipsilateral initial contact) using a kinetic and kinematic initial contact and

pre-swing detection method[222]. Kinetic initial contact was determined when the vertical component of the GRF surpassed 20N, pre swing was determined when the vertical component of the GRF fell below 20N[222]. Kinematic initial contact was calculated as the maximal anterior displacement between the origin of the pelvis markers and heel marker[222]. The kinetic initial contact method was used to determine the first initial contact and toe-off events, and the kinematic method was used to calculate ipsilateral initial contact due to lack of force platform inputs. High-to-excellent day-to-day reliability has been found for sagittal plane knee kinematic outcomes in individuals with moderate knee OA during overground walking (ICC = 0.74-0.77)[223], and healthy individuals during treadmill walking have shown excellent test-retest reliability for sagittal plane knee range of motion (ROM) outcomes (ICC = 0.90)[218].

3.4.2 Kinetics

Raw GRF and moment data were filtered using a 30Hz lowpass fourth-order recursive Butterworth filter[218] in Visual 3D (v2023.04.2, C-motion Inc., Germantown, MD, U.S.A) and three-dimensional external joint moments were calculated using inverse dynamics[155,224]. Segment inertial characteristics (segment mass, segment center of mass and segment moment of inertia), along with kinematic outcomes (position of the center of mass, linear velocity, linear acceleration, angular velocity and angular acceleration) were calculated for each segment. Using linear acceleration and mass of the foot, Newton's second law was applied to calculate the ankle joint reaction force (Formula 3-1: ($F_a = m_f(a_f - g) - F_{grf}$))[155]. Assuming equal and opposite forces, a similar equation estimated the joint reaction force at the knee (Formula 3-2: ($F_k = (m_l - g) + F_a$))[155]. To compute

joint moments, segment inertial contributions to the joint moments were calculated[155,224]. Combining the segment inertial contributions with moment data from the GRF, joint reaction forces, and anthropometrics of the ankle, joint moments were calculated (Formula 3-3: $(\tau_a = \tau_f^I - \tau_{grf} - \left[\left(r_{a.grf} - r_{a.f}\right) * F_{grf}\right] + (r_{a.f} * F_a)))$[155]. Last, using Newton's third law the knee joint moment was calculated from the ankle moment using the same method as Formula 3-2. All joint moments were filtered with a 10Hz lowpass fourth-order recursive Butterworth filter and normalized to body mass (Nm/kg)[218]. All moment waveforms were time normalized to 100% of stance (initial contact to pre swing). Kinetic initial contact was determined when the vertical component of the GRF surpassed 20N, pre swing was determined when the vertical component of the GRF fell below 20N[222]. Discrete metrics extracted from sagittal and frontal plane knee moments have shown moderate-to-excellent test-retest reliability in individuals with knee OA including peak knee adduction moment (KAM) (ICC = 0.86-0.91)[181,223], peak knee flexion moment (KFM) (ICC = 0.57)[223] and knee rotation moment (KRM) (ICC = 0.88)[223]. During treadmill walking, healthy asymptomatic individuals have demonstrated excellent test-retest reliability in sagittal plane knee moment range (ICC = 0.93)[218].

3.4.3 Knee Flexion and Extension Strength

A Biodex Isokinetic Dynamometer (Advantage BX Software 5.2, Shirley, NY, U.S.A) was used to collect knee flexion and extension strength data bilaterally. Muscle strength was measured as torque, and a 500ms moving average window determined the maximum torque generated during either of the three-second maximum strength trials and normalized to body mass (Nm/kg)[218]. Excellent test-retest reliability has been found for

isometric knee extension and flexion strength in individuals with knee OA and asymptomatic individuals (ICC = 0.93=0.99)[218,225].

3.5 Data Analysis

This subsection provides an overview of the general data analysis plan for the thesis. Specific data analyses for each study and the corresponding objectives are outlined in Chapters 4-6. Data acquired for the affected knee (i.e., the self-reported dominant knee for asymptomatic individuals and the affected knee in participants with knee OA) and the contralateral knee were used in the analyses. For Objective 1, a subset of individuals with self-reported knee OA were matched for sex, age (± 4 years), and BMI (± 3 kg/m^2) with individuals with clinically diagnosed knee OA. Upper and lower limits of total joint moment ($TJM = \sqrt{KFM^2 + KAM^2 + KRM^2}$) asymmetry were calculated using gait data from asymptomatic individuals to determine the distribution of participants with symmetric versus asymmetric joint loading in each knee OA group. Objectives 2 and 3 pooled all participants with knee OA into a single group (participants with self-reported plus clinically diagnosed knee OA) and dichotomized into symmetric and asymmetric groups based on the limits of TJM asymmetry calculated from the asymptomatic individuals in Objective 1.

For Objectives 1-i, 1-ii, 1-iii, 2-i, and 2-ii, baseline patient-reported outcomes and the initial overground walking trials (i.e., prior to a treadmill walking protocol) were used for cross-sectional analyses. For Objectives 3-i, 3-ii and 3-iii, observational pre-post analyses examined the effects of a bout of physical activity (i.e., 30-minute walking protocol) on knee biomechanical outcomes and knee pain, using the overground walking

trials before and after the 30-minute walk. For Objectives 1-3, the primary biomechanical outcomes of interest included the sagittal plane kinematic (flexion-extension angle), frontal plane kinetic (KAM), and sagittal plane kinetic (KFM) waveforms analyzed with statistical parametric mapping[226]. Other primary outcomes focused on discrete metrics including the peak TJM (extracted from 0-40% stance), knee flexion range from initial contact to peak stance flexion angle calculated as the difference in maximum flexion during the first 30% of stance and flexion at initial contact (Figure 3-5), first peak external KAM to midstance unloading range, calculated as the excursion between maximum first peak KAM (extracted from 0-50% of stance) and minimum midstance KAM (extracted from 40%-80% of stance) (Figure 3-6), and sagittal plane knee moment range, calculated as the excursion between maximum KFM (extracted from 0-50% stance), and minimum knee extension moment (KEM) (extracted from 50-100% stance) (Figure 3-7). Peak KRM was extracted and only used for the calculation of the TJM[190]. Outcomes used for descriptive and group assignment purposes included the TJM[190], absolute TJM symmetry indices ($((X_A - X_C)/(0.5(X_A + X_C)) * 100)$)[201], in which X_A represents the first peak TJM in the affected knee and Xc represents first peak TJM in the contralateral knee. A symmetry value of zero represents perfect symmetry between knees. Upper and lower limits of the absolute TJM symmetry index were also calculated ($SI_{UI} = 0 \pm t_{df(0.05)} * SD$)[201], where $t_{df(0.05)}$ represents the critical t-value based on the degrees of freedom and an alpha level of 0.05.

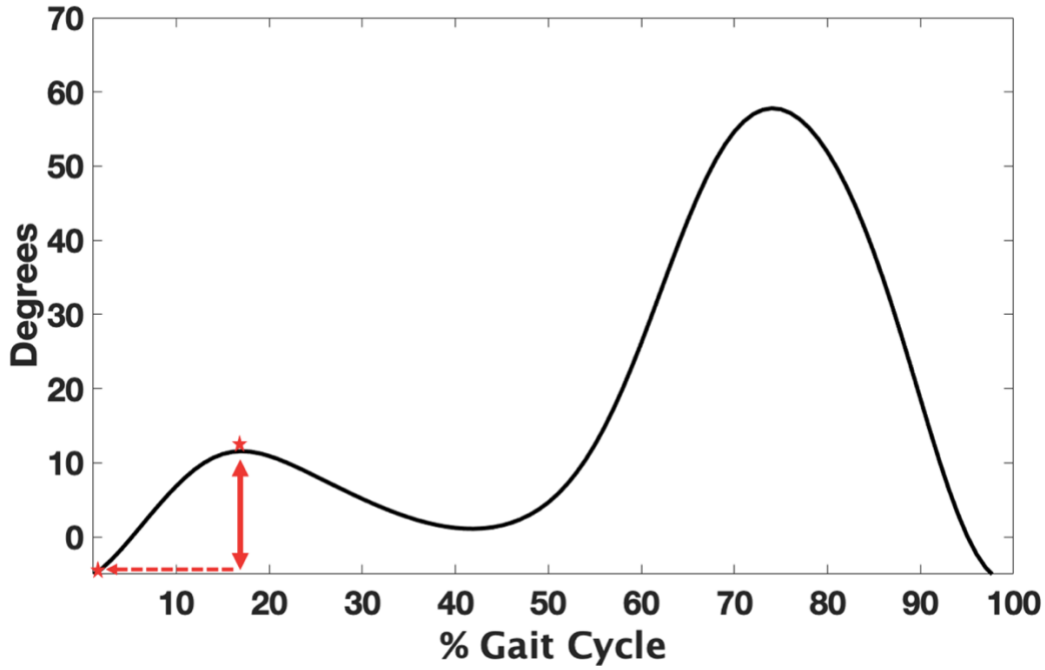


Figure 3-5: Ensemble averaged sagittal plane knee motion waveform illustrating the knee flexion range from initial contact to peak stance flexion angle.

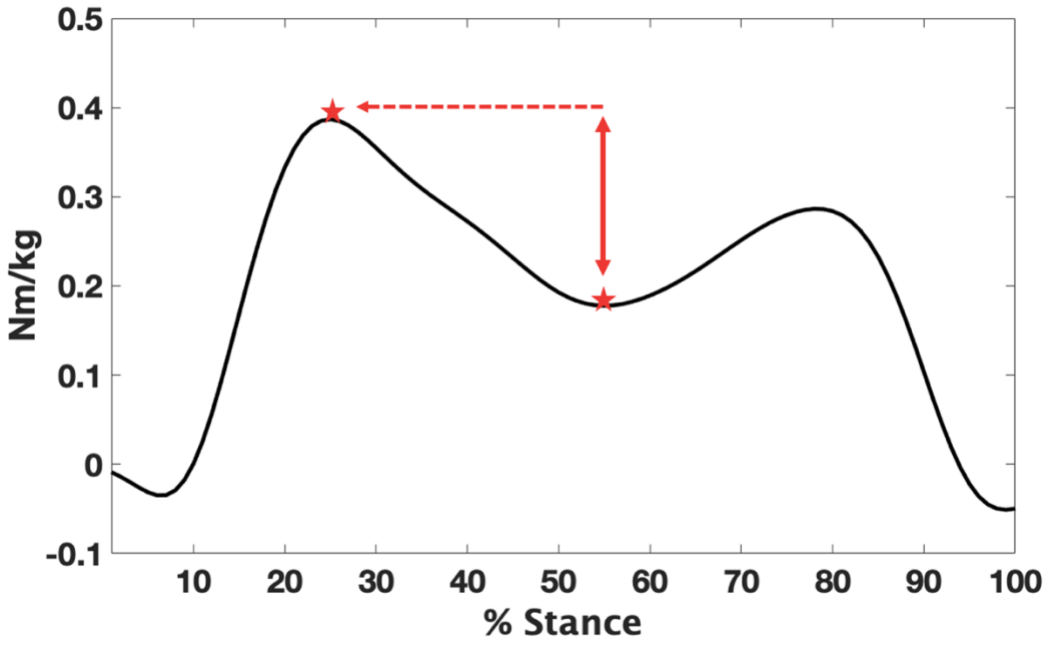


Figure 3-6: Ensemble averaged external knee adduction moment waveform illustrating the first peak knee adduction moment to midstance unloading.

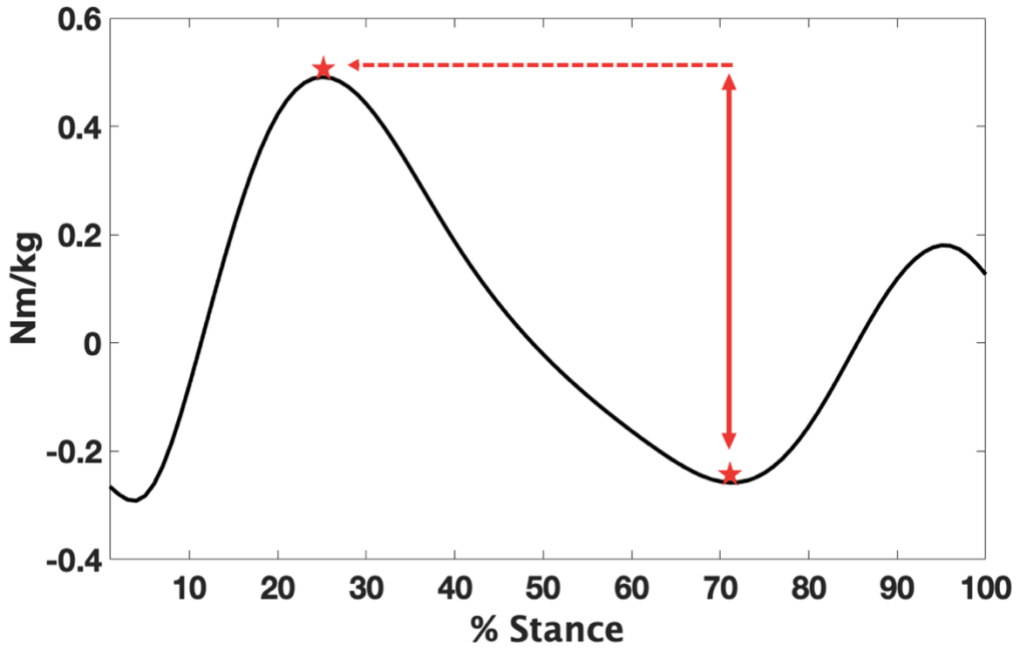


Figure 3-7: Ensemble averaged external sagittal plane knee moment waveform illustrating the sagittal plane knee moment range from peak knee flexion in early stance to peak knee extension in late stance.

3.6 Sample Size

To our knowledge, no study has previously assessed for differences in knee biomechanics between individuals with self-reported and clinically diagnosed knee OA, or individuals with knee OA dichotomized with having symmetrical or asymmetrical knee loading. Therefore, for Objectives 1 and 2 a sample size was calculated using previously reported differences in the KAM between moderate and severe knee OA (mean difference (pooled standard deviation) = 0.15 (0.17) Nm/kg)[227]. A sample size calculation based on independent samples t-test was used to determine the number of observations required to test the null hypothesis of no difference for the external peak KAM between individuals with self-reported and clinically diagnosed knee OA. Using an

alpha level of 0.05, a sample of 16 participants per group was required to maintain at least 80% power.

To our knowledge, no study has previously assessed the biomechanical response between the affected and contralateral knees in individuals with knee OA dichotomized with having symmetrical or asymmetrical knee loading before and after 30-minutes of walking. Therefore, for Objective 3 a sample size based on a 2x2 repeated measures analysis of variance to determine the number of observations required to test the null hypothesis of no difference for the external peak KAM between the affected and contralateral knees before and after 30-minutes of walking was calculated in G*power[228]. To achieve a moderate effect size with a critical F-statistic of 2.80 and an alpha level of 0.05, a sample of 18 participants per group was required to maintain at least 80% power.

CHAPTER 4: Comparing Participant Recruitment Methods in Knee Osteoarthritis: Implications for Community Recruitment and its Effects on Clinical and Biomechanical Outcomes

4.1 Introduction

Osteoarthritis (OA) is one of the most prevalent musculoskeletal diseases in the world, affecting approximately 23% of individuals aged over 40-years globally[229]. Knee OA, is a multifactorial disease with multiple variables contributing to its development, including muscle strength, joint injury, obesity, age, genetics, and sex[9]. Despite the known multifactorial nature of knee OA, and the wide range of individuals affected, only 5% of Canadian health studies used nationally representative data to study health outcomes[10], leaving a large gap in our ability to generalize findings to the greater population. A major limitation to properly representative data in Canadian health research is access to specialized healthcare[11]. Community based recruitment strategies are a proposed way to circumvent the need for access to specialized healthcare to participate in health research[11]. These community-based recruitment strategies are developing a consistent presence among knee OA research[12–17,230]; however, it is not known whether individuals recruited through community based self-reported methodologies present with similar patient-reported outcomes or biomechanical adaptations during walking compared to individuals clinically diagnosed.

This recruitment shift underscores the illness component of knee OA, focusing more on the patient response to the disease or any experiences felt by the patient because of the disease[73,75]. Two widely recognized tools to assess the illness component of knee OA are the Knee Injury and Osteoarthritis Outcome Score (KOOS), and Intermittent and

Constant Knee Osteoarthritis Pain (ICOAP) score. The KOOS captures individual perceptions about the knee and associated problems, evaluating both short and long-term perceptions[145]. In contrast, the ICOAP captures the frequency of pain, its intensity, and whether the pain happens without warning, or in response to a trigger[146]. However, there is a known discordance between symptoms and radiographic knee OA severity[79,231], and simply evaluating patient experience may not allow for a full understanding of the potential structural changes these individuals may have. Several gait characteristics have been closely linked to knee OA progression[33,37,39] and may act as a proxy for potential structural adaptations.

Gait has been used extensively as a model to understand joint function, measuring kinematics (joint angles) and kinetics (joint moments). There have been several biomechanical features linked closely to the progression of knee OA[33,36,39,232,233], primarily focusing on frontal plane mechanics. Most individuals with knee OA walk with an increased peak knee adduction moment (KAM) combined with a reduction in mid-stance unloading, thus shifting from a traditional bimodal ambulatory pattern in the frontal plane to a more unimodal waveform[33,34,36,37,185]. Further, evidence suggests that individuals with knee OA walk with a reduced peak knee flexion moment (KFM), reduced overall sagittal plane knee moment range[39,110,189], and reduced early stance sagittal plane knee range of motion (ROM)[23,40,41,156–158], which have also previously been linked to knee OA progression[33,39,233]. There is a high incidence rate of bilateral knee OA for individuals with unilateral disease[234], and work has begun to examine contralateral knee biomechanics in individuals with unilateral knee OA to better understand a potential pathway toward bilateral knee OA development[235]. Individuals with unilateral knee OA were found to walk

with elevated KAM in their contralateral limb compared to asymptomatic individuals, underscoring the importance of examining gait biomechanics bilaterally[235]. Comparing gait biomechanics between individuals with self-reported knee OA and individuals with clinically diagnosed knee OA may provide insight into whether these individuals walk with biomechanical characteristics consistent with the disease.

As the understanding of knee OA progresses, in the absence of injury, there is often uncertainty about why one limb contracts the disease while the other does not. Previous research has shown that individuals with unilateral knee OA walk with elevated KAM values in their contralateral knee[235], potentially indicating risk of OA development. Symmetry analysis may give unique insights into the pathogenesis of unilateral disease and highlight risk factors for bilateral knee OA development. However, current evidence is lacking on what bounds a symmetrical gait, and the prevalence of gait asymmetry in knee OA is poorly understood. Therefore, the specific objectives of this study were to: determine whether patient-reported outcomes reflecting pain, function and quality of life differ between individuals with self-reported and clinically diagnosed knee OA; evaluate differences in sagittal and frontal plane biomechanics between individuals with self-reported versus clinically diagnosed knee OA; and explore the prevalence and magnitude of inter-limb asymmetry within individuals with self-reported and clinically diagnosed knee OA.

4.2 Methodology

4.2.1 Participant Recruitment

Participants with knee OA were recruited using two different techniques. Individuals with self-reported knee OA were recruited from the community based on the inclusion criteria: >40 years of age, activity-related knee pain on most days in the past month, pain experienced for at least the past three months, pain ranging between 40-to-90 on a 100-point numeric rating scale (0 "no pain", 100 "worst pain imaginable"), and morning stiffness lasting <30-minutes[12,13,15–17]. Individuals with clinically diagnosed moderate knee OA were diagnosed by an orthopaedic surgeon based on the clinical signs and symptoms consistent with the American College of Rheumatology Guidelines[18]. Inclusion criteria included: age >40 years and moderate knee OA, defined as a Kellgren-Lawrence Grade of 2 and 3[76]. The exclusion criteria applied to both groups were age <40, bilateral symptoms, bilateral activity related pain, inflammatory arthritis in either limb, previous lower limb surgery, lower limb injury within the past year, or any cardiovascular, muscular, or neurological conditions that would affect their ability to walk or ambulate stairs. Asymptomatic individuals were recruited from the community using convenience sampling and the following criteria: (i) age >40 years, (ii) no history of lower limb pathology, or symptoms within the past year, (iii) no lower limb injury within the past year, (iv) absence of neurological or cardiovascular conditions that would affect their walking ability, (v) able to walk independently without gait aids, (vi) and no lower limb surgery within the past 12-months. Ethics approval was obtained from the local institutional ethics review board and participants provided informed consent prior to testing.

4.2.2 Data Collection

Participants completed the KOOS[145] and ICOAP[146] questionnaires, and baseline knee pain using an 11-point numeric pain rating scale (NPRS) (0 "no pain at all", 10 "worst pain imaginable") prior to testing. Knee pain using the NPRS was assessed in the asymptomatic individuals' self-reported dominant knee. Aligning with the explicit inclusion and exclusion study criteria (i.e., participants could not report experiences of any discomfort or activity related knee pain (NPRS=0) in their contralateral knee), NPRS was only assessed in the affected knee of individuals with knee OA. Participants were then asked to change into form-fitting shorts and a t-shirt and wear their regular walking/running shoes. Anthropometrics were collected for height and weight, and circumference measures at the hip, waist, and bilateral thigh and shank. Rigid plastic plates containing clusters of four retroreflective markers were placed over the pelvis, and bilaterally over the lateral femurs, lateral shanks and feet, and secured using Velcro straps. Individual retroreflective markers were placed over the seventh cervical vertebrae and bilaterally over the acromion, lateral epicondyles, ulnar styloid processes, greater trochanters, iliac crests, anterior superior iliac spine, medial and lateral tibial and femoral epicondyles, lateral and medial malleoli, first, second and fifth metatarsal heads and posterior heels (Figure 3-1). Prior to the walking protocol, markers located at the medial femoral and tibial epicondyles, medial malleoli, the first and fifth metatarsal heads, lateral tibial epicondyles, anterior superior iliac spine, iliac crests and greater trochanters were removed.

Participants completed a minimum of five walking trials along a six-meter walkway at a comfortable, self-selected walking speed. Bilateral three-dimensional kinematic and ground reaction force data were captured using a 10-camera passive motion capture system

(Cortex, version 8.0, Motion Analysis Corporation, California, U.S.A) (100Hz) and synchronized with floor embedded force platforms (Advances Medical Technologies Inc, Watertown, MA) (1200Hz). Following the walking trials, affected knee pain was collected using an 11-point NPRS. The remaining retroreflective markers were then removed.

Participants underwent voluntary isometric strength testing for knee flexion and extension using a Biodex isokinetic dynamometer (Advantage BX Software 5.2, Shirley, NY, U.S.A.). During the assessment, participants were seated with their hip flexed to 90^{o} and the knee flexed to 45^{o}[218]. Velcro straps stabilized the participant's leg for each strength test. A warm-up, practice contraction was performed to familiarize the participant with the test protocol. Contractions were completed twice for three-seconds, with a 60-second break between contractions. Verbal encouragement was given to each participant to maximize effort and contraction consistency[219].

4.2.3 Data Processing and Analysis

Total KOOS and ICOAP scores along with their subscales were normalized to a 0-100-point scale (0 = "worse symptoms", 100 = "better symptoms"). All three-dimensional marker data were filtered with a 6Hz lowpass fourth-order recursive Butterworth filter[218] in Visual 3D (v2023.04.2, C-motion Inc., Germantown, MD, U.S.A). Bilateral knee angles were calculated using an XYZ (sagittal, frontal, transverse) rotation sequence, described as the distal segment moving about a fixed proximal segment[221] in Visual 3D (v2023.04.2, C-motion Inc., Germantown, MD, USA) (flexion, adduction and internal rotation represent positive angles). Kinematic data for the sagittal, frontal, and transverse planes were collected; however, only the sagittal plane was analyzed. Kinematic data was time

normalized to 100% of the gait cycle (initial contact to ipsilateral initial contact) using a kinetic-kinematic initial contact and pre swing detection method[222]. Initial contact was used to detect the start and end of each cycle and identified using a 20N threshold for the vertical component of the ground reaction force, with ipsilateral initial contact calculated as the maximal anterior displacement between the origin of the pelvis markers and heel marker[222]. Pre-swing was identified when the vertical component of the GRF fell below the 20N threshold[222]. Ground reaction force data was initially filtered with a 30Hz, lowpass, fourth-order, Butterworth recursive filter[218]. Net external joint moments were calculated using an inverse dynamics model[155] in Visual 3D (v2023.04.2, C-motion Inc., Germantown, MD, USA). External knee moments, including the knee adduction moment (KAM), knee flexion moment (KFM), and knee rotation moment (KRM) were filtered with a 10Hz, lowpass, fourth-order, Butterworth recursive filter, normalized to body mass (Nm/kg), and time normalized to stance (initial contact to pre-swing)[218]. The total joint moment (TJM)[190] was calculated bilaterally for each participant using the formula: $TJM = \sqrt{KFM^2 + KAM^2 + KRM^2}$. Absolute TJM symmetry indices were calculated using the formula: $((X_A - X_C)/(0.5(X_A + X_C)) * 100))$[201], in which X_A represents the first peak TJM in the affected knee and Xc represents first peak TJM in the contralateral knee, for asymptomatic individuals limbs were randomly assigned to either affected or contralateral in the equation. A symmetry value of zero represents perfect symmetry between knees, and higher values represent greater differences between knees. Upper and lower limits of the absolute TJM symmetry index were calculated in asymptomatic individuals only using the formula: $SI_{UI} = 0 \pm t_{df(0.05)} * SD$[201]. The upper and lower limits of absolute TJM symmetry calculated for the asymptomatic individuals was used as a cut-off value to

determine knee loading asymmetry in both knee OA groups. Maximum flexion and extension strength were calculated using a 500ms moving average window to determine the maximum torque generated during either of the three-second maximum strength trials and normalized to body mass (Nm/kg)[218].

4.2.4 Statistical Analysis

Independent t-tests were performed only between individuals with self-reported and clinically diagnosed knee OA to detect group differences in demographics, patient-reported outcomes, maximum knee flexion and extension strength, TJM asymmetry indices and the relative contribution of the first peak KAM, KFM and KRM to the TJM. All mean difference and 95% bootstrapped confidence intervals were calculated as self-reported minus clinically diagnosed, where a positive value indicates that self-reported is greater than clinically diagnosed, and a negative value indicates that clinically diagnosed is greater than self-reported. Chi-square analysis was used to assess differences in prevalence of males and females and asymmetry between groups. Parametric descriptive statistics included mean and standard deviation for each group. Statistical parametric mapping independent t-tests (SPM{t})[226] were used to analyse the time normalized mean sagittal plane knee angles, KAM and KFM waveforms in Matlab (Mathworks Inc., Massachusetts, USA, version 2022a). Random field theory calculated the critical T-statistic, and the null hypothesis was rejected if the computed t-value for the waveforms exceeded this value[226]. Only differences identified by SPM in joint moments between 10-90% of stance were interpreted to align with most common kinetic metrics reported for individuals with knee OA[33,37,40,42,51,63]. All five walking trials were used in the final SPM{t} analyses to include

the stride-to-stride variability for each group (80 gait cycles per group = 160 total cycles). Due to the inability of SPM to evaluate ranges, between group differences in the TJM, knee flexion angle range from initial contact to peak stance flexion (ICPF), the first peak knee adduction moment to midstance unloading range (KAMR), and the sagittal plane knee moment range (SPROM) were analyzed and interpreted using mean differences and 95% bootstrapped confidence intervals in SPSS (Version 28.0, IBM Corp., Armonk, NY, USA). The calculation of these outcomes is described in Section 3.3 of this thesis. All between group biomechanical analyses were completed for the affected and contralateral knees separately between groups. All statistical analyses were interpreted using an alpha level of 0.05 to determine statistical significance. Normality and equal variance were assessed using the Kolmogorov-Smirnov and Levene's tests.

4.3 Results

Twenty-one asymptomatic individuals and 32 individuals with self-reported (n=16) and clinically diagnosed (n=16) knee OA were recruited. Participant demographic characteristics, and muscle strength are presented in Table 4-1. Knee OA groups were statistically similar in age, distribution of males and females, BMI, and gait speed (p=0.542-0.991); however, individuals with self-reported knee OA had significantly less knee flexion strength compared to individuals with clinically diagnosed knee OA (p=0.048).

Table 4-1: Participant demographics and clinical characteristics for individuals with self-reported or clinically diagnosed knee OA and asymptomatic individuals (n=53)

	Self-Reported Knee OA	Clinically Diagnosed Knee OA	Asymptomatic Individuals
n	16	16	21
Age	62 ± 9	64 ± 6	61 ± 10
Sex. no. of females (%)	7 (44)	7 (44)	8 (38)
BMI, kg/m^2	28.7 ± 6.2	28.7 ± 3.7	27.9 ± 3.7
Gait Speed, m/s	1.24 ± 0.16	1.29 ± 0.19	1.37 ± 0.12
KLG 2	-	11	-
KLG 3	-	5	-
Affected knee NPRS before walk	2.16 ± 1.96	1.00 ± 1.59	-
Affected knee NPRS after walk	1.69 ± 1.81	0.61 ± 1.40	-
Affected knee strength (Nm/kg)			
Flexion	**0.63 ± 0.21**	**0.91 ± 0.34**	0.82 ± 0.17
Extension	1.21 ± 0.28	1.28 ± 0.32	1.61 ± 0.34
Contralateral knee strength (Nm/kg)			
Flexion	0.72 ± 0.21	0.88 ± 0.26	0.78 ± 0.19
Extension	1.36 ± 0.35	1.37 ± 0.38	1.58 ± 0.35
Asymmetric, no. (%)	7 (44)	8 (50)	14 (66)
TJM asymmetry (%)	32.4 (36.7)	40.8 (35.1)	10.2 (6.30)

Note: Values are listed as mean and standard deviation unless otherwise indicated. KLG = Kellgren Lawrence Grade. NPRS = numeric pain rating scale. Bolded values indicate between-group differences ($p<0.05$).

4.3.1 Patient-Reported Outcomes

No significant differences were noted for either KOOS-Total (mean difference: 4.72, 95% CI [-3.84,12.7], p=0.284), KOOS-Symptoms (mean difference: 2.42, 95% CI [-6.19,10.9], p=0.577), KOOS-Pain (mean difference: 3.84, 95% CI [-6.42,15.0], p=0.515), KOOS-ADL (mean difference: -5.49, 95% CI [-15.1,4.09], p=0.264), KOOS-Sport (mean difference: 3.28, 95% CI [-12.5,17.5], p=0.6.88), KOOS-QoL (mean difference: 2.29, 95% CI [-7.81,12.7], p=0.482), ICOAP-Total (mean difference: 0.11, 95% CI [-11.9,11.4], p=0.980), ICOAP-Constant (mean difference: 2.23, 95% CI [-12.2,15.4], p=0.729) or ICOAP-Intermittent (mean difference: -3.31, 95% CI [-16.1,9.44], p=0.617) between knee OA groups (Figure 4-1 & Figure 4-2).

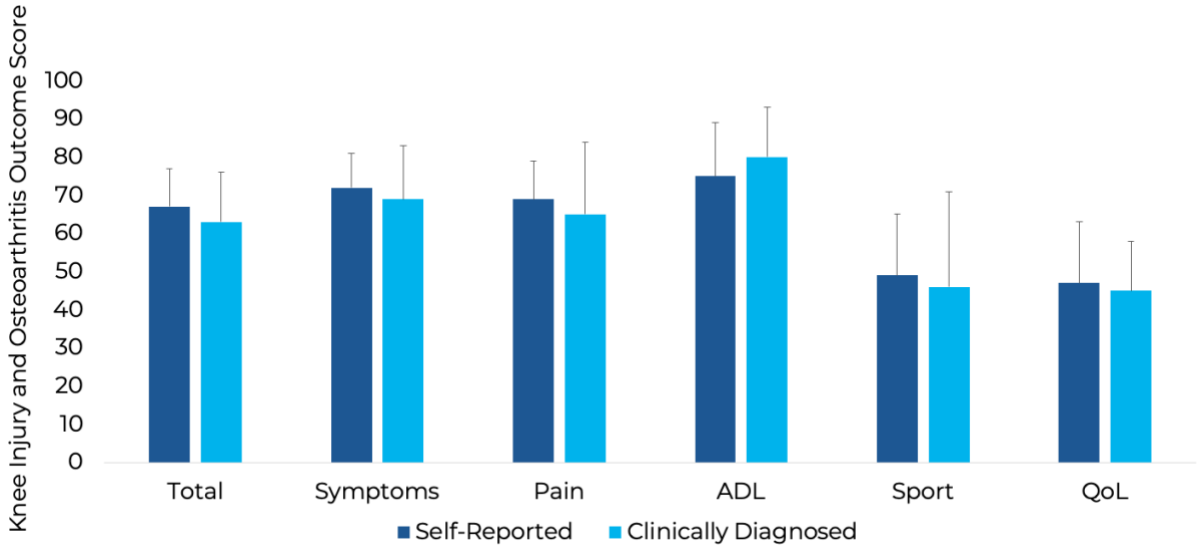


Figure 4-1: Means and standard deviations for total and subscale scores of the Knee Injury and Osteoarthritis Outcome Score for individuals with self-reported and clinically diagnosed knee OA. ADL = activities of daily living. QoL = quality of life. Asterisks (*) indicate significant between group differences ($p<0.05$).

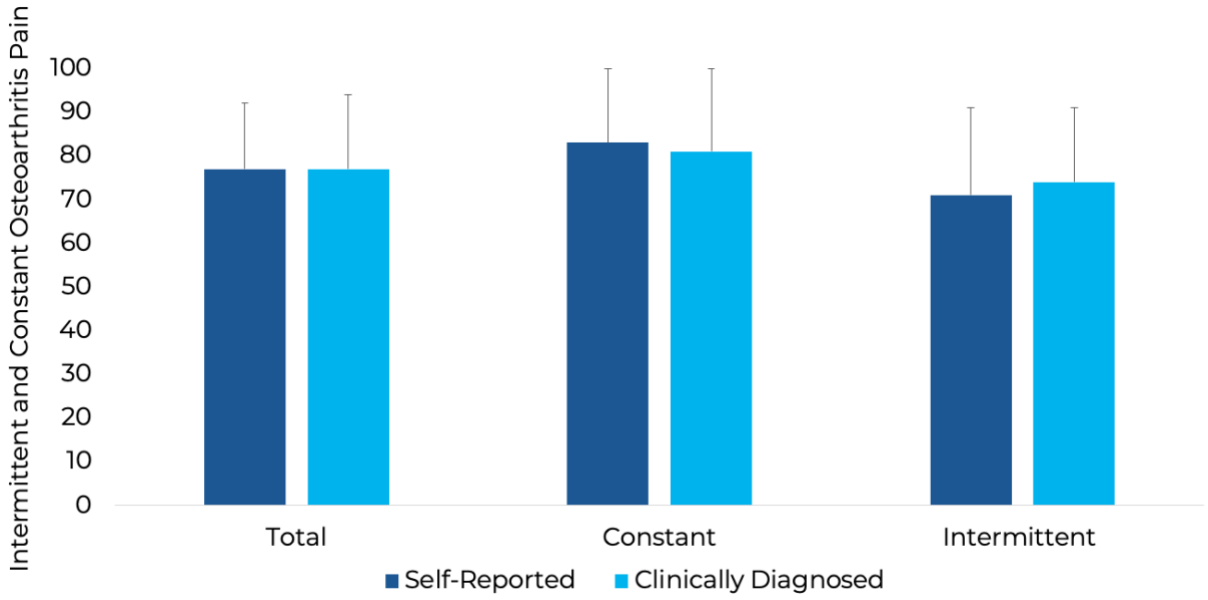


Figure 4-2: Means and standard deviations for total and subscale scores of the Intermittent and Constant Knee Osteoarthritis Pain Score for individuals with self-reported and clinically diagnosed knee OA. Asterisks (*) indicate significant between group differences ($p<0.05$).

4.3.2 Between Group Biomechanical Outcomes

The relative contributions of KAM, KFM and KRM to the TJM in the affected knee are presented in Figure 4-3 and Figure 4-4, and were not significantly different between knee OA groups ($p=0.136$-0.909). Sagittal plane knee angles were significantly different between groups ($p<0.001$). Individuals with self-reported knee OA had less knee flexion through loading response to mid-stance, and during swing, compared to individuals with clinically diagnosed knee OA (Figure 4-5). First peak KAM ($p=0.015$), KFM ($p<0.001$), and KAMR (Table 4-2) were also significantly less in individuals with self-reported knee OA. No significant differences in ICPF or SPROM were noted between groups (Table 4-2).

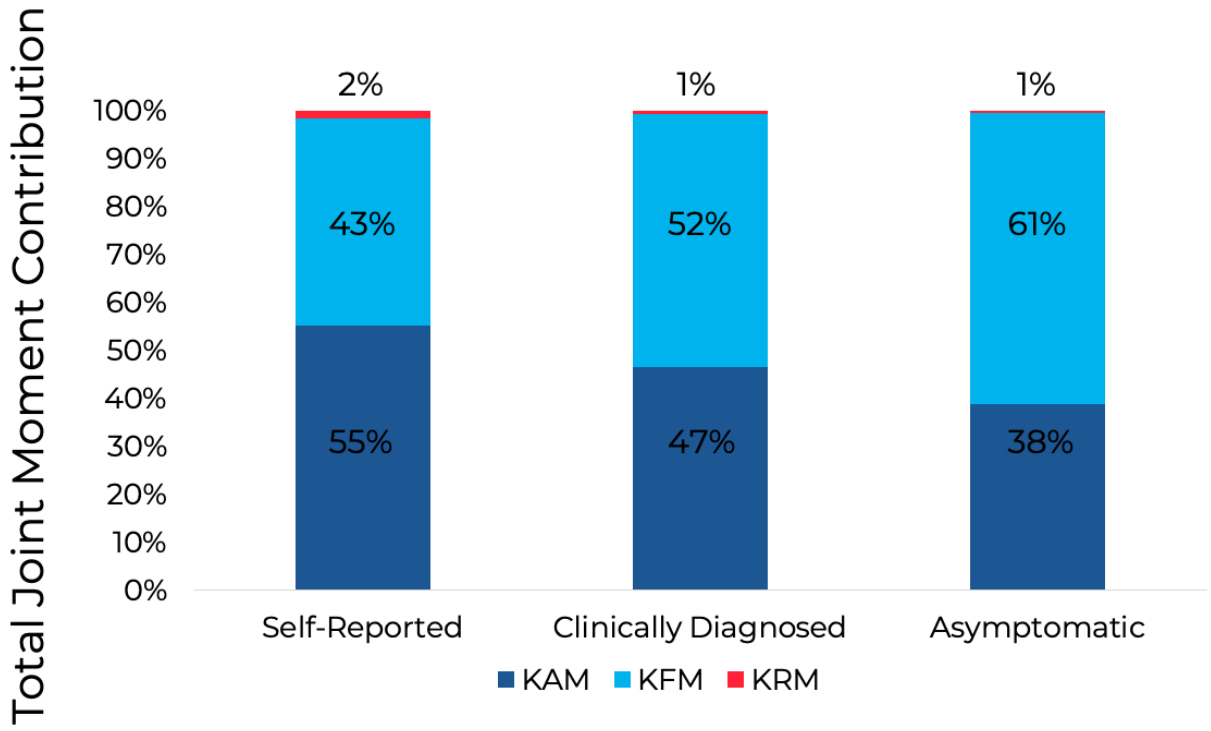


Figure 4-3: The relative external knee moment contributions to the total joint moment in the affected knee of individuals with self-reported or clinically diagnosed knee OA and asymptomatic individuals. KAM = first peak knee adduction moment. KFM = peak knee flexion moment. KRM = peak knee rotation moment.

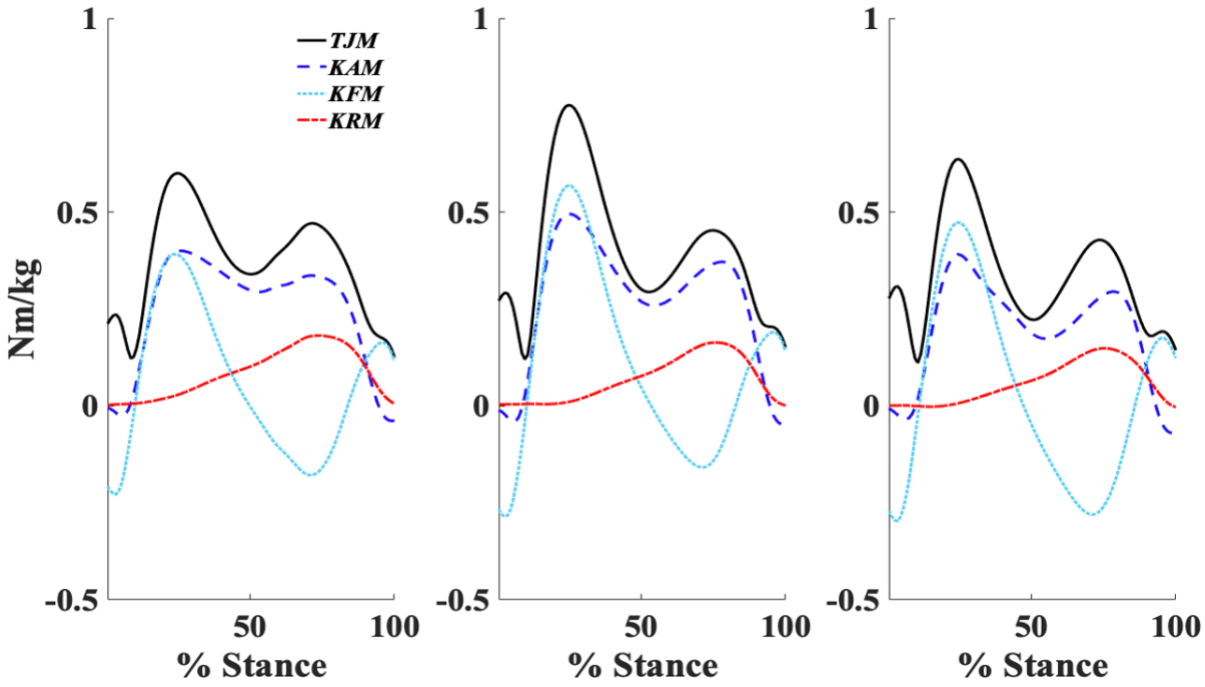


Figure 4-4: Ensemble averaged waveforms for the total joint moment and relative external knee moment contributions for the affected knee in individuals with self-reported knee OA (left), clinically diagnosed knee OA (middle) and asymptomatic (right) participants.

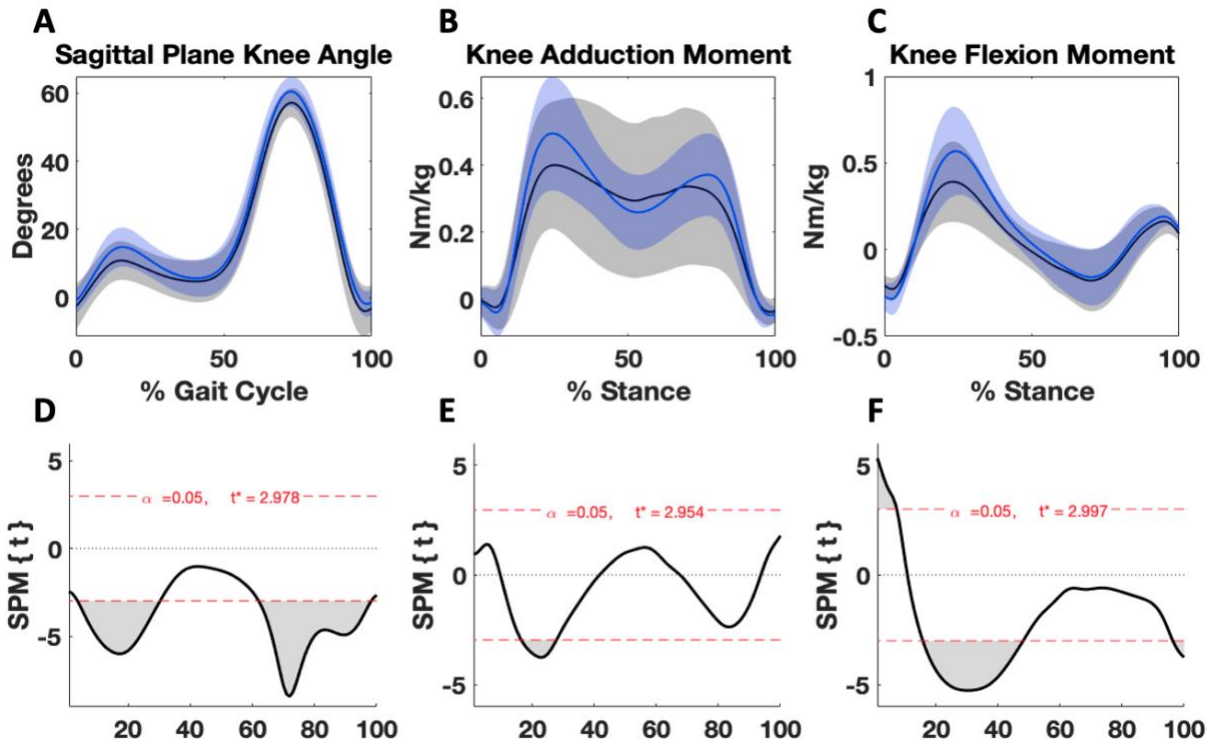


Figure 4-5: Affected knee ensemble average waveforms for sagittal plane knee angles (A), knee adduction (B) and knee flexion moments (C) in individuals with self-reported (black line) and clinically diagnosed (blue line) knee OA. Independent samples t-test statistical parametric maps indicate between group differences as a percentage of the gait cycle (D) or a percentage of the stance phase (E,F). Shaded areas in each statistical parametric map (D-F) represent regions of significant difference.

The relative contributions of KAM, KFM and KRM to the TJM in the contralateral knee are presented in Figure 4-6 and Figure 4-7, and were not significantly different between groups (p=0.259-0.914). Sagittal plane knee angles were significantly different between groups (p<0.001). Individuals with self-reported knee OA had less knee flexion through loading response to mid-stance, and during swing, compared to individuals with clinically diagnosed knee OA (Figure 4-8). First peak KAM (p<0.001) and KAMR (Table 4-2) were also significantly less in individuals with self-reported knee OA (Figure 4-8). No significant differences were noted for TJM, ICPF, SPROM, or KFM waveforms between groups (Table 4-2).

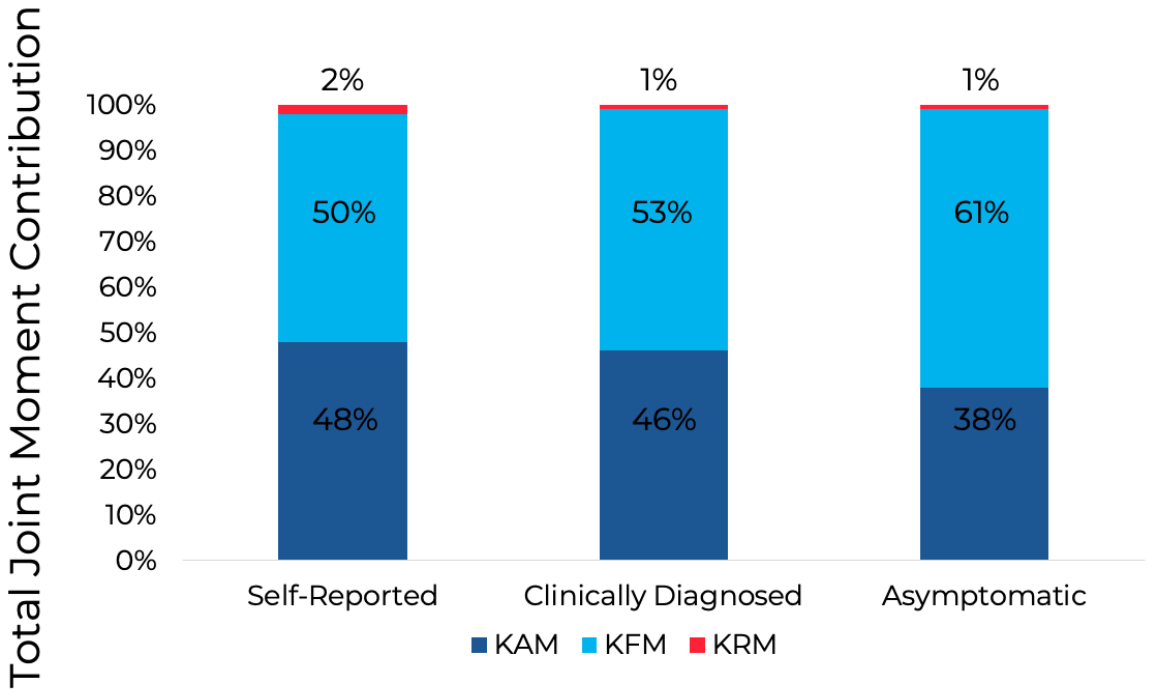


Figure 4-6: The relative external knee moment contributions to the total joint moment in the contralateral knee of individuals with self-reported or clinically diagnosed knee OA and asymptomatic individuals. KAM = first peak knee adduction moment. KFM = peak knee flexion moment. KRM = peak knee rotation moment.

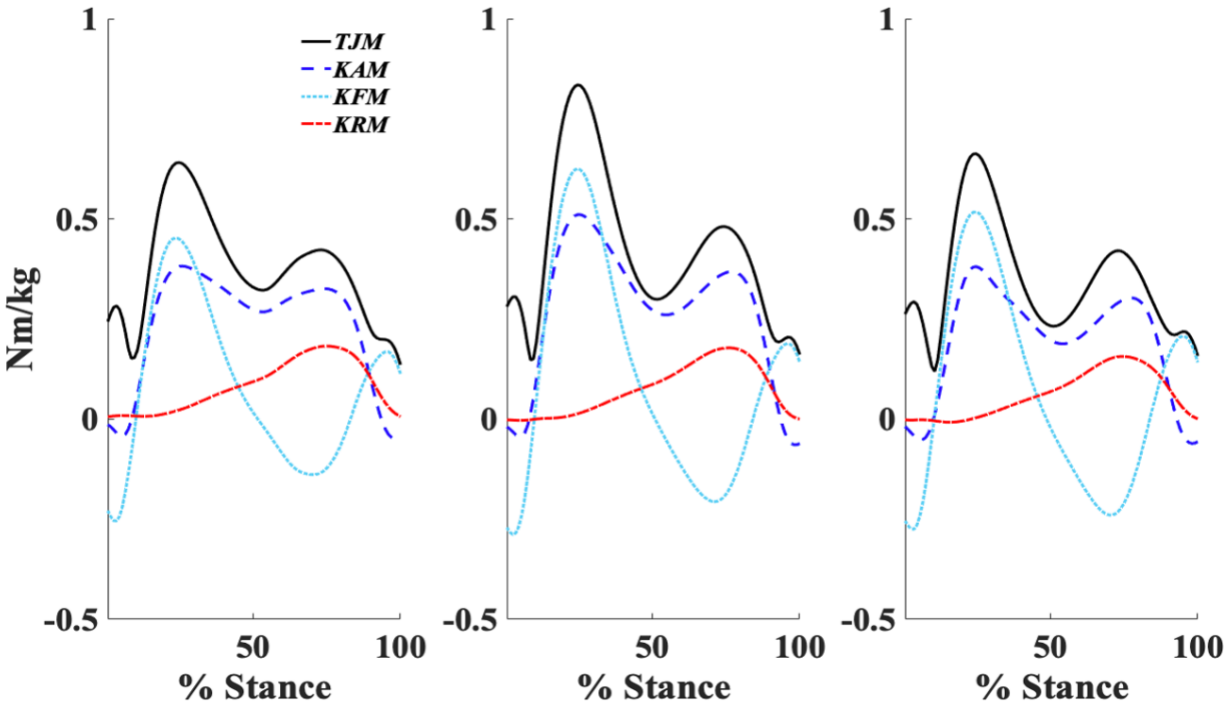


Figure 4-7: Ensemble averaged waveforms for the total joint moment and relative external knee moment contributions for the contralateral knee in individuals with self-reported knee OA (left) clinically diagnosed knee OA (middle) and asymptomatic (right) participants.

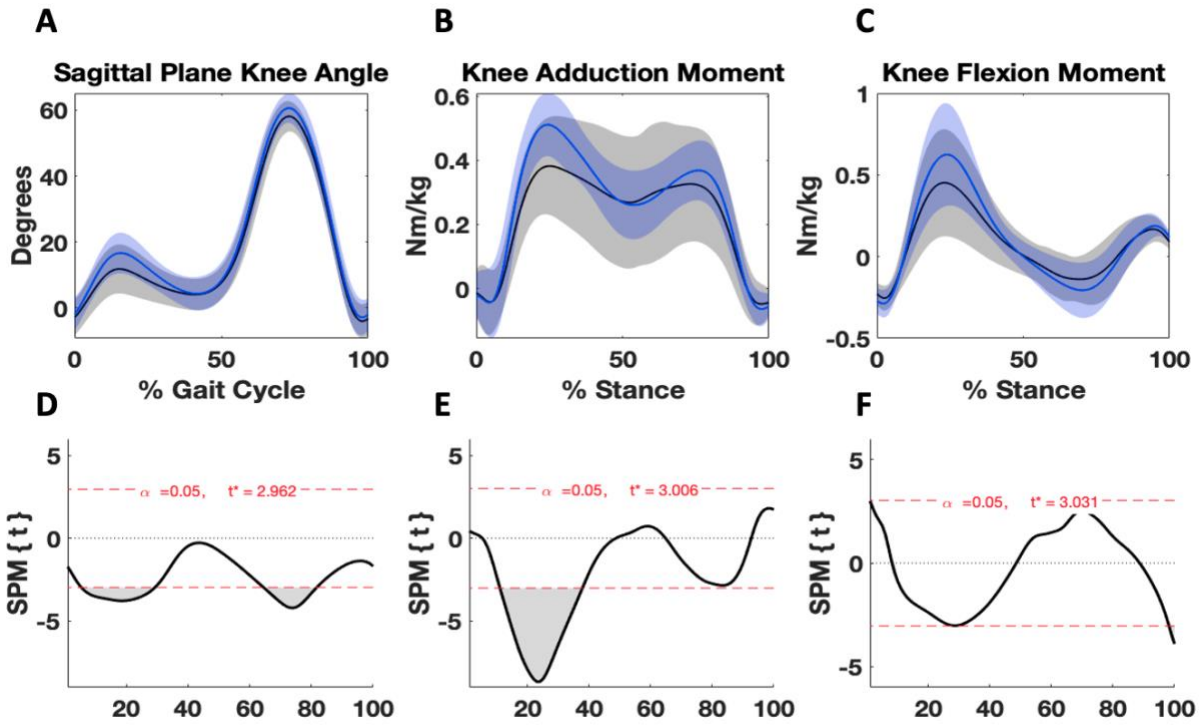


Figure 4-8: Contralateral knee ensemble average waveforms for sagittal plane knee angles (A), knee adduction (B) and knee flexion moments (C) in individuals with self-reported (black line) and clinically diagnosed (blue line) knee OA. Independent samples t-test statistical parametric maps indicate between group differences as a percentage of the gait cycle (D) or a percentage of the stance phase (E,F). Shaded areas in each statistical parametric map (D-F) represent regions of significant difference.

Table 4-2: Between group differences for biomechanical outcomes in individuals with self-reported or clinically diagnosed knee OA.

	Self-Reported (n=16)	Clinically diagnosed (n=16)	Mean Difference [95% CI]
Affected Knee			
TJM (Nm/kg)	0.62 (0.23)	0.73 (0.29)	-0.11 [-0.29: 0.06]
ICPF (°)	14.0 (5.00)	16.0 (4.00)	-2.00 [-5.43: 0.90]
KAMR (Nm/kg)	0.18 (0.08)	0.27 (0.13)	**-0.09 [-0.17: -0.01]**
SPROM (Nm/kg)	0.61 (0.25)	0.74 (0.33)	-0.12 [-0.81: 0.32]
Contralateral Knee			
TJM (Nm/kg)	0.65 (0.25)	0.78 (0.30)	-0.13 [-0.34: 0.05]
ICPF (°)	15.0 (5.00)	19.0 (5.00)	-4.00 [-7.18: 0.28]
KAMR (Nm/kg)	0.16 (0.08)	0.29 (0.08)	**-0.12 [-0.18: -0.06]**
SPROM (Nm/kg)	0.64 (0.21)	0.82 (0.35)	-0.19 [-0.43: 0.04]

Note: CI = confidence interval. TJM = first peak total joint moment. ICPF = initial contact to peak knee flexion range. KAMR = first peak knee adduction moment to midstance unloading range. SPROM = sagittal plane knee moment range. Mean differences are presented as self-reported minus clinically diagnosed, where a positive value indicates that self-reported is greater than clinically diagnosed, and a negative value indicates that clinically diagnosed is greater than self-reported. Bolded values indicate between-group differences for which the 95% CI does not cross zero.

4.3.3 Total Joint Moment Asymmetry

Absolute TJM symmetry was found to be 10.0% ± 6.8% for asymptomatic individuals. For a two-tailed distribution with an alpha level of 0.05, the critical t-value used to calculate the upper and lower limits of absolute TJM symmetry was 2.08. This critical t-value generates an expected limit of asymmetry of 14% within an asymptomatic population. Fifteen individuals with knee OA (n=7 self-reported knee OA and n=8 clinically diagnosed knee OA) were determined to have asymmetric knee loading (>14%) (Table 4-1). Absolute TJM symmetry was not found to be statistically different between individuals with self-reported knee OA and clinically diagnosed knee OA (mean difference: -8.40, 95% CI [-33.6,19.3], p=0.565). Further, the prevalence of TJM asymmetry (i.e., n=7 versus n=8) was not found to be significantly different between groups (p=0.852).

4.4 Discussion

This study describes patient-reported and biomechanical differences between individuals with self-reported and clinically diagnosed knee OA. Both groups displayed similar KOOS subscale scores to previously reported values for individuals with mild-to-moderate knee OA[40]; however, both groups reported better ICOAP scores compared to previous values for individuals with knee OA[151]. The lack of differences between KOOS and ICOAP subscales suggests that perceptions of disease effects on pain, function and QoL are similar between groups. However, individuals with self-reported and clinically diagnosed knee OA demonstrated significant differences in both affected and contralateral knee biomechanics. The current study presents novel information regarding patient-reported outcomes and gait biomechanics associated with contrasting diagnostic and recruitment methodologies.

Biomechanical differences between groups do suggest that individuals with self-reported knee OA may be more functionally severe compared to individuals with clinically diagnosed knee OA. The reductions in peak KAM, KAMR, sagittal plane knee angles, and KFM in the affected knees of individuals with self-reported versus clinically diagnosed knee OA show a trend consistent with severe versus moderate medial compartment knee OA[42]. Individuals with clinically diagnosed knee OA walked with increased affected knee peak KAM, which has been linked to radiographic knee OA progression in a recent meta-analysis[33]; however, they also walked with a greater KAMR indicating a more dynamic loading pattern. Previous research has suggested that increased peak KAM values accompanied with a more dynamic KAM, actually reduced the KAM impulse compared to a lower peak KAM and less dynamic KAM pattern[236], possibly indicating lower knee load

magnitudes throughout stance[237]. These findings suggest that employing a self-reported knee OA recruitment protocol, may lead to a sample of individuals displaying more severe affected knee biomechanics compared to individuals clinically diagnosed.

The contralateral knee in individuals with self-reported knee OA showed significantly less knee flexion angles at initial contact through loading response, first peak KAM, and KAMR compared to the contralateral knee in individuals with clinically diagnosed knee OA. Similar to the affected knee, although the contralateral knee in individuals with self-reported knee OA had a lower peak KAM, the reductions in KAMR indicate that overall loading per stride may be similar compared to individuals with clinically diagnosed knee OA[237]. There is potential that individuals with self-reported knee OA may walk with reduced SPROM in their contralateral knee, for example, mean differences and 95% CIs suggest less SPROM in individuals with self-reported knee OA; however, higher variability in individuals with clinically diagnosed knee OA may explain why no significant difference was found. Consistent with observations for the affected knee, individuals with self-reported knee OA walked with less dynamic frontal plane loading in their contralateral knee, a metric typically indicating more severe knee OA[42].

No differences were noted in the TJM between groups for either knee although the contributions of the KAM, KFM and KRM offer potential insight into the level of disease severity between groups. A natural progression study following individuals with mild-to-moderate knee OA over five-years has shown that, at baseline, percent contributions to the TJM for the KAM, KFM and KRM were 45%, 54% and 1% respectfully. At the five-year timepoint disease severity had worsened to moderate-to-severe knee OA and TJM contributions transitioned to 71%, 27% and 1%[190]. These findings propose that as knee OA

progresses, the frontal plane commands a larger portion of the TJM[190]. The TJM contributions in the affected knee of individuals with self-reported knee OA show a greater KAM contribution, potentially signifying worse disease severity compared to individuals with clinically diagnosed knee OA.

The incidence of TJM asymmetry was comparable across self-reported and clinically diagnosed groups, despite differences in biomechanical attributes. These findings indicate that approximately half of individuals with knee OA walk with asymmetrical knee loading, irrespective of self-reported versus clinically diagnosed categorization. Notably, the magnitudes of TJM asymmetry observed in this study among individuals with knee OA were marginally greater compared to previously reported figures for both unilateral and bilateral knee OA cohorts[63]. Previous research by Messier et al. (2016)[63] reported asymmetry magnitudes for peak KAM ranging from 34% to 37%, and for peak KFM ranging from 24% to 26% among individuals with unilateral and bilateral knee OA, respectively[63]. The TJM calculation amalgamates KAM, KFM, and KRM into a singular metric, encapsulating the collective asymmetry across these three-gait outcomes. This integration potentially explains why TJM asymmetry surpassed previously recorded values for KAM and KFM. Additional work is needed to better understand the best metric to define asymmetry in individuals with knee OA.

This work is the first study to our knowledge that quantifies clinical and biomechanical differences between individuals with self-reported and clinically diagnosed knee OA. However, the current study does have methodological limitations that should be acknowledged. Radiographic and symptomatic outcomes for the contralateral knee in individuals with clinically diagnosed knee OA are advised for future investigations that

employ knee biomechanics to establish the threshold for symmetry versus asymmetry. Education is a core treatment component recommended by many international OA management guidelines[19–21], and while individuals clinically diagnosed with knee OA would have the opportunity for education from their healthcare provider, community recruitment doesn't guarantee this opportunity. It would be recommended to include the Osteoarthritis Knowledge Scale (OAKS)[238] as a patient-reported outcome when engaging in recruitment, to better assess participant knowledge surround knee OA. A copy of the OAKS is provided in Appendix C. There are known differences in the rates of OA between males and females, and biological sex is known to influence walking mechanics for individuals with knee OA[239–242]; however, due to sample size constraints we were unable to assess sex differences in the current study.

4.5 Conclusion

Individuals with self-reported knee OA exhibited walking patterns with biomechanical characteristics indicative of more severe knee OA in both the affected and contralateral knees, compared to individuals with clinically diagnosed knee OA. Reduced sagittal plane knee flexion angles during gait, KAMR and SPROM have previously been linked to more severe knee OA[42,186]. Interestingly, these biomechanical characteristics were not accompanied by differences in patient-reported outcomes, or prevalence and magnitude of knee loading asymmetry. Although neither recruitment strategy is superior, these data support that employing a self-report recruitment criterion may yield individuals who walk with gait patterns more closely resembling severe knee OA[42]. The results indicate that approximately 50% of individuals with knee OA walk with symmetrical

versus asymmetrical knee loading, and future research should examine these individuals separately to gain a better understanding surrounding what may be driving these asymmetries.

CHAPTER 5: The Association of Inter-Limb Asymmetry with Patient-Reported Outcomes and Gait Biomechanics in Individuals with Knee Osteoarthritis

5.1 Introduction

Osteoarthritis (OA) affects more then 10% of Canadians, with estimates that 25% of individuals (>10M) will be affected over the next decade[4]. With no cure for OA, current management practices often focus on pharmacological pain relief on an unsustainable pathway to end-stage treatment using joint replacement surgery[19]. Recent evidence has suggested that up to 25% of individuals who undergo knee replacement surgery are diagnosed with knee OA in their contralateral limb within five years[48], which increases to 62% after nine years[49]. Authors have proposed that pain in the affected knee during walking may contribute to the onset of inter-limb asymmetries that overload the contralateral limb and possibly accelerate bilateral knee OA progression[29,198]. The results of Chapter 4 of this thesis suggested that approximately 50% of individuals with knee OA walk with inter-limb asymmetries; however, what might be driving these asymmetries isn't currently understood.

Knee OA is well associated with poor patient-reported outcomes[42,141] with further declines in pain, function and quality of life when bilateral disease is present[243,244]. Despite this knowledge, an existing evidence gap inhibits the clinical interpretation of gait asymmetry and its association with patient-reported outcomes in individuals with knee OA. Previous work has suggested a possible link between spatiotemporal asymmetries and an increased odds of contralateral total knee replacement (TKA)[199] such that every 1cm increase in step-length asymmetry (i.e., shorter step length on the contralateral limb)

increased the odds of contralateral TKA two-fold[199]. Further, research in anterior cruciate ligament injuries have demonstrated that individuals who walked with a lower peak vertical ground reaction force (vGRF) symmetry index (i.e., a lower peak vGRF in their injured versus uninjured limb) reported worse patient-reported outcomes (e.g, Knee Injury and Osteoarthritis Outcome Score (KOOS) pain, activities of daily living, sport and recreation and quality of life) 12-months post-surgery[245]. Conversely, individuals who walked with a higher peak vGRF symmetry index (i.e., a higher peak vGRF in their injured versus uninjured limb) increased the odds of reporting acceptable patient-reported outcomes 12-months post-surgery (defined as >85/100 on the KOOS subdomains)[245] 13-fold. Although these collective findings are limited, both in magnitude of evidence and the asymmetry outcomes assessed, they propose a potential link between inter-limb asymmetry during walking and patient-reported outcomes while underscoring that further research is needed to elucidate the implications of inter-limb asymmetry for individuals with knee OA.

Walking and physical activity are highlighted management strategies across clinical practice guidelines for individuals with knee OA[21,59,60]; however, increased pain during walking has been associated with asymmetrical lower limb movement patterns as a strategy to reduce joint symptoms[50,61,62]. Research has begun to examine inter-limb asymmetries during walking in individuals with knee OA[50,51,63], grouping individuals on the presence of either unilateral or bilateral symptoms (knee pain >3/10 on a visual analog scale) and radiographic evidence (Kellgren-Lawrence Grade ≥2)[50,51,63]. However, previous research examining whether individuals with unilateral or bilateral disease walk with inter-limb asymmetries have produced conflicting results[50,51,63], with mixed reports as to whether higher prevalence of asymmetry exits in individuals with bilateral symptomatic knee OA[50]

or unilateral symptomatic knee OA[51]. In contrast, Messier et al., (2016)[63] found that both individuals with unilateral and bilateral knee OA walked with similar magnitudes of inter-limb asymmetry. Several methodological inconsistencies between studies could potentially explain the discrepancy in findings, including walking at a fixed speed[50] versus self-selected[51,63], defining symmetry as a difference between affected and contralateral knees[50,51] versus using a symmetry index[63], and assessing only kinematic[50] versus kinematic and kinetic outcomes[51,63].

Symmetrical walking patterns are a conjectured representation of a physiologically healthy and pain free gait[43]; however, minimal-to-no supporting evidence exists in individuals with knee OA[50,51,63]. Despite the even distribution of individuals with symmetrical versus asymmetrical knee loading noted in Chapter 4, there is currently a poor understanding surrounding what may be driving these inter-limb asymmetries. Further, the clinical implications of symmetrical versus asymmetrical gait patterns within a knee OA population require further investigation to better interpret findings. Therefore, the specific objectives of this study were to: determine whether patient-reported outcomes reflecting pain, function and quality of life, differ between individuals with knee OA who were dichotomized as having either symmetrical or asymmetrical knee loading; and examine sagittal and frontal plane biomechanical differences in the affected and contralateral knees between individuals with knee OA who were dichotomized as having either symmetrical or asymmetrical knee loading.

5.2 Methodology

5.2.1 Participant Recruitment

Individuals with knee OA were recruited to participate from the community and through an orthopaedic clinic. Individuals from the community were recruited based on the inclusion criteria: 1) >40 years of age, 2) activity related knee pain on most days in the past month, 3) knee pain experienced for at least the past three months, 4) affected knee pain ranging between 40 to 90 on a 100-point numeric rating scale (0 = "no pain", 100 = "worst pain imaginable"), and 5) morning stiffness lasting <30-minutes[12–17]. Individuals diagnosed by an orthopaedic surgeon were recruited using the inclusion criteria: 1) >40 years of age, and 2) symptomatic and moderate knee OA based on the American College of Rheumatology criteria[18]. The exclusion criteria applied to both groups were age <40, bilateral symptoms, bilateral activity related pain, inflammatory arthritis in either limb, previous lower limb surgery, lower limb injury within the past year, or any cardiovascular, muscular, or neurological conditions that would affect their ability to walk or ambulate stairs. The study protocol was approved by the institution's research ethics board and all participants provided informed consent prior to testing.

5.2.2 Data Collection

Participants completed the KOOS[145] and Intermittent and Constant knee Osteoarthritis Pain (ICOAP)[146] questionnaires, and baseline affected knee pain using an 11-point numeric pain rating scale (NPRS) (0 = "no pain at all", 10 = "worst pain imaginable") prior to testing. Aligning with the explicit inclusion and exclusion study criteria (i.e., participants could not report experiences of any discomfort or activity related

knee pain (NPRS=0) in their contralateral knee), NPRS was only assessed in the affected knee of individuals with knee OA. Participants were then asked to change into form-fitting shorts, a t-shirt, and wear their regular walking/running shoes. Anthropometrics including height, weight, hip, waist, and bilateral thigh and shank circumferences were measured. Rigid plastic plates containing clusters of four retroreflective markers were placed over the pelvis, and bilaterally over the lateral femur, lateral shank and feet, and secured using Velcro straps. Individual retroreflective markers were placed over the seventh cervical vertebrae and bilaterally over the acromion, lateral epicondyle. ulnar styloid processes, greater trochanters, iliac crests, anterior superior iliac spine, medial and lateral tibial and femoral epicondyles, lateral and medial malleoli, first, second and fifth metatarsal heads and posterior heels (Figure 3-1). Prior to the walking protocol, markers located at the medial femoral and tibial epicondyles, medial malleoli, the first and fifth metatarsal heads, lateral tibial epicondyles, anterior superior iliac spine, iliac crests and greater trochanters were removed.

Participants completed a minimum of five walking trials along a six-meter walkway at a comfortable, self-selected walking speed. Three-dimensional kinematic and ground reaction force data were captured bilaterally using a 10-camera passive motion capture system (Cortex, version 8.0, Motion Analysis Corporation, California, U.S.A) and synchronized with two floor embedded force platforms (Advances Medical Technologies Inc, Watertown, MA). All kinematic data were collected at 100Hz, and kinetic data collected at 1200Hz. Immediately after the walking trials, participants were again asked to rate the pain in their affected knee using an 11-point NPRS. The remaining retroreflective markers were then removed.

Participants completed knee flexion and extension maximum voluntary isometric strength using a Biodex isokinetic dynamometer (Advantage BX Software 5.2, Shirley, NY, U.S.A.). Maximum knee flexion and extension strength were collected with the participant seated, the hip flexed to 90^{o} and the knee flexed to 45^{o}[218]. Velcro straps were used to stabilize the participant's leg for each strength test. A warm-up, practice contraction was performed to familiarize the participant with the test protocol. Contractions were completed twice for three-seconds, with a 60-second break between contractions. Verbal encouragement was given to each participant to maximize effort and contraction consistency[219].

5.2.3 Data Processing and Analysis

Total KOOS and ICOAP scores along with their subscales were normalized to a 0-100-point scale (0 = "worse symptoms", 100 = "better symptoms"). Three-dimensional marker data were filtered with a 6Hz lowpass fourth-order recursive Butterworth filter and three-dimensional ground reaction forces and moments were initially filtered with a 30Hz lowpass fourth-order, recursive Butterworth filter[218] using Visual 3D (v2023.04.2, C-motion Inc., Germantown, MD, USA). Knee angles were calculated bilaterally using an XYZ (sagittal, frontal, transverse) rotation sequence, described as the distal segment moving about a fixed proximal segment[221]. Flexion, adduction and internal rotation represent positive angles. Net external joint moments were calculated using an inverse dynamics model[155] in Visual 3D (v2023.04.2, C-motion Inc., Germantown, MD, USA). External knee moments, including the knee adduction moment (KAM), knee flexion moment (KFM), and knee rotation moment (KRM) were filtered with a 10Hz lowpass

fourth-order recursive Butterworth filter, and normalized to body mass (Nm/kg), and time normalized to stance[218]. Maximum strength was calculated using a 500ms moving average window to determine maximum torque generated during the three-second MVIC trial[246]. The highest torque value calculated from either of the two MVIC trials was recorded as the maximum flexion or extension strength, and amplitude normalized to body mass (Nm/kg).

Kinematic data was time normalized to 100% of the gait cycle (initial contact to ipsilateral initial contact) and kinetic data were time normalized to stance (initial contact to pre-swing), using a kinetic-kinematic initial contact and pre-swing detection method[222]. Initial contact was identified using a 20N threshold for the vertical component of the GRF[222], and ipsilateral initial contact was calculated as the maximal anterior displacement between the origin of the pelvis markers and heel marker[222]. Pre-swing was identified when the vertical component of the GRF fell below the 20N threshold[222]. Kinematic, and kinetic data were extracted bilaterally for both groups. Kinematic data for the sagittal, frontal, and transverse planes were collected; however, only the sagittal plane was analyzed. The total joint moment (TJM)[190] was calculated bilaterally for each participant using the formula: $TJM = \sqrt{KFM^2 + KAM^2 + KRM^2}$. Absolute TJM symmetry indices were calculated using the formula: $((X_A - X_C)/(0.5(X_A + X_C)) * 100))$[201], in which X_A represents the first peak TJM in the affected knee and Xc represents first peak TJM in the contralateral knee. A symmetry value of zero represents perfect symmetry between knees, and higher values represent greater differences between knees.

5.2.4 Statistical Analysis

Participants were dichotomized based on the absolute TJM symmetry status using the threshold (14%) calculated in Chapter 4 (4.3.3 Total Joint Moment Asymmetry). Independent t-tests calculated between group differences for continuous demographics, and patient-reported outcomes and Chi-square was used for categorical variables. Mean difference and 95% bootstrapped confidence intervals were calculated as symmetrical minus asymmetrical, where a positive value indicates that symmetrical is greater than asymmetrical, and a negative value indicates that asymmetrical is greater than symmetrical. If differences were found in KOOS or ICOAP subscales, individual questions were analyzed descriptively using the mode of the responses between groups. Independent samples t-tests were used to assess for between group differences in knee extension and flexion strength. Statistical parametric mapping independent t-tests (SPM{t}) were used to detect group differences across the gait cycle or stance phase for sagittal plane knee angles, KAM and KFM waveforms in Matlab (Mathworks Inc., Massachusetts, USA, version 2022a). Random field theory calculated the critical T-statistic, and the null hypothesis was rejected if the computed t-value for the waveforms exceeded this value[226]. Only differences identified by SPM in joint moments between 10-90% of stance were interpreted to align with most common kinetic metrics reported for individuals with knee OA[33,37,40,42,51,63]. All five walking trials were used in the final SPM{t} analyses to include the stride-to-stride variability for each group (95 gait cycles per group = 190 total cycles). Due to the inability of SPM to evaluate ranges, between group differences in the TJM, knee flexion angle range from initial contact to peak stance flexion (ICPF), the first peak knee adduction moment to midstance unloading range (KAMR), and the sagittal plane knee moment range (SPROM)

were analyzed and interpreted using mean differences and 95% bootstrapped confidence intervals in SPSS (Version 28.0, IBM Corp., Armonk, NY, USA). The calculation of these outcomes is described in Section 3.3. All statistical analyses were interpreted using an alpha level of 0.05 to determine statistical significance. Normality and equal variance were assessed using the Kolmogorov-Smirnov and Levene's tests.

5.3 Results

Forty-three individuals with knee OA were recruited and dichotomized into symmetrical (n=19) and asymmetrical (n=24) knee loading. Table 5-1 describes demographic, and muscle strength outcomes between groups. Individuals with symmetrical, compared to asymmetrical, knee loading had a significantly ($p=0.036$) higher BMI (Table 5-1). Individuals with symmetrical knee loading also had significantly lower TJM asymmetry compared to individuals with asymmetrical knee loading ($p<0.001$) (Table 5-1). No differences were noted for age ($p=0.404$), distribution of males and females $p=0.864$), gait speed ($p=0.065$), and knee flexion ($p=0.207$-0.262) or extension ($p=0.399$-0.352) strength between groups (Table 5-1).

Table 5-1: Participant demographics and clinical characteristics for individuals with symmetrical or asymmetrical knee loading (n=43)

	Symmetric (n=19)	Asymmetric (n=24)
Age	58 ± 9	60 ± 10
Sex. no. of females (%)	9 (47)	12 (50)
Clinically Diagnosed. no. (%)	8(42)	8 (33)
BMI, kg/m^2	**31.1 ± 6.1**	**26.6 ± 7.0**
Gait Speed, m/s	1.21 ± 0.15	1.30 ± 0.19
Affected knee NPRS before walk (0-10)	2.06 ± 1.96	1.45 ± 1.43
Affected knee NPRS after walk (0-10)	1.00 ± 1.59	0.75 ± 1.22
TJM asymmetry (%)	**8.19 ± 3.43**	**48.1 ±26.9**
Affected knee strength (Nm/kg)		
Knee flexion	0.73 ± 0.28	0.81 ± 0.31
Knee extension	1.21 ± 0.44	1.31 ± 0.27
Contralateral knee strength (Nm/kg)		
Knee flexion	0.77 ± 0.23	0.82 ± 0.27
Knee extension	1.32 ± 0.49	1.44 ± 0.35

Note: Values are listed as mean and standard deviation unless otherwise indicated. KLG = Kellgren Lawrence Grade. NPRS = numeric pain rating scale. Bolded values indicate between-group differences ($p<0.05$).

5.3.1 Patient-Reported Outcomes

Individuals with symmetrical knee loading reported significantly worse KOOS activities of daily living (KOOS-ADL) compared to individuals with asymmetrical knee loading (mean difference: -9.72, 95% CI [-18.5,-1.00], p=0.041) (Figure 5-1). Descriptive analyses revealed that most individuals with symmetrical knee loading reported more difficulty in questions 2 (ascending stairs), 3 (rising from sitting), 5 (picking up an object), 8 (shopping), 9 (putting on socks), 11 (taking off socks), 13 (getting out of the bath), 15 (getting off the toilet) and 16 (heavy domestic duties) (Figure 5-2). No significant differences were noted for either KOOS-Total (mean difference: -5.56, 95% CI [-13.8,2.56], p=0.204), KOOS-Symptoms (mean difference: -5.16, 95% CI [-13.9,2.85], p=0.210), KOOS-Pain (mean difference: -2.78, 95% CI [-12.7,7.15], p=0.572), KOOS-Sport (mean difference: -8.07, 95% CI [-22.1,4.52], p=0.258), KOOS-QoL (mean

difference: 0.19, 95% CI [-9.57,9.32], p=0.964), ICOAP-Total (mean difference: -7.35, 95% CI [-16.9,2.70], p=0.152), ICOAP-Constant (mean difference: -6.11, 95% CI [-16.2,4.74], p=0.164) or ICOAP-Intermittent (mean difference: -8.66, 95% CI [-18.8,2.54], p=0.127) between groups (Figure 5-1 & Figure 5-3). Participant individual responses for all non-significant KOOS and ICOAP subscales are provided in Appendix B.

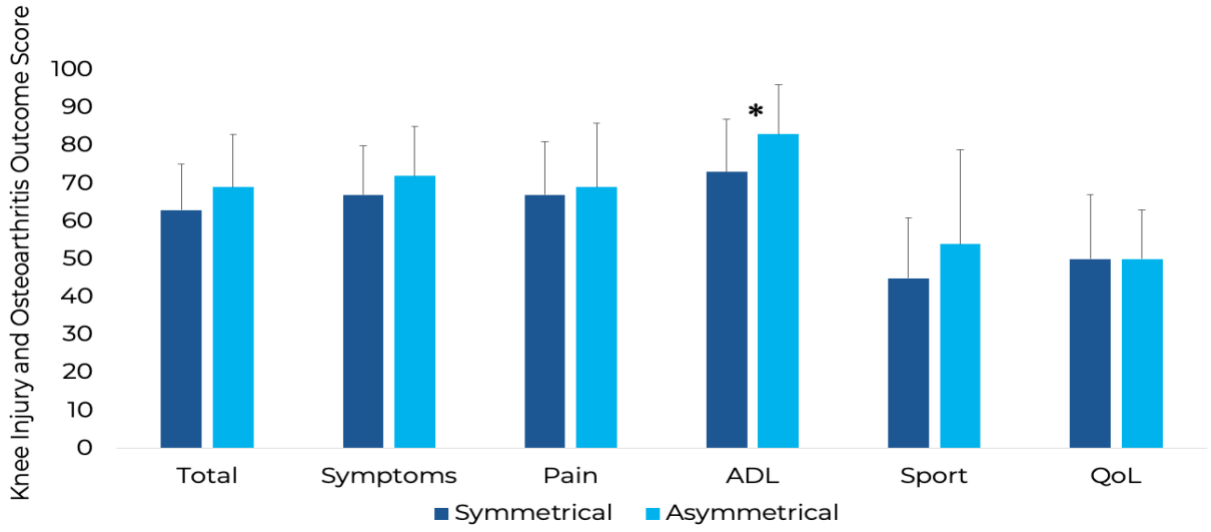


Figure 5-1: Means and standard deviations for total and subscale scores of the Knee Injury and Osteoarthritis Outcome Score for individuals with knee OA dichotomized as having symmetrical versus asymmetrical knee loading. ADL = activities of daily living. QoL = quality of life. Asterisks (*) indicate significant between group differences ($p<0.05$).

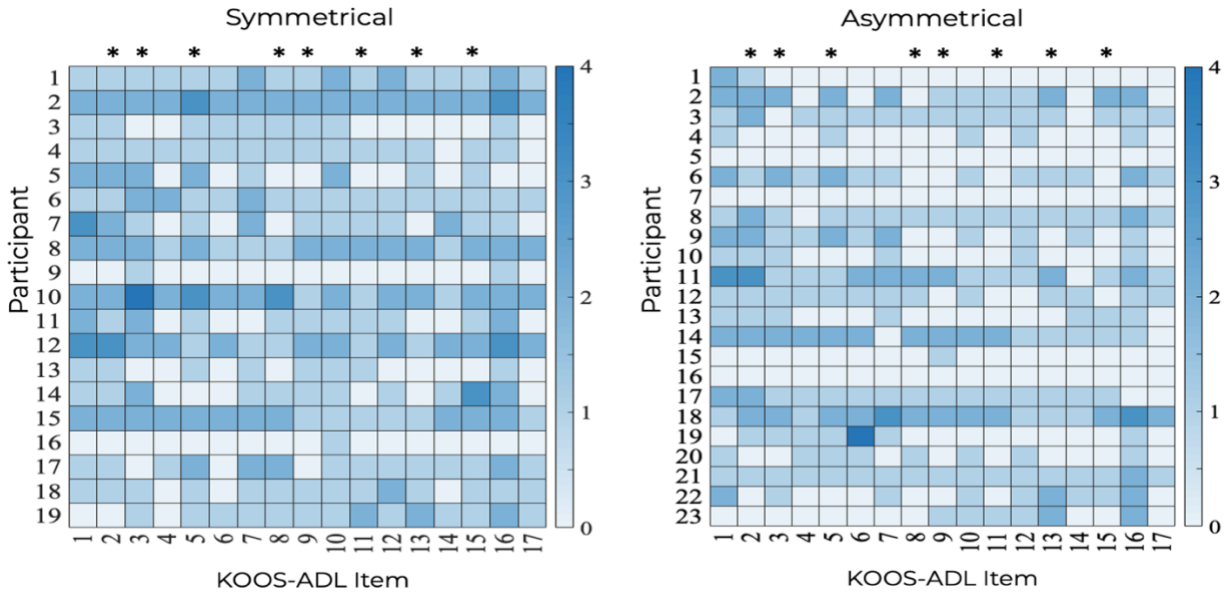


Figure 5-2: Heatmaps depicting the distribution of Likert scale responses for the Knee injury and Osteoarthritis Outcome Score (KOOS) - Activities of Daily Living (ADL) sub-scale. The heatmap displays the responses for each item within the KOOS-ADL sub-scale across all respondents. Color intensity represents the degree of difficulty, with darker shades indicating higher scores or worse difficulty. The left subplot shows responses from individuals with symmetrical knee loading, while the right subplot displays responses from individuals with asymmetrical knee loading. Each row represents a respondent, and each column represents an item within the KOOS-ADL sub-scale. Asterisks (*) indicate differences in the mode between groups.

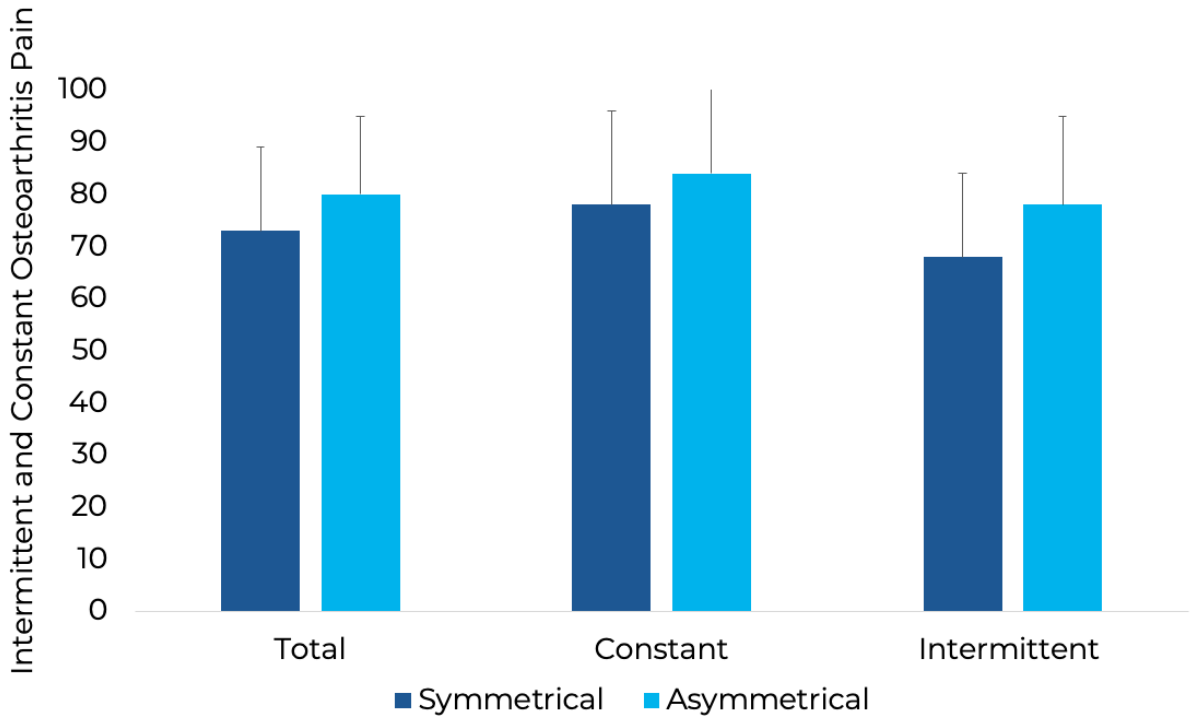


Figure 5-3: Means and standard deviations for total and subscale scores of the Intermittent and Constant Knee Osteoarthritis Pain Score for individuals with knee OA dichotomized as having symmetrical versus asymmetrical knee loading. Asterisks (*) indicate significant between group differences ($p<0.05$).

5.3.2 Between Group Biomechanical Outcomes

The relative contributions of the KAM, KFM and KRM to the TJM in the affected knee are presented in Figure 5-4 and Figure 5-5, and showed no differences between groups ($p=0.569$-0.922). SPM{t} analyses showed no differences between groups across sagittal plane knee angles ($p=0.247$) or KAM waveforms ($p=0.072$). Individuals with symmetrical knee loading walked with less knee extension moment (KEM) during late stance ($p=0.031$) (Figure 5-6), and a lower KAMR compared to individuals with asymmetric knee loading (Table 5-2). No significant differences in TJM, ICPF or SPROM were found between groups (Table 5-2).

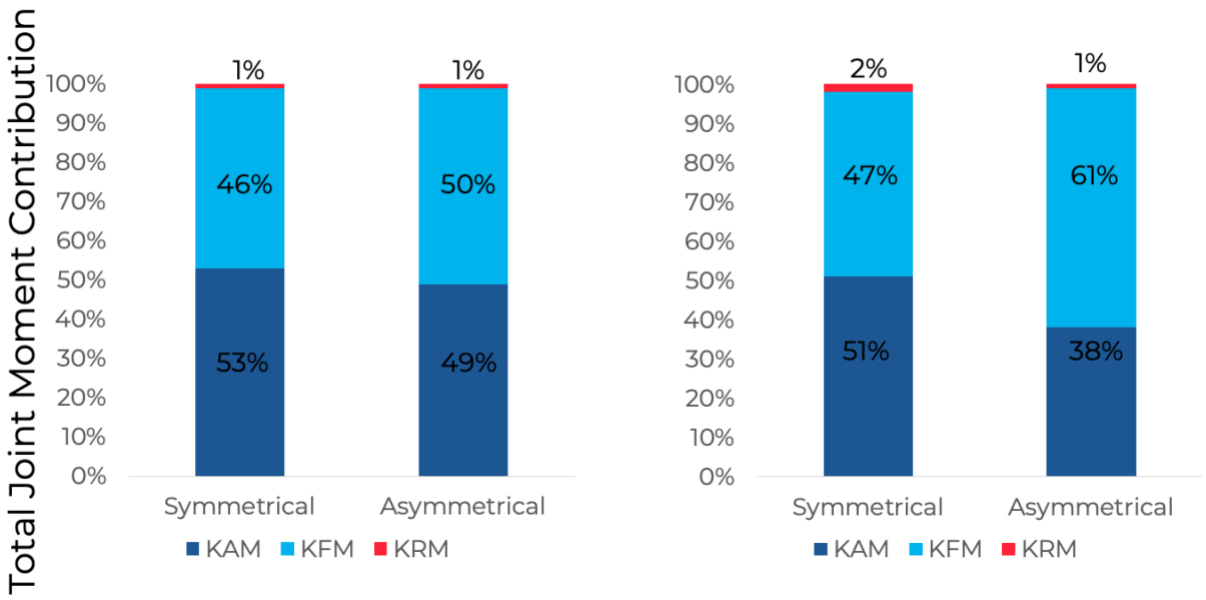


Figure 5-4: The relative external knee moment contributions to the total joint moment in the affected knee (left) and contralateral knee (right) of individuals with knee OA dichotomized with symmetrical versus asymmetrical knee loading. KAM = first peak knee adduction moment. KFM = peak knee flexion moment. KRM = peak knee rotation moment.

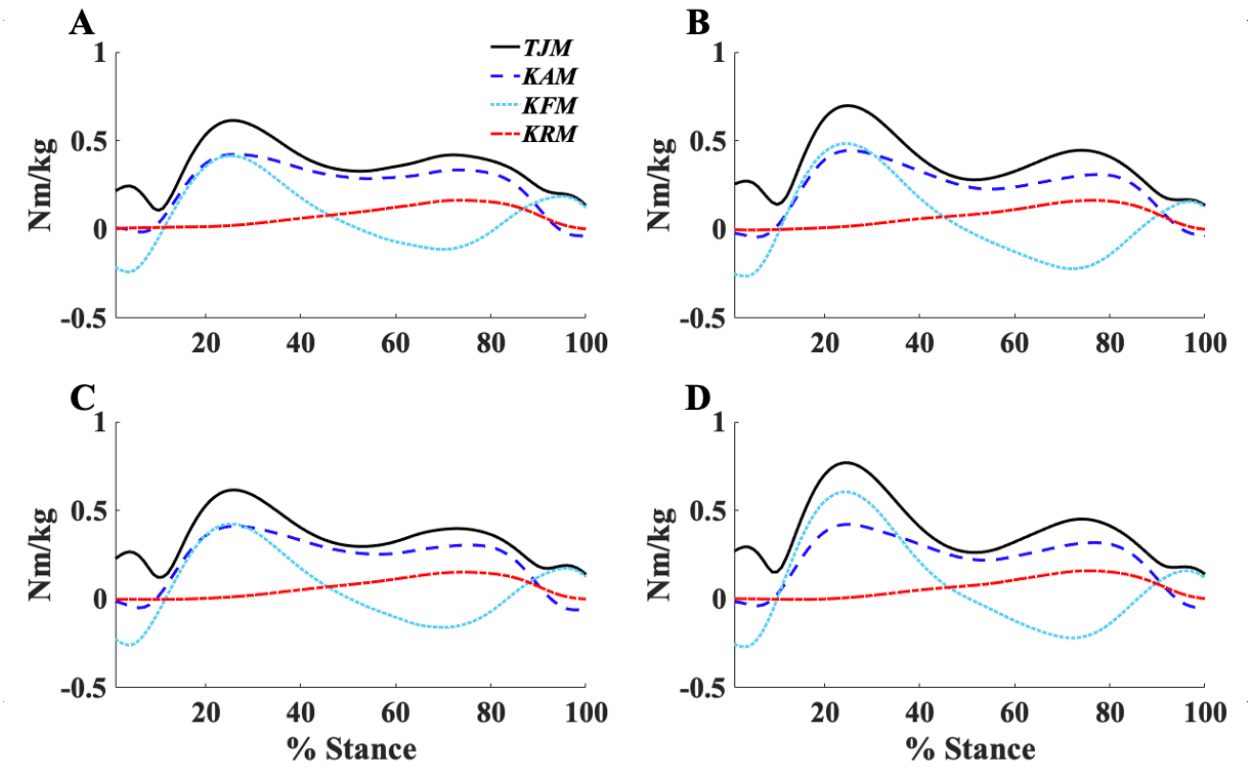


Figure 5-5: Ensemble averaged waveforms for the total joint moment and relative external knee moment contributions for the affected (A & C) and contralateral (B & D) knees for individuals with symmetrical (top) and asymmetrical (bottom) knee loading.

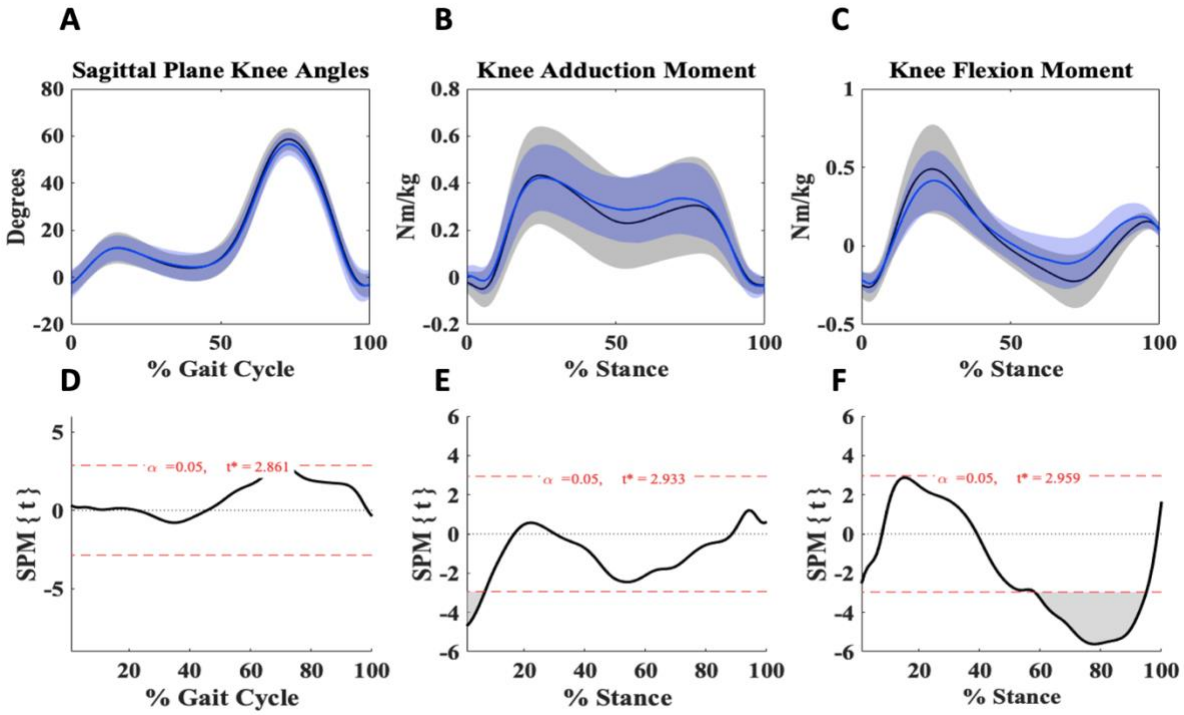


Figure 5-6: Affected knee ensemble average waveforms for sagittal plane knee angles (A), knee adduction (B) and knee flexion moments (C) in individuals with symmetrical (blue line) and asymmetrical (black line) knee loading. Independent samples t-test statistical parametric maps indicate between group differences as a percentage of the gait cycle (D) or a percentage of the stance phase (E,F). Shaded areas in each statistical parametric map (D-F) represent regions of significant difference.

The relative contributions of KAM, KFM and KRM to the TJM in the contralateral knee are presented in Figure 5-4 and Figure 5-5, and showed no differences between groups (p=0.141-0.379). SPM{t} analyses indicated that individuals with symmetrical knee loading walked with lower knee flexion angles during loading response (p=0.011) and swing (p=0.003), less midstance KAM (p=0.011) and lower peak KFM (p<0.001) during loading response compared to individuals with asymmetrical knee loading (Figure 5-7). Individuals with symmetrical knee loading also walked with less TJM, ICPF, KAMR, and SPROM in their contralateral knee compared to individuals with asymmetrical knee loading (Table 5-2).

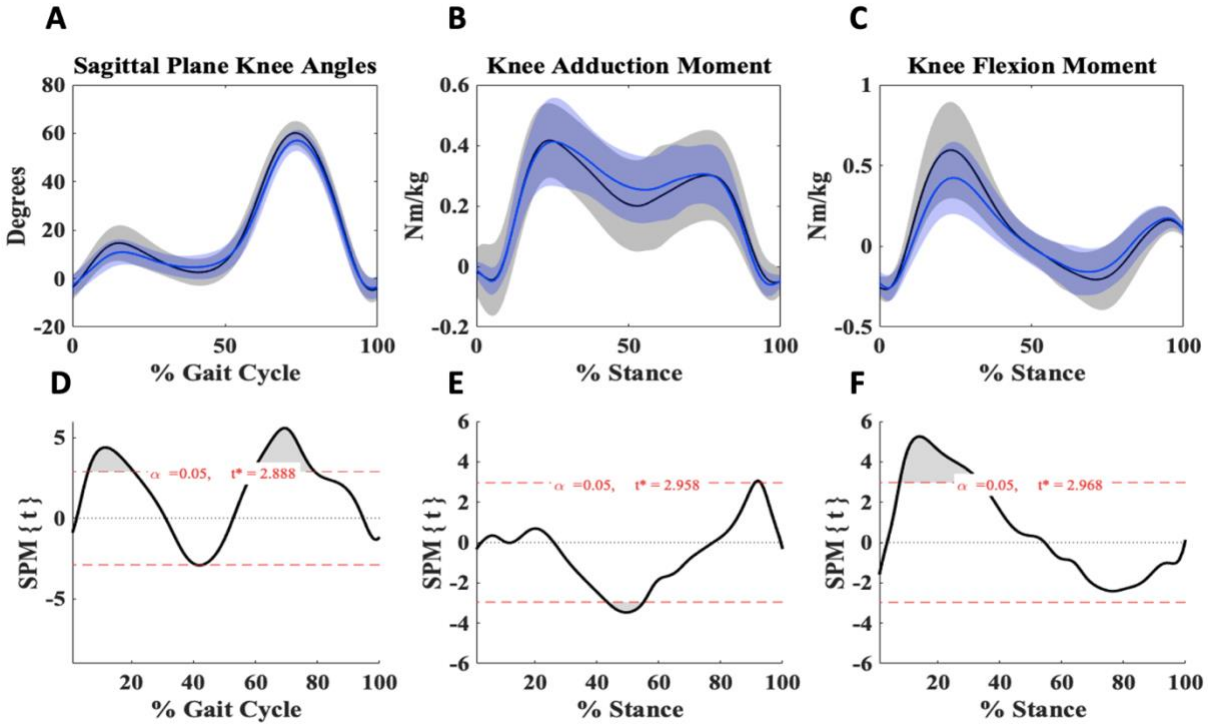


Figure 5-7: Contralateral knee ensemble average waveforms for sagittal plane knee angles (A), knee adduction (B) and knee flexion moments (C) in individuals with symmetrical (blue line) and asymmetrical (black line) knee loading. Independent samples t-test statistical parametric maps indicate between group differences as a percentage of the gait cycle (D) or a percentage of the stance phase (E,F). Shaded areas in each statistical parametric map (D-F) represent regions of significant difference.

Table 5-2: Between group differences for biomechanical outcomes in individuals with knee OA and symmetrical or asymmetrical knee loading.

	Symmetrical (n=19)	Asymmetrical (n=24)	Mean Difference [95% CI]
Affected Knee			
TJM (Nm/kg)	0.62 (0.17)	0.72 (0.25)	-0.10 [-0.22: 0.02]
ICPF (°)	14.0 (4.00)	15.0 (5.00)	-1.00 [-3.38: 1.59]
KAMR (Nm/kg)	0.18 (0.08)	0.26 (0.13)	**-0.08 [-0.15: -0.02]**
SPROM (Nm/kg)	0.56 (0.21)	0.74 (0.29)	-0.18 [-0.34: 0.03]
Contralateral Knee			
TJM (Nm/kg)	0.62 (0.19)	0.79 (0.25)	**-0.17 [-0.30: -0.04]**
ICPF (°)	15.0 (4.00)	19.0 (5.00)	**-4.00 [-5.66: -0.35]**
KAMR (Nm/kg)	0.18 (0.08)	0.25 (0.11)	**-0.07 [-0.12: -0.01]**
SPROM (Nm/kg)	0.61 (0.23)	0.86 (0.33)	**-0.25 [-0.42: -0.10]**

Note: CI = confidence interval. TJM = first peak total joint moment. ICPF = initial contact to peak knee flexion range. KAMR = first peak knee adduction moment to midstance unloading range. SPROM = sagittal plane knee moment range. Mean differences are presented as symmetrical minus asymmetrical, where a positive value indicates that symmetrical is greater than asymmetrical, and a negative value indicates that asymmetrical is greater than symmetrical. Bolded values indicate between-group differences for which the 95% CI does not cross zero.

5.4 Discussion

To our knowledge, this is the first study to comprehensively examine patient-reported and biomechanical outcomes in individuals with symmetrical and asymmetrical knee loading. Results indicate that individuals with symmetrical knee loading have significantly higher BMI values and significantly worse KOOS-ADL scores compared to individuals with asymmetrical knee loading. Although knee biomechanical outcomes were varied between groups in the affected knee and contralateral knee, separately, contralateral knee mechanics in individuals with asymmetrical knee loading more closely resembled asymptomatic individuals (Figure 4-3). These novel findings suggest that the collective interpretation of patient-reported and knee biomechanical outcomes between individuals with symmetrical versus asymmetrical knee loading do not support prior assumptions that

inter-limb symmetry resembles a physiologically healthy gait, when quantified by knee mechanics for individuals with knee OA.

The relative external knee moment contributions to the TJM in the affected knee across both groups (Figure 5-4) are consistent with previous external knee moment distributions reported for individuals with mild-to-moderate knee OA[190], suggesting the affected knees in both groups display gait characteristics consistent for knee OA. However, less KAMR and KEM magnitudes in the affected knee during mid-to-late stance in individuals with symmetrical loading were notable biomechanical differences previously linked to more severe knee OA[42]. Less medial compartment offloading[233] (KAMR) is associated with increases in KAM impulse and likely contributing to higher knee load magnitudes throughout stance[237]. Gait speed differences between groups are close to previously reported minimal clinically important differences[247], suggesting that although not statistically significant, may influence loading parameters. Gait speed has been shown to influence both KAMR[248] and KAM impulse[236], with slower gait speeds leading to significant reduction in both values. Previously reported gait speed differences between slow and self-selected conditions were twice as large (0.2m/s)[236,248] compared to speed differences between symmetrical and asymmetrical groups (0.09m/s), suggesting that while gait speed may have played a role in KAM differences, it may not have strongly influenced the results of the current project. These findings suggest that individuals with symmetrical and asymmetrical knee loading display gait characteristics consistent with knee OA; however, individuals with symmetrical knee loading appear to walk with more severe knee OA characteristics.

Individuals with symmetrical versus asymmetrical knee loading were found to be obese (BMI<30)[249] and overweight (BMI ≥25kg/m^2 to <30kg/m^2)[249], respectively. Differences in BMI have previously been shown to influence biomechanical characteristics in individuals with knee OA[250], potentially explaining the reduced KAMR and peak KEM in the affected knee of individuals with symmetrical knee loading. Previous research classifying individuals with knee OA into healthy-weight (<25kg/m^2), overweight (≥25kg/m^2 to <30kg/m^2), and obese (>30kg/m^2) BMI reported sustained frontal plane loading (KAM) throughout midstance when individuals were classified as obese[250], which is consistent with the current results for both the affected and contralateral knees. Further, their findings suggested that a reduced peak KEM was associated with obesity, irrespective of whether individuals had knee OA or not[250], which is consistent with KEM reductions found in the affected limb of individuals with symmetrical knee loading in the current study. In contrast, the contralateral peak KEM was not different between individuals with symmetrical versus asymmetrical knee loading and may suggest a knee-specific role of obesity on joint loading when interpreting inter-limb asymmetry.

The relative external knee moment contributions to the TJM in the contralateral knee of individuals with symmetrical, but not asymmetrical, knee loading were also consistent with previous external knee moment distributions reported for individuals with mild-to-moderate knee OA[190]. In contrast, the contralateral knee of individuals with asymmetrical knee loading demonstrated relative external knee moment contributions to the TJM closely resembling asymptomatic individuals (Figure 4-3). The gait characteristics demonstrated by individuals with symmetrical knee loading suggest that their contralateral knee may be more functionally severe than individuals with asymmetrical knee loading.

Reduced ICPF, KAMR and SPROM have previously been associated with increased risk of clinical knee OA progression defined as progression to total knee arthroplasty[39,233]. Further, the magnitude of differences in ICPF, KAMR, peak KFM and SPROM between the contralateral knee of individuals with symmetrical versus asymmetrical knee loading are consistent with the biomechanical differences previously reported between individuals with mild-to-moderate knee OA and asymptomatic individuals[40]. These differences in contralateral knee biomechanics suggest that symmetrical knee loading may be a proxy for bilateral disease in this population; however, further studies are needed to confirm this.

Individuals with symmetrical knee loading had consistently lower magnitudes for KOOS and ICOAP sub-scales compared to individuals with asymmetrical knee loading; however, only the KOOS-ADL was statistically different between groups. Both groups displayed similar KOOS subscale scores to previously reported values for individuals with mild-to-moderate knee OA[40]. However, the mean difference in KOOS-ADL and KOOS-Sport scores between individuals with symmetrical versus asymmetrical knee loading were two times greater than previous differences reported between individuals with severe (Kellgren-Lawrence grade = 4) and mild (Kellgren-Lawrence grade = 2) knee OA[251]. The KOOS-ADL subscale is designed to assess patient perceived physical function during ADLs[145]. Descriptive analyses revealed that the majority of individuals with symmetrical knee loading reported worse difficulty with getting out of a chair, off a toilet or ascending stairs. Poorer KOOS-ADL scores reported by individuals with symmetrical knee loading may reflect the inability of their contralateral knee to compensate for functional deficits in their affected knee. Previous research has shown that during stair ambulation[252] or rising from a chair[253], individuals with knee OA disproportionately load their contralateral knee

to complete the activity[252,253]. Individuals with symmetrical knee loading may perceive their contralateral knee to be less trustworthy compared to individuals with asymmetrical knee loading. Although participant perceptions of the contralateral knee were not collected in the present study, its potential effect on patient-reported outcomes for the affected knee may explain the difference in KOOS-ADL scores between groups. Future research investigating objective contralateral knee function and patient-reported ADL performance in individuals with knee OA may support this hypothesis.

Despite the novel relationships identified in the present study, several methodological limitations should be acknowledged. The TJM, reflective of the relative external knee moment contributions, was the driving biomechanical outcome used to define who was or was not symmetrical during walking. The technology used to calculate this metric is not readily available to most healthcare providers and thus lacks immediate clinical implementation. Future research assessing inter-limb asymmetry with more clinically applicable methods such as markerless motion capture or spatial-temporal measures are warranted. The contralateral knee for all individuals in the current study was asymptomatic; however, individuals with symmetrical knee OA displayed contralateral knee biomechanics similar to individuals with knee OA. Without imaging of the contralateral knee, we cannot confirm the presence or absence of knee OA in the joint.

5.5 Conclusion

Comparing patient-reported and biomechanical outcomes in individuals with knee OA who were dichotomized with symmetrical versus asymmetrical knee loading highlights novel findings about the potential disease state of individuals with knee OA. Individuals

with symmetrical knee loading reported poorer patient-reported function (KOOS-ADL) driven by worse reported difficulty ambulating stairs and getting out of a chair, which may reflect an inability to rely on their contralateral knee during ADLs. Biomechanical differences between the affected and contralateral knees between groups suggest that individuals with symmetrical knee loading may represent a subgroup of individuals with or at risk for bilateral disease. Future research quantifying whether knee OA severity in the contralateral knee influences inter-limb asymmetry in individuals with knee OA is warranted.

CHAPTER 6: A Response To 30-Minutes of Continuous Walking: Does Inter-Limb Asymmetry Alter Knee Pain and Gait Biomechanics in Individuals with Knee Osteoarthritis?

6.1 Introduction

Osteoarthritis (OA) is a progressive joint disease and a leading cause of pain and functional disability worldwide[19,70,254]. Clinical practice guidelines consistently recommend physical activity for the treatment and self-management of knee OA for symptomatic and functional benefits[19,21,59,60]. However, difficulty with walking remains an important mobility challenge for individuals with knee OA, with knee pain as a key patient-reported barrier to engaging in physical activity[54]. The results from Chapter 5 indicated that individuals with symmetrical knee loading walked with affected and contralateral knee biomechanics mirroring gait consistent with knee OA. Further, individuals with symmetrical knee loading reported worse KOOS-ADL scores compared to individuals with asymmetrical knee loading. Previous work has shown similar baseline differences in KOOS-ADL scores between individuals with knee OA who experienced, and did not experience, a pain flare during 20-minutes of walking[55], which was also reflected in their group-specific biomechanical responses proposing that baseline patient reported function may play a role in the response to prolonged walking.

Current physical activity guidelines recommend 150-minutes per week or 30-minutes per day of moderate-to-vigorous physical activity[52]. These recommendations are poorly tailored for individuals with knee OA, and increased knee pain may lead to poor adherence to physical activity recommendations[255]. Individuals with knee pain have observable walking patterns associated with increased knee stiffness, decreased knee

motion and compensatory movement patterns to redistribute knee load, with the cumulative intent of reducing knee pain[41]. A breadth of evidence exists examining how acute bouts of physical activity influence gait mechanics in individuals with knee OA[55,195,196], suggesting that minimal increases in affected knee pain (~1-point increase on an 11-point NPRS), results in both increased loading magnitudes[195] and more dynamic gait characteristics[196], typically associated with improved joint function[196]. These results are contradicted by Boyer and Hafer (2019) [55] who found that a pain increase of 1.5 points (0-11 NPRS) over 20-minutes of walking, resulted in reduced first and second peak KAM compared to individuals with knee OA who did not experience a pain flare, and peak KFM compared to asymptomatic individuals[55]. These differences may be attributed to physical function variability across study participants such that gait speed ranged from 0.92m/s[55] to 1.07m/s[196]. A gait speed below 1.0m/s is highly correlated with increased mortality and suggests that the participant cohort for Boyer and Hafer (2019)[55] may be more functionally severe than other studies[195,196]. Therefore, aligning with guideline recommendations, 30-minutes of walking may be a sufficient stimulus duration to prompt a biomechanical response in individuals with knee OA, depending on their functional status[55,195,196].

The patient-reported and biomechanical differences observed between individuals with symmetrical and asymmetrical knee loading in Chapter 5 suggest a potential difference in functional status between these groups and warrants investigation into whether they respond similarly to 30-minutes of walking. Therefore, the specific objectives of this study were to: examine how knee pain responds to 30-minutes of continuous walking in individuals with knee OA who were dichotomized as having either symmetrical or asymmetrical knee loading; whether affected and contralateral knee biomechanics

respond differently to 30-minutes of continuous walking in individuals with knee OA who were dichotomized as having either symmetrical or asymmetrical knee loading; and assess the responsiveness of inter-limb asymmetry to 30-minutes of continuous walking between individuals with knee OA who are dichotomized as having either symmetrical or asymmetrical knee loading.

6.2 Methodology

6.2.1 Participant Recruitment

Individuals with knee OA were recruited to participate from the community and through an orthopaedic clinic. Individuals from the community were recruited based on the inclusion criteria: 1) >40 years of age, 2) activity related knee pain on most days in the past month, 3) knee pain experienced for at least the past three months, 4) affected knee pain ranging between 40 to 90 on a 100-point numeric rating scale (0 = "no pain, 100 = "worst pain imaginable"), and 5) morning stiffness lasting <30-minutes[12–17]. Individuals diagnosed by an orthopaedic surgeon were recruited using the inclusion criteria: 1) >40 years of age, and 2) symptomatic and moderate knee OA based on the American College of Rheumatology criteria[18]. The exclusion criteria applied to both groups were age <40, bilateral symptoms, bilateral activity related pain, inflammatory arthritis in either limb, previous lower limb surgery, lower limb injury within the past year, or any cardiovascular, muscular, or neurological conditions that would affect their ability to walk or ambulate stairs. The study protocol was approved by the institution's research ethics board and all participants provided informed consent prior to testing.

6.2.2 Data Collection

Participants completed the Knee Injury and Osteoarthritis Outcome Score (KOOS)[145] and Intermittent and Constant knee Osteoarthritis Pain (ICOAP)[146] questionnaires, and baseline affected knee pain using an 11-point numeric pain rating scale (NPRS) (0 = “no pain at all”, 10 = “worst pain imaginable”) prior to testing. Aligning with the explicit inclusion and exclusion study criteria (i.e., participants could not report experiences of any discomfort or activity related knee pain (NPRS=0) in their contralateral knee), NPRS was only assessed in the affected knee of individuals with knee OA. Participants were asked to change into form-fitting shorts, a t-shirt, and wear their regular walking/running shoes. Anthropometric measurements were collected including height, weight, waist, hip, thigh and shank circumferences, then participants were outfitted with a full-body retroreflective marker set including seven rigid clusters each containing four retroreflective markers placed over the pelvis, and bilaterally over the lateral femurs, lateral shanks and feet, secured using Velcro straps. Individual retroreflective markers were placed over the seventh cervical vertebrae and bilaterally over the acromion, lateral epicondyles, ulnar styloid processes, greater trochanters, iliac crests, anterior superior iliac spine, medial and lateral tibial and femoral epicondyles, lateral and medial malleoli, first, second and fifth metatarsal heads and posterior heels (Figure 3-1). Prior to the walking protocol, markers located at the medial femoral and tibial epicondyles, medial malleoli, the first and fifth metatarsal heads, lateral tibial epicondyles, anterior superior iliac spine, iliac crests and greater trochanters were removed.

Participants completed a minimum of five overground walking trials at a self-selected pace across a six-meter walkway. Three-dimensional kinematic data was collected

at 100Hz using a ten-camera passive motion capture system (Cortex, version 8.0, Motion Analysis Corporation, California, U.S.A). Ground reaction force (GRF) data was collected at 1200Hz synchronized with two floor embedded force platforms (Advances Medical Technologies Inc, Watertown, MA). Participant self-selected overground walking speed was calculated and extracted from these trials using the average forward speed of the four-pelvis cluster markers and averaged across the five trials. Immediately after the walking trials, participants rated their affected knee pain using an 11-point NPRS.

Following the overground walking trials, participants completed a 30-minute continuous treadmill walk. Treadmill speed was set at ± 10% of the participant's average walking speed calculated during their overground trials. The 30-minute walk was completed on a Biodex treadmill (RTM600, Biodex Medical Systems, Inc., New York, U.S.A). Participants attached the treadmill safety clip before beginning the continuous walk. During the walk, participants were asked to rate their affected knee pain using an 11-point NPRS, and their rating of perceived exertion (RPE) using the Borg scale ranging from 6 "no exertion" to 20 "maximal exertion"[217]. The recommended aerobic training intensity for individuals with knee OA is 40-60% of age adjusted maximum heart rate (220-age) corresponding to a Borg scale of ~12-13[22]. Three-dimensional kinematic data, knee pain and RPE exertion were collected at 10-minute intervals during the 30-minute walk (i.e., once treadmill reached full speed, 10-, 20-, and 30-minutes). Immediately after completing the 30-minute walk, participants repeated the overground walking protocol, and the remaining retroreflective markers were then removed.

Knee flexion and extension maximum voluntary isometric strength was calculated using a Biodex isokinetic dynamometer (Advantage BX Software 5.2, Shirley, NY,

U.S.A.). Maximum knee flexion and extension strength were collected with the participant seated, the hip flexed to 90^{o} and the knee flexed to 45^{o}[218]. Velcro straps were used to stabilize the participant's leg for each strength test. A warm-up, practice contraction was performed to familiarize the participant with the test protocol. Contractions were completed twice for three-seconds, with a 60-second break between contractions. Verbal encouragement was given to each participant to maximize effort and contraction consistency[219].

6.2.3 Data Processing and Analysis

Total KOOS and ICOAP scores along with their subscales were normalized to a 0-100-point scale (0 = "worse symptoms", 100 = "better symptoms"). Three-dimensional kinematic data were filtered (6Hz lowpass fourth-order, recursive Butterworth filter)[218] and knee angles were calculated bilaterally using an XYZ (sagittal, frontal, transverse) rotation sequence, described as the distal segment moving about a fixed proximal segment[221]. Flexion, adduction and internal rotation represent positive angles. Three-dimensional GRF and moments were initially filtered (30Hz lowpass fourth-order, recursive Butterworth filter)[218]. Net external joint moments were calculated using an inverse dynamics model[155]. The external knee adduction moment (KAM), knee flexion moment (KFM), and knee rotation moment (KRM) were filtered (10Hz lowpass fourth-order recursive Butterworth filter)[218], normalized to body mass (Nm/kg), and time normalized to stance. All kinematic and kinetic data processing was completed using Visual 3D (v2023.04.2, C-motion Inc., Germantown, MD, USA). Maximum isometric strength was calculated using a 500ms moving average window to determine maximum torque generated during the three-second

MVIC trial[246]. The highest torque value calculated from either of the two MVIC trials was recorded as the maximum flexion or extension strength, and amplitude normalized to body mass (Nm/kg).

Kinematic data was time normalized to 100% of the gait cycle (initial contact to ipsilateral initial contact) and kinetic data were time normalized to stance (initial contact to pre-swing), using a kinetic-kinematic initial contact and pre-swing detection method[222]. Initial contact was identified using a 20N threshold for the vertical component of the GRF[222], and ipsilateral initial contact was calculated as the maximal anterior displacement between the origin of the pelvis markers and heel marker[222]. Pre-swing was identified when the vertical component of the GRF fell below the 20N threshold[222]. Kinematic, and kinetic data were extracted bilaterally for both groups. Kinematic data for the sagittal, frontal and transverse planes were collected; however, only the sagittal plane was analyzed. The total joint moment (TJM)[190] was calculated bilaterally for each participant using the formula: $TJM = \sqrt{KFM^2 + KAM^2 + KRM^2}$. Absolute TJM symmetry indices were calculated using the formula: $((X_A - X_C)/(0.5(X_A + X_C)) * 100))$[201], in which X_A represents the first peak TJM in the affected knee and Xc represents first peak TJM in the contralateral knee. A symmetry value of zero represents perfect symmetry between knees, and higher values represent greater differences between knees.

6.2.4 Statistical Analysis

Participants were dichotomized based on the absolute TJM symmetry status using the threshold (14%) calculated in Chapter 4 (4.3.3 Total Joint Moment Asymmetry). Independent t-tests calculated between group differences for demographics, patient-

reported outcomes, knee extension and flexion strength. Mixed 2x2 analysis of variance (ANOVA) statistical parametric maps (SPM{f})[226] were used to analyze limb by time interactions, between and within knee differences in time normalized sagittal plane knee angles, KAM and KFM waveforms. Only differences identified by SPM in joint moments between 10-90% of stance were interpreted to align with most common kinetic metrics reported for individuals with knee OA[33,37,40,42,51,63]. Separate SPM analyses were completed for individuals with symmetrical and asymmetrical knee loading. Random field theory calculated the critical F-statistic, and the null hypothesis was rejected if the computed f-value for the waveforms exceeded this value[226]. All ten overground walking trials were used in the final SPM analyses to include the stride-to-stride variability. A total of 380 cycles (95 gait cycles per knee per condition) for individuals with symmetrical knee loading and a total of 480 cycles (120 gait cycles per knee per condition) for individuals with asymmetrical knee loading were included in the final SPM analysis. The TJM, knee flexion angle range from initial contact to peak stance flexion (ICPF), first peak knee adduction moment to midstance unloading range (KAMR), and sagittal plane knee moment range (SPROM) were analyzed using a 2x2 ANOVA, and between knee post-hoc analyses were interpreted using mean differences and 95% bootstrapped confidence intervals. A mixed ANOVA was used to determine the main effects of time (i.e., minutes 0, 10, 20, 30) and group, and their interaction, on pain and RPE during the treadmill walk. Mean difference and 95% bootstrapped confidence intervals were calculated as symmetrical minus asymmetrical, where a positive value indicates that symmetrical is greater than asymmetrical, and a negative value indicates that asymmetrical is greater than symmetrical. The calculation of these outcomes is described in Section 3.3. All statistical analyses were

interpreted using an alpha level of 0.05 to determine statistical significance. Normality and equal variance were assessed using the Kolmogorov-Smirnov and Levene's tests.

6.3 Results

Forty-three individuals with knee OA were recruited and dichotomized into symmetrical (n=19) and asymmetrical (n=24) knee loading. Table 6-1 describes demographic, patient-reported outcomes and muscle strength outcomes between groups. Individuals with symmetrical knee loading had a significantly (p=0.036) higher BMI and worse KOOS-ADL scores (p=0.041) than individuals with asymmetrical knee loading (Table 6-1). No differences were found for age (p=0.404), distribution of males and females p=0.864), gait speed (p=0.065), and knee flexion (p=0.207-0.262) or extension (p=0.399-0.352) strength between groups (Table 6-1).

Table 6-1: Participant demographics and clinical characteristics for individuals with symmetrical or asymmetrical knee loading (n=43)

	Symmetrical (n=19)	Asymmetrical (n=24)
Age	58 ± 9	60 ± 10
Sex. no. of females (%)	9 (47)	12 (50)
BMI, kg/m^2	**31.1 ± 6.1**	**26.6 ± 7.0**
Gait Speed before treadmill, m/s	1.21 ± 0.15	1.30 ± 0.19
Gait Speed after Treadmill, m/s	1.23 ± 0.16	1.35 ± 0.20
Total Steps Taken	3285 ± 307	3217 ± 387
TJM asymmetry before (%)	**8.19 ± 3.43**	**48.1 ± 26.9**
TJM asymmetry after (%)	**13.5 ± 9.16**	**46.2 ± 24.9**
KOOS Total	63.2 ± 12.9	68.7 ± 14.1
KOOS Symptoms	66.8 ± 13.0	72.0 ± 12.7
KOOS Pain	66.7 ± 13.6	69.4 ± 17.7
KOOS ADL	**73.4 ± 14.8**	**83.1 ± 13.2**
KOOS Sport	45.3 ± 20.4	53.3 ± 24.0
KOOS QoL	49.6 ± 14.0	49.5 ± 17.9
ICOAP Total	73.1 ± 16.1	80.4 ± 15.5
ICOAP Constant	78.8 ± 18.4	84.8 ± 17.2
ICOAP Intermittent	68.4 ± 17.0	77.1 ± 17.9
Affected knee strength (Nm/kg)		
Knee flexion	0.73 ± 0.28	0.81 ± 0.31
Knee extension	1.21 ± 0.44	1.31 ± 0.27
Contralateral knee strength (Nm/kg)		
Knee flexion	0.77 ± 0.23	0.82 ± 0.27
Knee extension	1.32 ± 0.49	1.44 ± 0.35

Note: Values are listed as mean and standard deviation unless otherwise indicated. TJM = total joint moment. KOOS = Knee Injury and Osteoarthritis Outcome Score. ADL = activities of daily living. QoL = Quality of life. ICOAP = Intermittent and Constant Osteoarthritis Pain. Bolded values indicate between-group differences ($p<0.05$).

6.3.1 Patient-Reported Outcomes

Individuals with symmetrical knee loading experienced larger increases in knee pain over 30-minutes of walking compared to individuals with asymmetrical knee loading ($p=0.040$) (Figure 6-1). Post-hoc analyses indicated that both groups significantly increased knee pain from baseline to 30-minutes, with an average increase of 2.02 for individuals with symmetrical knee loading and 1.00 for individuals with asymmetrical knee loading. Within groups analyses suggested that individuals with symmetrical knee loading

had a significant increase in knee pain during every 10-minute interval (i.e., baseline-10-minutes (mean difference: 0.89, 95% CI [0.55,1.29]), 10-20-minutes (mean difference: 0.50, 95% CI [0.18,0.84]), 20-30-minutes (mean difference: 0.55, 95% CI [0.29,0.84]), while individuals with asymmetrical knee loading experienced similar significant increases in knee pain during the first two 10-minute intervals (i.e., baseline-10-minutes (mean difference: 0.42, 95% CI [0.06,0.81]), 10-20-minutes (mean difference: 0.43, 95% CI [0.01,0.83]) then the increases in pain minimally changed for the remainder of the walking intervention (mean difference: 0.16, 95% CI [-0.13,0.42]).

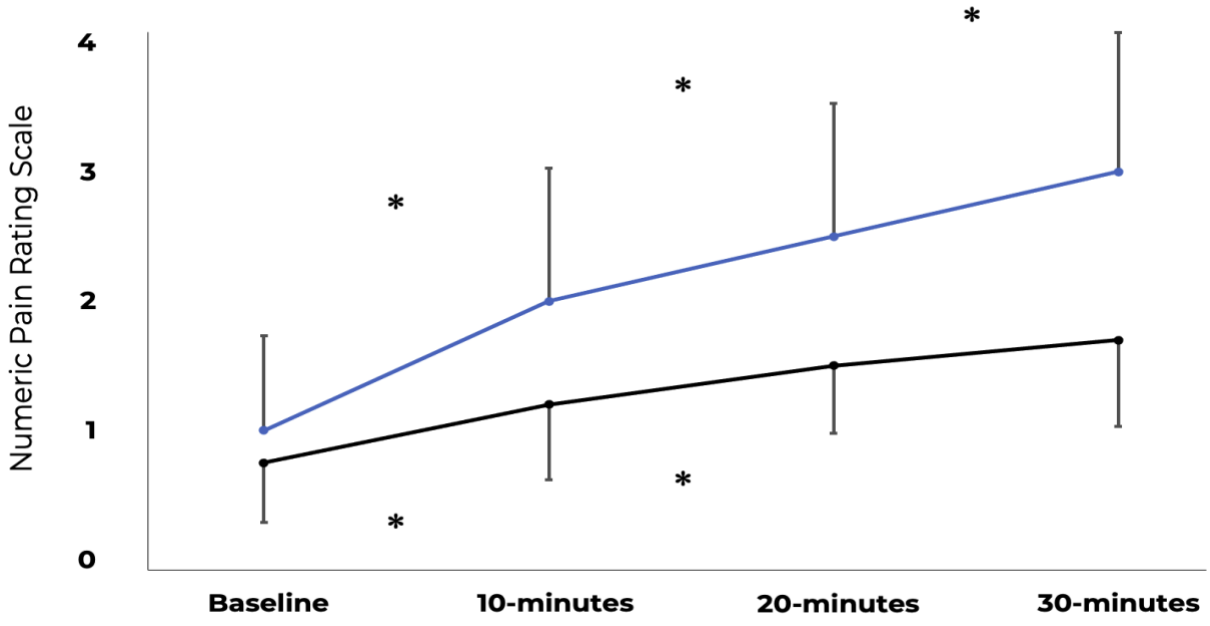


Figure 6-1: Means and 95% confidence intervals for self-reported affected knee pain (NPRS 0-10) during 30-minutes of walking at baseline, 10-, 20-, and 30-minute intervals for individuals with symmetrical (blue line) and asymmetrical (black line) knee loading. Asterisks (*) indicate within-group differences between in 10-minute intervals (i.e., baseline-10-minutes, 10-20-minutes, 20-30-minutes).

Both groups reported similar increases in effort following 30-minutes of walking ($p<0.001$) (Figure 6-2), with an average RPE increase of 4.36 for individuals with symmetrical knee loading and 4.25 for individuals with asymmetrical knee loading between baseline (0-minutes) and the end of the 30-minute walk. Post-hoc analyses indicated that individuals with symmetrical knee loading significantly increased RPE during every 10-minute interval (i.e., baseline-10-minutes (mean difference: 2.84, 95% CI [2.10,3.57]), 10-20-minutes (mean difference: 0.74, 95% CI [0.021,1.31]), 20-30-minutes (mean difference: 0.80, 95% CI [0.32,1.26]), while individuals with asymmetrical knee loading showed significant increases in effort during the first two intervals (i.e., baseline-10-minutes (mean difference: 3.12, 95% CI [2.29,3.95]), 10-20-minutes (mean difference: 0.88, 95% CI [0.54,1.21]) then plateaued for the remainder of the walking intervention (mean difference: 0.25, 95% CI [-0.04,0.58]).

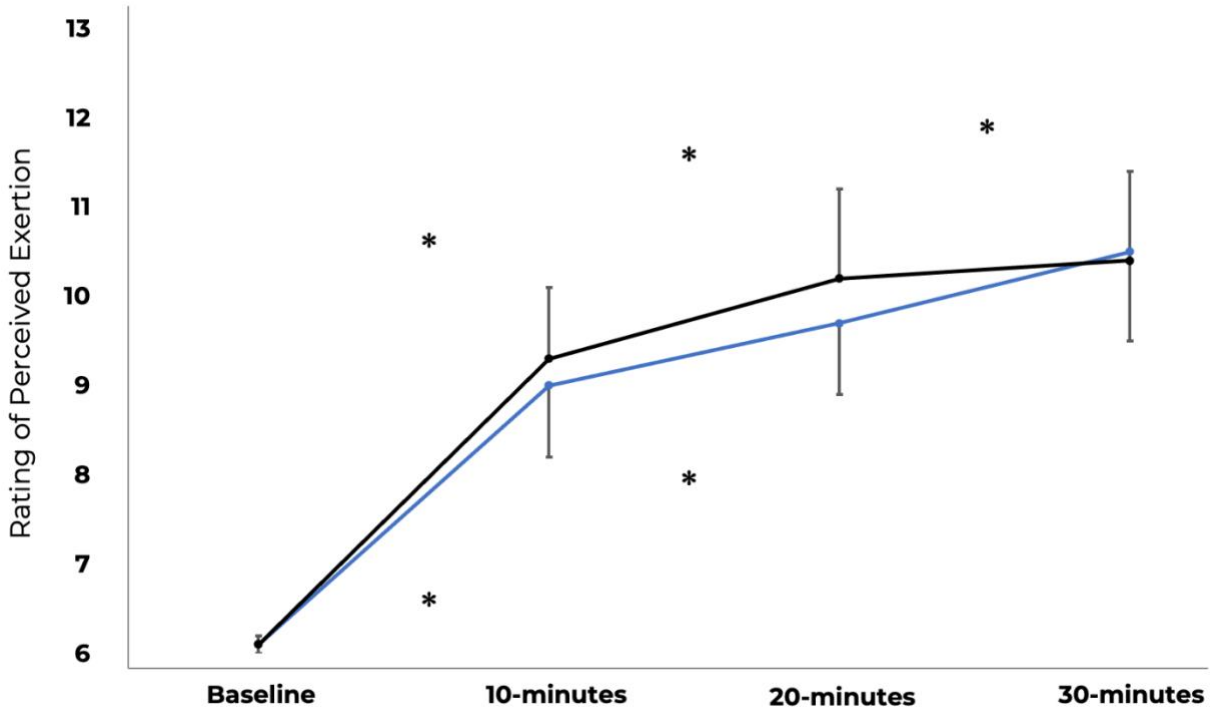


Figure 6-2: Means and 95% confidence intervals for rating of perceived exertion during 30-minutes of walking at baseline, 10, 20, and 30-minute intervals for individuals with symmetrical (blue line) and asymmetrical (black line) knee loading. Asterisks (*) indicate within-group differences between in 10-minute intervals (i.e., baseline-10-minutes, 10-20-minutes, 20-30-minutes).

6.3.2 Biomechanical Outcomes

6.3.2.1 Individuals with Symmetrical Knee Loading

The knee flexion angle during loading response in the affected knee significantly increased ($p=0.011$) after 30-minutes of walking, with no significant change in knee flexion angle in the contralateral knee (Figure 6-3). The KAM during midstance in the affected knee significantly decreased ($p<0.001$) after 30-minutes of walking, with no significant change in midstance KAM in the contralateral knee (Figure 6-4). The affected and contralateral knees had similar significant ($p<0.001$) increases in the KFM (Figure 6-5), TJM ($p<0.001$), KAMR ($p=0.003$), and SPROM ($p=0.007$) after 30-minutes of walking.

Raw data and change scores for the TJM, ICPF, KAMR and SPROM are presented in Table 6-2.

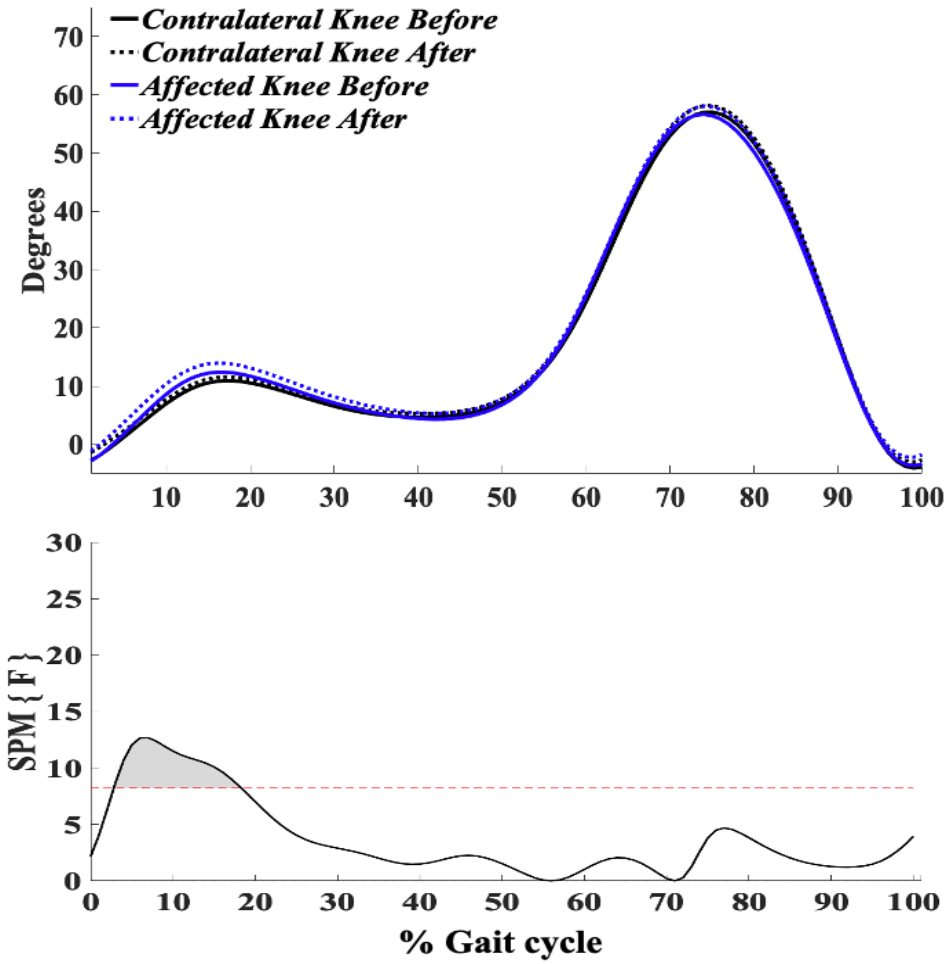


Figure 6-3: Sagittal plane knee angle ensemble averaged waveforms for the affected (blue) and contralateral (black) knees in individuals with symmetrical knee loading, before (solid line) and after (dashed line) 30-minutes of walking. Analysis of variance statistical parametric maps indicate knee*time interactions as a function of the gait cycle (bottom). Shaded areas in the statistical parametric maps represent regions of significant difference.

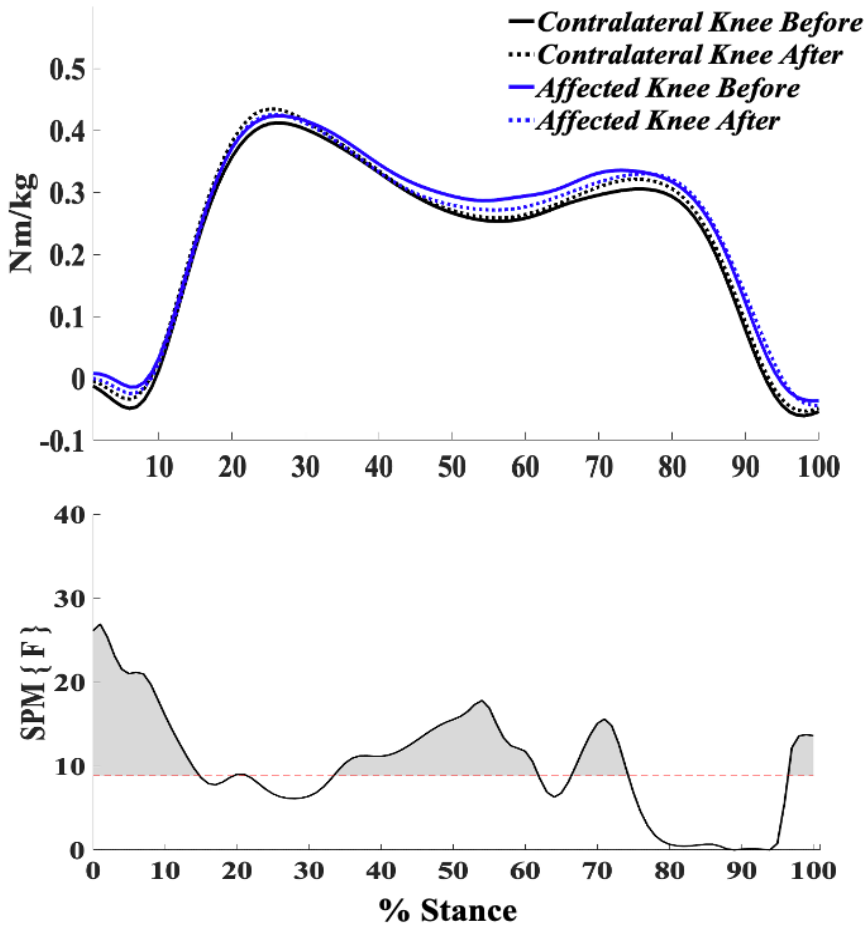


Figure 6-4: Knee adduction moment ensemble averaged waveforms for the affected (blue) and contralateral (black) knees in individuals with symmetrical knee loading, before (solid line) and after (dashed line) 30-minutes of walking. Analysis of variance statistical parametric maps indicate knee*time interactions as a function of stance (bottom). Shaded areas in the statistical parametric maps represent regions of significant difference.

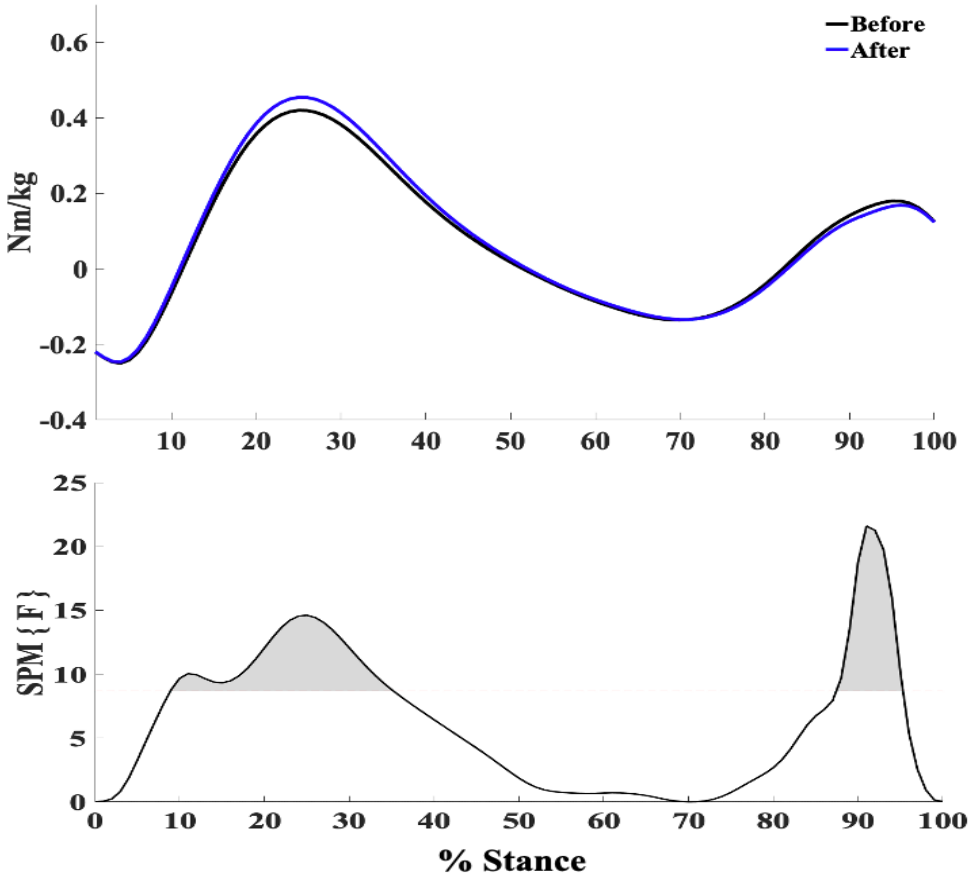


Figure 6-5: Knee flexion moment ensemble averaged waveforms (top) before (black) and after (blue) 30-minutes of walking for individuals with symmetrical knee loading. Analysis of variance statistical parametric maps indicates a time effect as a function of stance (bottom). Shaded areas in the statistical parametric maps represent regions of significant difference.

Table 6-2: Within knee differences for biomechanical outcomes in individuals with knee OA and symmetrical knee loading before and after 30-minutes of walking (n=19).

	Before Treadmill	After Treadmill	Mean Difference [95% CI]
Affected Knee			
TJM (Nm/kg)	0.63 (0.18)	0.67 (0.18)	**0.04 [0.01: 0.07]**
ICPF (°)	14.0 (4.00)	13.0 (3.50)	-1.00 [-1.64: 0.01]
KAMR (Nm/kg)	0.18 (0.08)	0.20 (0.09)	0.02 [-0.01: 0.04]
SPROM (Nm/kg)	0.56 (0.21)	0.59 (0.22)	0.03 [-0.01: 0.06]
Contralateral Knee			
TJM (Nm/kg)	0.62 (0.19)	0.67 (0.20)	**0.05 [0.02: 0.07]**
ICPF (°)	15.0 (4.0)	15.0 (3.00)	0.00 [-0.60: 1.00]
KAMR (Nm/kg)	0.18 (0.08)	0.21 (0.09)	**0.03 [0.01: 0.05]**
SPROM (Nm/kg)	0.61 (0.23)	0.65 (0.24)	**0.04 [0.01: 0.08]**

Note: CI = confidence interval. TJM = total joint moment. ICPF = initial contact to peak knee flexion range. KAMR = first peak knee adduction moment to midstance unloading range. SPROM = sagittal plane knee moment range. Mean differences are presented as after treadmill minus before treadmill, where a positive value indicates that after treadmill is greater than before treadmill, and a negative value indicates that before treadmill is greater than after treadmill. Bolded values indicate significant between-group differences as the 95% CI does not cross zero.

6.3.2.2 Individuals with Asymmetrical Knee Loading

The affected and contralateral knees had similar significant ($p<0.001$) increases in knee flexion angles during loading response and midstance (Figure 6-6), the first peak KAM ($p=0.028$) (Figure 6-7), peak KFM ($p=0.010$) (Figure 6-8), TJM ($p<0.001$), KAMR ($p<0.001$), SPROM ($p=0.003$) and reduced midstance KAM ($p<0.001$) after 30-minutes of walking. Before and after 30-minutes of walking the affected knee had significantly ($p<0.001$) lower knee flexion angles (Figure 6-6), KFM ($p<0.001$) (Figure 6-8), and TJM compared to the contralateral knee. Raw data and change scores for the TJM, ICPF, KAMR and SPROM are presented in Table 6-3.

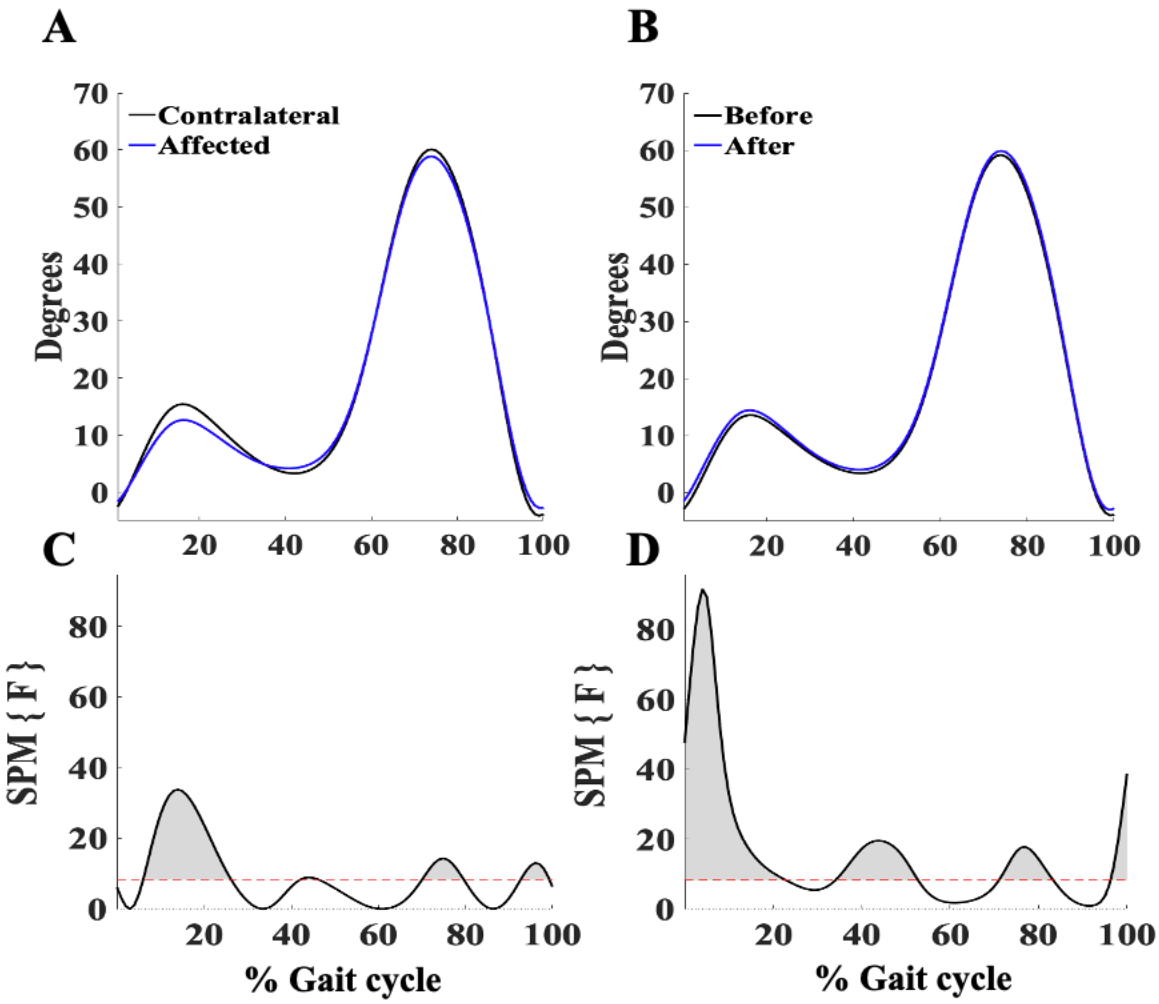


Figure 6-6: Sagittal plane knee angle ensemble averaged waveforms for the affected (blue) and contralateral (black) (A), and before (black) and after (blue) (B) 30-minutes of walking. Analysis of variance statistical parametric maps indicate knee (C) and time (D) main effects as a function of the gait cycle. Shaded areas in the statistical parametric maps represent regions of significant difference.

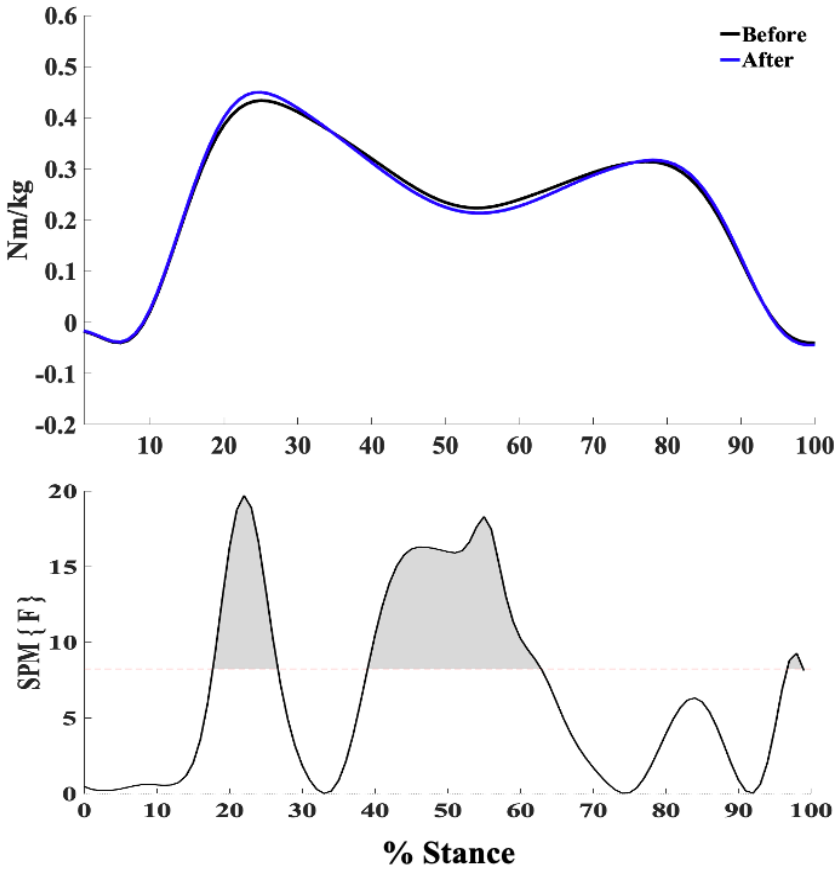


Figure 6-7: Knee adduction moment ensemble averaged waveform (top) before (black) and after (blue) 30-minutes of walking for individuals with asymmetrical knee loading. Analysis of variance statistical parametric maps indicates a time effect as a function of stance (bottom). Shaded areas in the statistical parametric maps represent regions of significant difference.

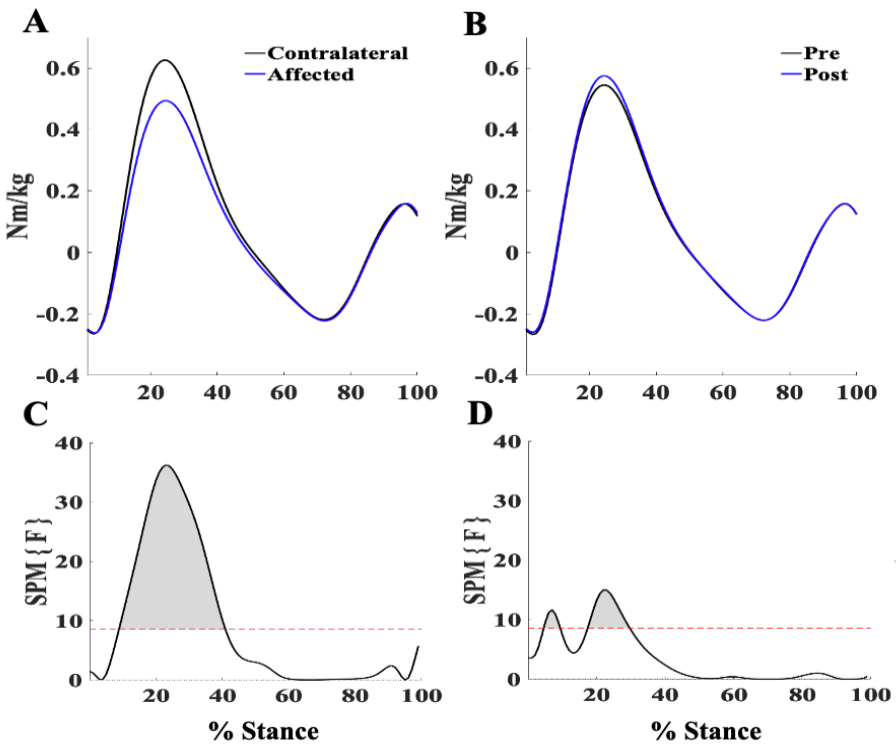


Figure 6-8: Knee flexion moment ensemble averaged waveforms for the affected (blue) and contralateral (black) (A) knees, and before (black) and after (blue) (B) 30-minutes of walking. Analysis of variance statistical parametric maps indicate knee (C) and time (D) main effects as a function of the gait cycle. Shaded areas in the statistical parametric maps represent regions of significant difference.

Table 6-3: Within knee differences for biomechanical outcomes in individuals with knee OA and asymmetrical knee loading before and after 30-minutes of walking (n=24).

	Pre-Treadmill	Post Treadmill	Mean Difference [95% CI]
Affected Knee			
TJM (Nm/kg)	0.72 (0.25)	0.75 (0.26)	0.03 [0.00: 0.05]
ICPF (°)	15.0 (5.00)	15.0 (5.00)	0.00 [-1.01: 0.19]
KAMR (Nm/kg)	0.26 (0.13)	0.29 (0.15)	**0.03 [0.01: 0.05]**
SPROM (Nm/kg)	0.74 (0.30)	0.76 (0.32)	0.02 [-0.01: 0.38]
Contralateral Knee			
TJM (Nm/kg)	0.79 (0.25)	0.83 (0.27)	**0.04 [0.01: 0.06]**
ICPF (°)	18.0 (6.00)	18.0 (6.00)	**0.00 [1.00: 0.40]**
KAMR (Nm/kg)	0.25 (0.12)	0.27 (0.12)	**0.02 [0.01: 0.03]**
SPROM (Nm/kg)	0.86 (0.33)	0.90 (0.35)	**0.04 [0.01: 0.06]**

Note: CI = confidence interval. TJM = total joint moment. ICPF = initial contact to peak knee flexion range. KAMR = first peak knee adduction moment to midstance unloading range. SPROM = sagittal plane knee moment range. Mean differences are presented as after treadmill minus before treadmill, where a positive value indicates that after treadmill is greater than before treadmill, and a negative value indicates that before treadmill is greater than after treadmill. Bolded values indicate significant between-group differences as the 95% CI does not cross zero.

6.3.3 Total Joint Moment Asymmetry

Individuals with symmetrical knee loading had a significantly lower ($p<0.001$) TJM asymmetry index compared to individuals with asymmetrical knee loading, regardless of time. After 30-minutes of walking, individuals with symmetrical knee loading increased their TJM asymmetry index (5% more asymmetric) in contrast to individuals with asymmetrical knee loading who decreased their TJM asymmetry index (2% more symmetric) (Figure 6-9). The relative external knee moment contributions of the KAM, KFM and KRM to the TJM for both knees before and after 30-minutes of walking are presented in Figure 6-10 and Figure 6-12. Ensemble averaged waveforms for the TJM, KAM, KFM and KRM are presented in Figure 6-11 and Figure 6-13.

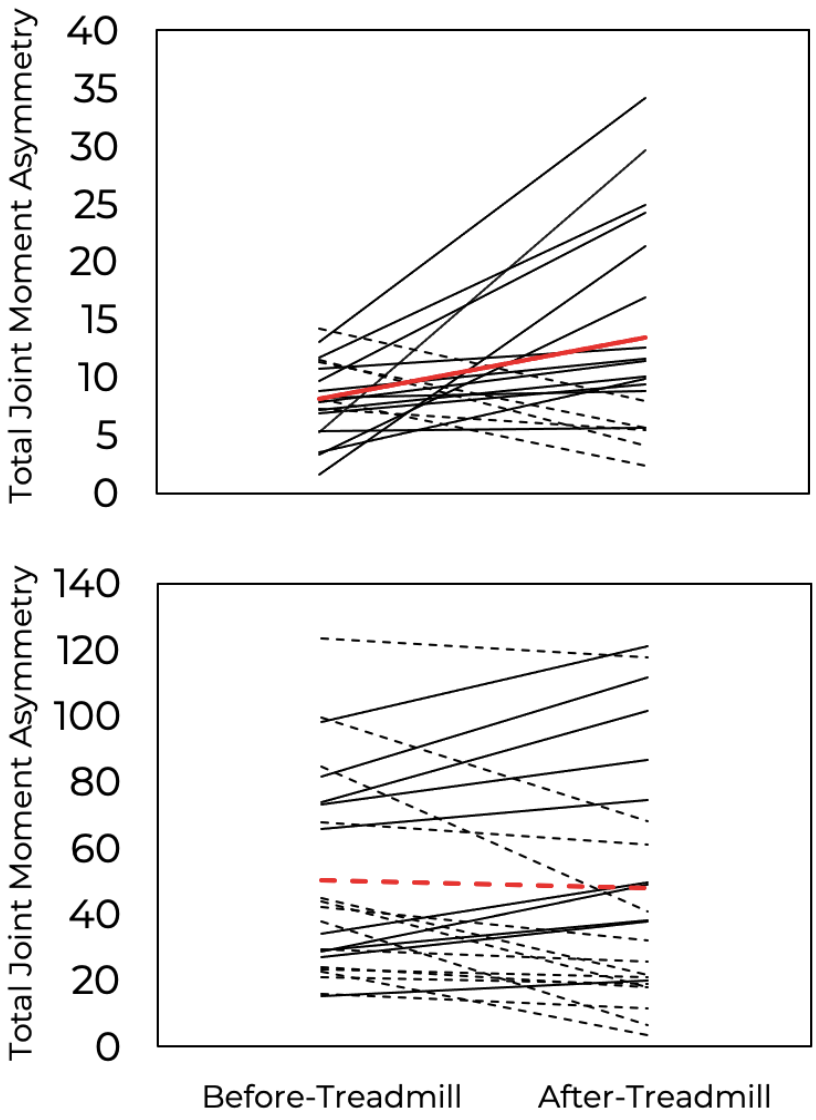


Figure 6-9: Total joint moment asymmetry indices before and after 30-minutes of walking for each participant in individuals with symmetrical knee loading (top) and asymmetrical knee loading (bottom). Solid lines indicate individuals who increased asymmetry and dashed lines indicate individuals who decreased asymmetry. The red line in each panel represents the respective group average at each timepoint and the corresponding direction of change over time.

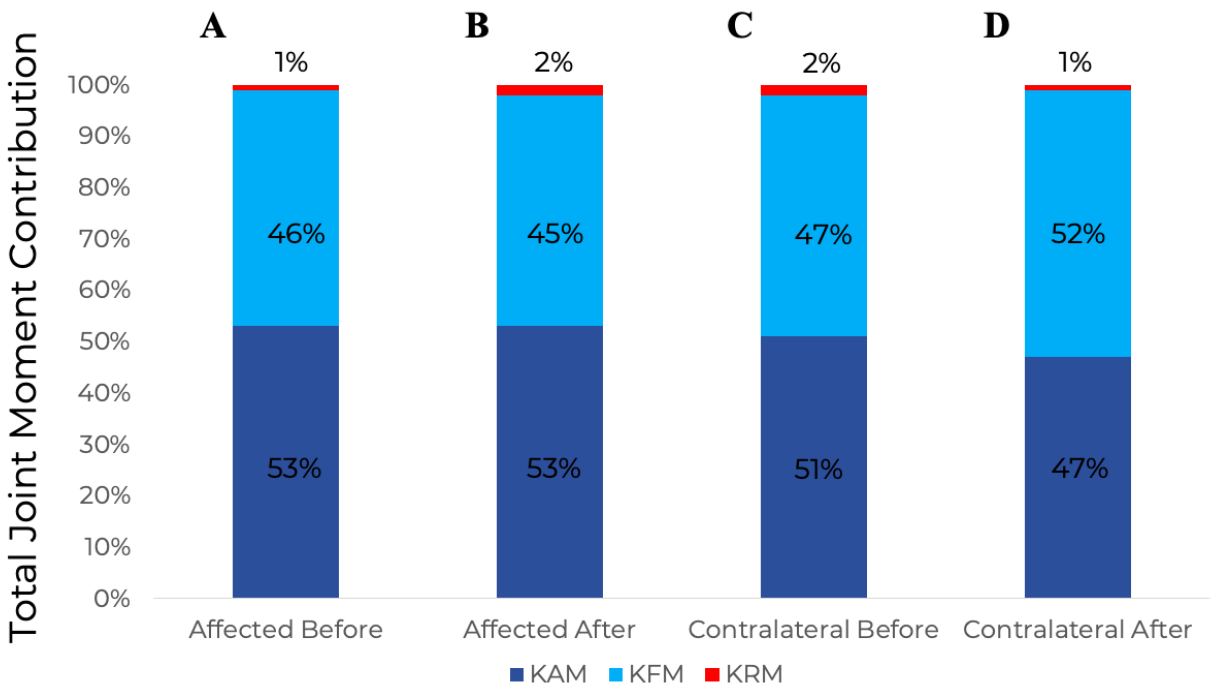


Figure 6-10: The relative external knee moment contributions to the total joint moment in the affected (A,B) and contralateral (C,D) knees before (A,C) and after (C,D) 30-minutes of walking in individuals with knee OA and symmetrical knee loading. KAM = first peak knee adduction moment. KFM = peak knee flexion moment. KRM = peak knee rotation moment.

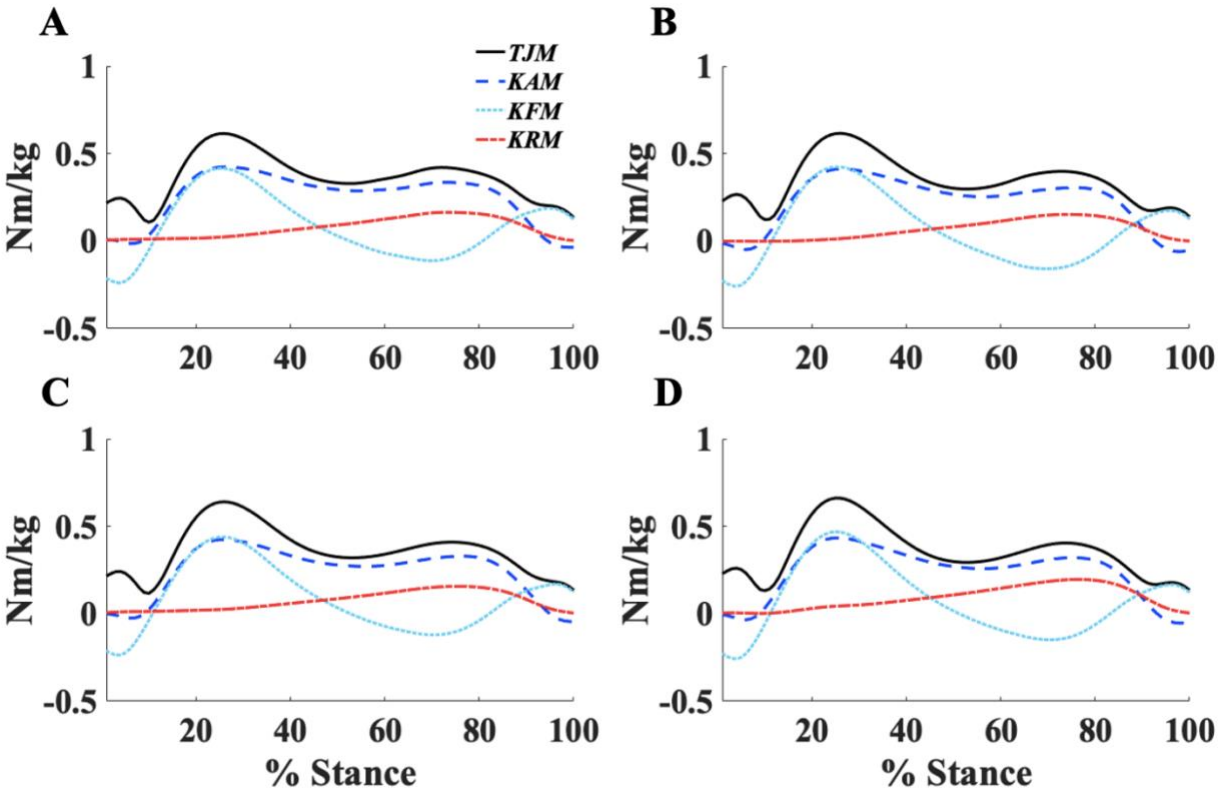


Figure 6-11: Ensemble averaged waveforms for the total joint moment and relative external knee moment contributions for the affected (A & C) and contralateral (B & D) knees before (top) and after (bottom) 30-minute of walking for individuals with symmetrical knee loading.

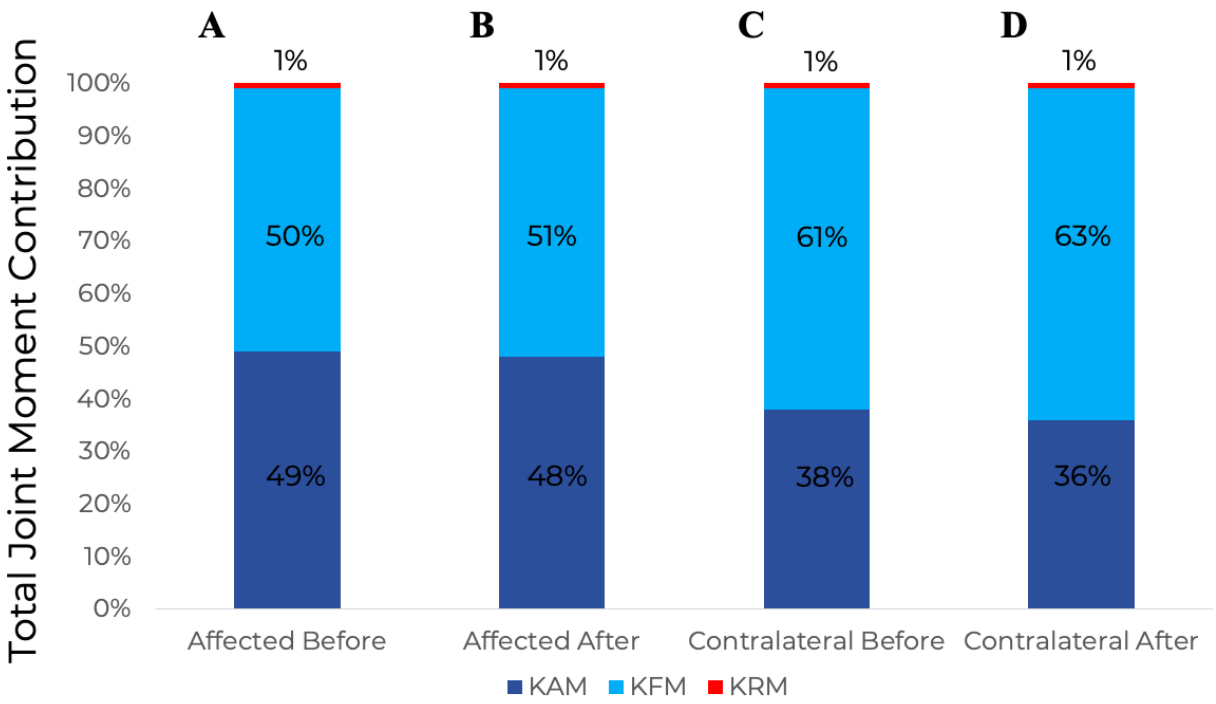


Figure 6-12: The relative external knee moment contributions to the total joint moment in the affected (A,B) and contralateral (C,D) knees before (A,C) and after (C,D) 30-minutes of walking in individuals with knee OA and asymmetrical knee loading. KAM = first peak knee adduction moment. KFM = peak knee flexion moment. KRM = peak knee rotation moment.

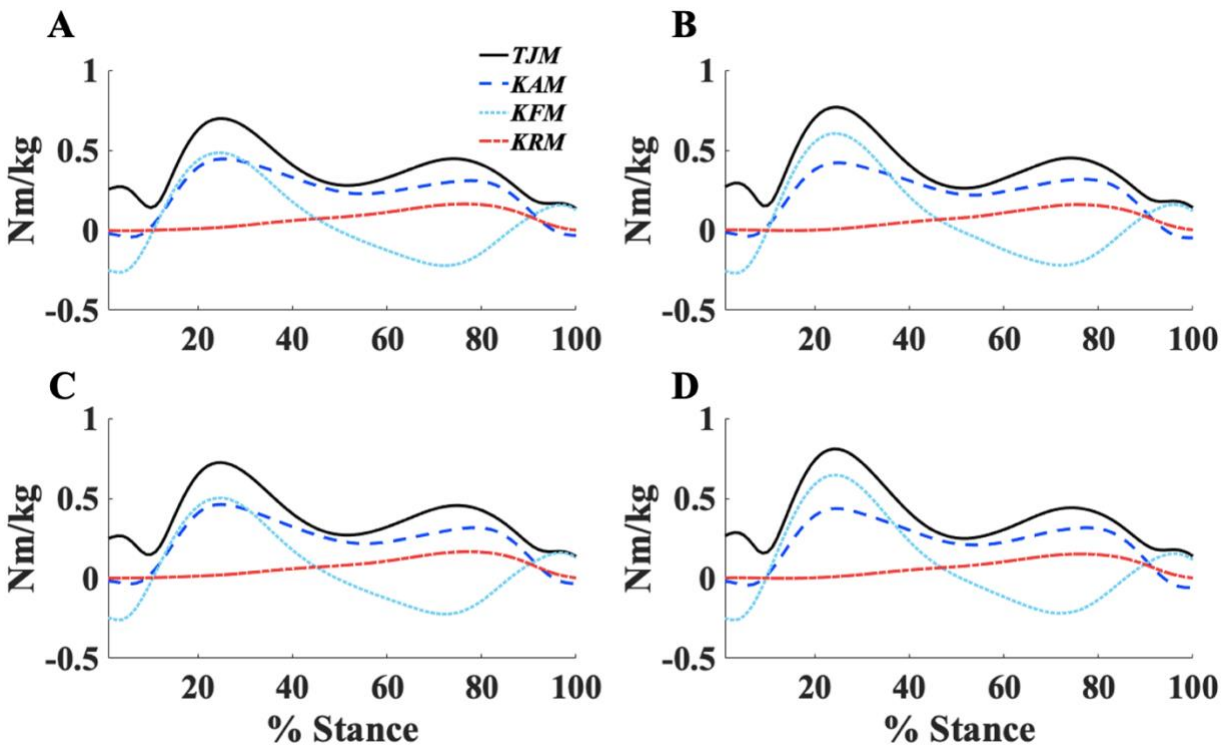


Figure 6-13: Ensemble averaged waveforms for the total joint moment and relative external knee moment contributions for the affected (A & C) and contralateral (B & D) knees before (top) and after (bottom) 30-minute of walking for individuals with asymmetrical knee loading.

6.4 Discussion

This study captured the effects of a continuous 30-minute walk on patient-reported outcomes and quantified the interactive contributions of the affected and contralateral knees with respect to symmetrical and asymmetrical gait patterns. Both groups achieved an RPE of ~10/20 on the Borg scale, which has previously been found to coincide with 56.9% of age-adjusted maximal heart rate in this population[195], indicating that they achieved the recommended aerobic training intensity during the treadmill walk[22]. Individuals with symmetrical, versus asymmetrical knee loading reported a significantly larger pain response after 30-minutes of walking; however, their affected knee demonstrated minimal increases in flexion angles and reduced midstance KAM compared

to their contralateral knee. Both the affected and contralateral knees in individuals with symmetrical and asymmetrical knee loading moved with increased KAMR and SPROM after 30-minutes of walking, indicating increased dynamic loading. These results indicate that individuals with symmetrical, versus asymmetrical knee loading respond differently in terms of individualized pain responses but similar biomechanically after 30-minutes of walking.

The affected knee in individuals with symmetrical knee loading demonstrated a clinically meaningful increase in pain (>2 points)[256] over 30-minutes of walking, and the magnitude of that increase was similar to increases reported by individuals with knee OA experiencing a pain flare over 20-minutes of walking[55]. This knee pain increase was two-fold compared to individuals with asymmetrical knee loading (~1 point increase) who more closely aligned with individuals with knee OA who did not experience a pain flare during prolonged walking[55,196]. Moreover, individuals with symmetrical loading consistently reported more severe knee pain at every 10-minute interval, whereas those with asymmetrical loading reported minimal symptom changes after 20-minutes. Increases in knee pain, a commonly reported deterrent for engaging in physical activity among individuals with knee OA[54], underscores the significance of these findings. Individuals with symmetrical knee loading endured heightened knee pain following 30-minutes of walking, potentially elevating their susceptibility to physical inactivity. Individuals with symmetrical knee loading may benefit from shorter bouts of walking to facilitate pain self-management, which is in line with minimum duration recommendation for individuals with knee OA[257].

Despite increases in knee pain, individuals with symmetrical knee loading walked with 1° more knee flexion throughout loading response in their affected knee compared to their contralateral knee; however, their total ICPF actually decreased by 1°, indicating a slightly less dynamic sagittal plane knee motion. This 1° change is consistent with results from Rutherford and Colleagues[196], who showed that individuals with knee OA increased their knee flexion 1° following a 25-minute perturbation protocol[196]. However, this 1° change is likely clinically meaningless, and below previously reported minimal detectable change values[218]. The affected knee in individuals with symmetrical knee loading also demonstrated a decreased midstance KAM (i.e., a larger midstance valley) compared to the contralateral knee following 30-minutes of walking, indicating increased medial compartment offloading[233]. Although the affected knee changes in midstance KAM were small, the average number of steps taken over the 30-minute walk was 3285, and these small changes may reduce cumulative joint loading[187] compared to the contralateral knee. These results suggest that the affected knee may experience reduced medial compartment loading exposure over 30-minutes of walking compared to their contralateral knee, potentially indicating a beneficial effect of walking on affected knee loading. Both the affected and contralateral knees in individuals with symmetrical knee loading had an increase in peak KFM and SPROM after the 30-minute walking protocol. The magnitude of increase in peak KFM[195] and SPROM[196] are consistent with previous findings examining prolonged walking in individuals with knee OA[195,196]. Previously reported findings are mixed as to whether increases in peak KFM are associated with knee OA progression[37,110]. However, a previous study showing comparable rises in peak KFM after 30-minutes of walking (0.04Nm/kg) in individuals with knee OA reported no immediate alterations in

cartilage thickness measures, suggesting that 30-minutes of walking might not surpass a loading threshold necessary to elicit a structural response[195].

Both the affected and contralateral knees in individuals with asymmetrical knee loading increased their knee flexion angles during initial contact through midstance, first peak KAM, KAMR, KFM, and SPROM, and reduced midstance KAM following 30-minutes of walking. Increases in peak KAM suggest a potentially deleterious effect of walking on knee health as greater first peak KAM has been linked with structural knee OA development and progression[33,37]. Similar increases in peak KAM and KFM following 30-minutes of walking have been found previously in knee OA; however, were not associated with acute changes in cartilage thickness[195], suggesting that a prescribed duration of 30-minutes may not exceed a possible loading threshold required for structural adaptations[195]. Complimentary studies are needed to investigate the interplay between loading magnitude (peak KAM, KFM), duration (impulse) and frequency (cumulative loading) for understanding the impacts of these gait adaptations on knee health.

Individuals with symmetrical and asymmetrical knee loading demonstrated small but opposite changes in TJM asymmetry following 30-minutes of walking. Individuals with symmetrical knee loading had an increase in their TJM asymmetry index (5% more asymmetric) in contrast to individuals with asymmetrical knee loading who decreased their TJM asymmetry index (2% more symmetric). These findings are the first evidence to our knowledge on the responsiveness of inter-limb asymmetry to prolonged walking, which complicates the interpretation of these index changes. However, average TJM asymmetry indices for individuals with symmetrical knee loading were still below the asymmetrical threshold used for group assignment (14%). Individuals with symmetrical knee loading

also had a 5% shift in the relative external knee moment contributions to the TJM in their contralateral knee, as the primary contribution to the TJM was reallocated from the KAM to the KFM following 30-minutes of walking. The interpretation of these findings is also challenging. No previous work to our knowledge has assessed contribution changes to the TJM after prolonged walking; however, the findings in Chapter 4 indicate that the KFM was the primary contributor to the TJM in asymptomatic individuals (Figure 4-3). These findings indicate a potential beneficial response to prolonged walking from a loading perspective, reallocating KAM contributions to KFM. The relative external knee moment contributions of the KAM, KFM and KRM to the TJM for individuals with asymmetrical knee loading changed minimally (<2%). How these TJM contributions influence clinical outcomes and disease progression in individuals with knee OA should be further explored to determine whether optimal proportions of KAM, KFM and KRM exist to predict joint health over time.

This is the first study to our knowledge to comprehensively examine changes in patient-reported and bilateral biomechanical characteristics following a 30-minute walking intervention in individuals with symmetrical or asymmetrical knee loading; however, study limitations should be acknowledged. TJM asymmetry indices in both groups varied in response to 30-minutes of walking (i.e., increase, decrease or no change), which may be associated with knee pain proposed to alter inter-limb asymmetries during walking. A larger participant sample would enable investigations of inter-limb asymmetry among responder subgroups (increase versus decrease symmetry) and its potential correlation with individualized pain responses. Kinetic data was only collected before and after 30-minutes of walking, which limits the ability to detect when the changes to TJM symmetry occurred.

Although the existing treadmill does not enable kinetic outputs, kinematic asymmetries, and the addition of electromyography to quantify inter-limb asymmetry at the muscle level, may augment the interpretations of this work and timing of biomechanical responses over 30-minutes.

6.5 Conclusion

Knee pain in individuals with symmetrical knee loading increased two-fold following 30-minutes of walking compared to individuals with asymmetrical knee loading. The affected knee in individuals with symmetrical knee loading had reduced midstance KAM compared to the contralateral knee following 30-minutes of walking. Both the affected and contralateral knees had had more dynamic frontal and sagittal plane joint moments. Whether the magnitude of these changes are clinically meaningful requires further testing; however, the biomechanical response for both limbs suggest that the duration of walking had minimal-to-no negative consequences on mobility. The affected and contralateral knees in individuals with asymmetrical knee loading had similar biomechanical responses following 30-minutes of walking, reflecting a more dynamic gait pattern bilaterally. Additionally, this group did not report a clinically meaningful increase in knee pain suggesting that 30-minutes of walking could be encouraged for individuals with asymmetrical knee loading. The varied symptomatic and biomechanical responsiveness of inter-limb asymmetry to 30-minutes of walking in individuals with symmetrical and asymmetrical knee loading highlight its potential utility as a novel outcome measure for future intervention studies in individuals with, or at risk for, bilateral knee OA.

Chapter 7: Discussion and Conclusions

7.1 Summary of Findings

The main objective of this thesis was to investigate inter-limb asymmetry quantified using features of dynamic knee loading previously associated with knee osteoarthritis (OA) onset and progression, and examine its clinical utility based on its relationships with clinical and biomechanical characteristics of knee OA and responsiveness to physical activity. This objective was achieved by conducting three studies to address the primary aims of this thesis. Chapter 4 examined differences in patient-reported outcomes and gait biomechanics between individuals with self-reported and clinically diagnosed knee OA, and assessed the prevalence and magnitude of knee loading asymmetry in these groups; Chapter 5 dichotomized individuals as having either symmetrical or asymmetrical knee loading to determine whether differences exist in patient-reported and biomechanical characteristics between groups; Chapter 6 evaluated the responsiveness of inter-limb asymmetry to prolonged walking, assessing patient-reported and gait biomechanical responses to 30-minutes of continuous walking in individuals with knee OA who were dichotomized as having either symmetrical or asymmetrical knee loading.

7.1.1 Summary of Chapter 4

Chapter 4 addressed the first objective of this thesis, which investigated differences in patient-reported outcomes and gait biomechanics between individuals with knee OA who were recruited to participate using either self-reported knee OA criteria or a conventional definition for clinically diagnosed knee OA. Chapter 4 contributed to the

overall purpose of this thesis by examining patient-reported and biomechanical differences in participants differentiated by their recruitment method, specifically examining how the prevalence and magnitude of total joint moment (TJM) asymmetry varied between groups. This project presented novel information regarding patient-reported outcomes and gait biomechanics associated with varied, yet generalizable, recruitment strategies.

The results from Chapter 4 indicate that the gait characteristics observed in individuals with self-reported knee OA were consistent with gait characteristics previously reported for individuals with more severe knee OA[42]. The affected knee in individuals with self-reported knee OA moved with reduced knee flexion angles from initial contact through midstance, first peak knee adduction moment (KAM), first peak knee adduction moment to midstance unloading range (KAMR) and peak knee flexion moment (KFM) compared to individuals with clinically diagnosed knee OA. The combination of reduced sagittal plane motions and less dynamic frontal plane loading have been linked to more severe stages of knee OA[42,237]. In contrast, individuals with clinically diagnosed knee OA walked with higher peak KAM and KFM and more dynamic frontal plane loading represented by KAMR. Interestingly, these biomechanical characteristics were not accompanied by differences in patient-reported outcomes between groups. Despite the biomechanical similarities between individuals with self-reported and severe knee OA, the patient-reported outcomes suggest that both recruitment groups were consistent with mild-to-moderate knee OA[196]. Further, the number of individuals dichotomized as having either symmetrical or asymmetrical knee loading were similar between groups, with no differences in TJM magnitude. Overall, the results support that approximately 50% of

individuals with knee OA, regardless of recruitment strategy, may be classified as having an asymmetrical knee loading pattern.

7.1.2 Summary of Chapter 5

Chapter 5 addressed the second objective of this thesis, which assessed the association between inter-limb asymmetry using features of dynamic knee joint loading previously associated with knee OA onset and progression, with patient-reported outcomes and gait biomechanics in individuals with knee OA. Chapter 5 extended the results of Chapter 4 and previous inter-limb asymmetry research in knee OA by dichotomizing individuals as having either symmetrical or asymmetrical knee loading at baseline and assessed whether differences in patient-reported outcomes or biomechanical characteristics existed. Chapter 5 contributes to the current understanding of inter-limb asymmetries in knee OA and helps to inform the interpretation of symmetrical gait patterns, which may not be reflective of physiologically healthy patterns in this population.

The results of Chapter 5 suggest that individuals with symmetrical knee loading have poorer perceived physical function compared to individuals with asymmetrical knee loading. There were minimal differences in affected knee biomechanics between groups; however, the contralateral knee in individuals with symmetrical knee loading had lower knee flexion angles from initial contact through midstance, KAMR, peak KFM, sagittal plane knee moment range (SPROM) and higher midstance KAM compared to the contralateral knee in individuals with asymmetrical knee loading. Further, the relative contributions of the KAM, KFM and knee rotation moment (KRM) to the TJM in the contralateral knee of individuals with symmetrical knee loading resembled previous

evidence for individuals with mild-to-moderate knee OA[190], compared to individuals with asymmetrical knee loading, whose relative contributions in the contralateral knee resembled previous evidence for asymptomatic individuals (Figure 4-3). Although biomechanical characteristics in the affected knee resembled previously reported patterns for individuals with knee OA in both participant groups, the contralateral knee revealed unique mechanical group differences (i.e., knee OA patterns in individuals with symmetrical loading and asymptomatic patterns in individuals with asymmetrical loading) that were likely primary contributors for dichotomizing symmetrical versus asymmetrical groups. Individuals with symmetrical knee loading may be reflective of individuals with, or at increased risk for, bilateral knee OA given the mechanical but not symptomatic differences; however, prospective investigations are required to test this hypothesis.

7.1.3 Summary of Chapter 6

Chapter 6 further developed the results of Chapter 5 and addressed the third objective of this thesis, which evaluated the responsiveness of inter-limb asymmetry over a 30-minute walking intervention, assessing patient-reported and biomechanical responses to 30-minutes of continuous walking in individuals with knee OA who were dichotomized as having either symmetrical or asymmetrical knee loading. The biomechanical responses of the affected and contralateral knees were quantified, as well as their interactive contributions with respect to symmetrical and asymmetrical gait patterns after 30-minutes of walking. Chapter 6 expanded on previous work examining inter-limb asymmetries in knee OA[50,51,63,198], and our understanding of how symmetrical versus asymmetrical subgroups of knee OA respond to a prolonged, submaximal walking intervention[55,195,196].

The findings from Chapter 6 suggest that knee pain in individuals with symmetrical knee loading increased two-fold over 30-minutes of walking compared to individuals with asymmetrical knee loading. Despite a clinically meaningful increase in pain, individuals with symmetrical knee loading experienced a minimal rise in their TJM asymmetry index (5% more asymmetric). In contrast, individuals with asymmetrical knee loading decreased their TJM asymmetry index (2% more symmetric). The affected knee in individuals with symmetrical knee loading had a reduced midstance KAM compared to the contralateral knee following the 30-minute walk, indicating increased medial compartment unloading. Both the affected and contralateral knees had significant increases in KAMR and SPROM following 30-minutes of walking, suggesting that this duration of physical activity had minimal-to-no negative biomechanical consequences on mobility in this subgroup. However, since pain worsened over 30-minutes of walking, individuals with symmetrical knee loading may benefit from shorter bouts of physical activity to achieve a balance between symptom management and physical activity health benefits. Individuals with asymmetrical knee loading did not demonstrate a clinically meaningful increase in affected knee pain following the 30-minute walking bout. Biomechanically, their affected and contralateral knees had similar increases in peak KAM, peak KFM, KAMR and SPROM, demonstrating that both the magnitude and dynamic features of loading increased bilaterally. Although increased peak loads may be deleterious to joint health[33,37,110], previous research reporting similar increases in peak KAM and KFM following 30-minutes of walking were not accompanied by acute changes in cartilage thickness[195]. These results suggest that this duration of walking may not exceed a possible loading threshold required for structural adaptations[195]. The minimal-to-no increases in pain, combined with more

dynamic knee loading, support that 30-minutes of moderate intensity walking is a tolerable duration of walking for individuals with knee OA and asymmetrical knee loading.

7.2 Implications and Clinical Significance

Knee OA is a multifactorial disease that is susceptible to mechanical, inflammatory and biological processes, influencing patient-reported outcomes and knee joint structure[73]. Shifts in current diagnostic practices for OA no longer reinforce radiographic evidence for diagnosis if typical disease symptoms and presentation exist[56–58]; however, minimal-to-no research has assessed patient-reported or biomechanical differences between individuals using self-reported knee OA criteria versus individuals clinically diagnosed using conventional radiographic-centric practices. Recently, authors have proposed that pain in the affected knee during walking may be associated with inter-limb asymmetries that overload the contralateral knee and possibly accelerate bilateral knee OA onset and progression[29,198]. Current physical activity guidelines recommend 150-minutes per week or 30-minutes per day of moderate-to-vigorous physical activity[52]; however, research has reported that only 13% of men and 8% of women with knee OA achieve these guidelines[53]. Evidence suggests that individuals with knee OA are likely to avoid physical activity due to pain, or fear or accelerating/worsening the disease[54], and the likelihood of meeting these guidelines is further reduced with increasing BMI[54]. This thesis demonstrated that individuals with symmetrical knee loading reported worse baseline patient-reported function (Chapter 5), higher BMI (Chapter 5) and knee pain increased two-fold following 30-minutes of walking (Chapter 6) compared to individuals with asymmetrical knee

loading which, regardless of how knee OA was defined (i.e., self-reported versus clinically diagnosed), represented approximately 50% of individuals with knee OA (Chapter 4).

Despite noted differences in gait biomechanics between individuals with self-reported versus clinically diagnosed knee OA, the distribution of individuals dichotomized as having symmetrical and asymmetrical knee loading was similar. Although patient-reported outcomes and the frequency of inter-limb asymmetry was consistent between groups, individuals with self-reported versus clinically diagnosed knee OA demonstrated biomechanical movement patterns during walking consistent with more severe knee OA[42]. Therefore, a self-reported recruitment strategy may yield individuals with more severe knee OA compared to individuals clinically diagnosed using conventional diagnostic methods. Previous research has proposed that community recruitment strategies may yield individuals with limited access to healthcare[11]. Importantly, healthcare access was not tested in this thesis; however, a lack of access may indirectly suggest that individuals have had a longer duration of disease exposure, and possibly progression, than individuals with clinically diagnosed knee OA. Future research to assess whether individuals with self-reported knee OA have a family physician or have sought out healthcare, and in what capacity, would complement the interpretation of the present findings. In summary, these results highlight that common paradigms for knee OA recruitment (i.e., clinically diagnosed) may yield a select subset of individuals in this case representing a less clinically severe group compared to the wider Canadian population with knee OA[258], potentially diminishing generalizability. This may be dependent upon the healthcare provider, where family doctors or tertiary care centres may yield individuals earlier in the disease process;

however, prolonged wait times for orthopaedic surgeons may lead to individuals further along the disease pathway.

Employing a community based, self-reported recruitment approach may provide a more comprehensive representation of the population affected by knee OA[11]. It has been reported that only 5% of Canadian health studies used a nationally representative sample when examining health data[10]. Proposed barriers for achieving representative data include limited access to healthcare or healthcare specialist[11]. Implementing a community recruitment strategy has been recommended as a potential solution[11] for improving the generalizability of findings and tailoring interventions to diverse patient needs. Caution is warranted, however, as the community recruitment strategy used in this thesis yielded individuals with walking patterns that reflected more severe knee OA (Chapter 4). Therefore, thoughtful consideration is necessary for future study recruitment, particularly when mixed methods are implemented.

Importantly, the recruitment strategy comparison between self-reported and clinically diagnosed individuals with knee OA in Chapter 4 likely yielded a total cohort of participants with knee OA across the disease continuum, which enabled the prevalence of inter-limb asymmetry to be quantified and evaluated. Symmetry analyses have been utilized for over five-decades to assess gait changes in several chronic conditions such as individuals post stroke[45] and Parkinson's disease[259]. Although symmetry analysis has been used to identify gait changes among pathological populations, research examining inter-limb asymmetry in individuals with knee OA has produced inconsistent results[50,51,63]. Mills and colleagues (2013)[50] found that the prevalence of asymmetry was more common in bilateral symptomatic disease, while Creaby and colleagues (2012)[51] found that individuals

with unilateral knee pain demonstrated inter-limb asymmetry. Further, Messier et al., (2016)[63] found that both individuals with unilateral and bilateral knee OA walked with similar magnitudes of inter-limb asymmetry[63]. This thesis revealed that approximately half of individuals with knee OA walk with either symmetrical or asymmetrical knee loading (Chapter 4), symmetrical knee loading in individuals with knee OA may represent bilateral biomechanical characteristics of knee OA (Chapter 5), and that minimal changes in TJM asymmetry were observed following 30-minutes of walking regardless of symmetrical or asymmetrical knee loading (Chapter 6). The majority of individuals with symmetrical knee loading reported worse physical function during activities of daily living (ADLs) such as ambulating stairs, rising from sitting, shopping, and heavy domestic duties (Chapter 5). There is a known discordance between patient-reported and objectively measured function[260], suggesting that the perceived functional disability during ADLs for individuals with symmetrical knee loading may be pain related. Therefore, baseline patient-reported physical function may help explain why individuals with symmetrical knee loading increased knee pain two-fold following 30-minutes of walking compared to individuals with asymmetrical knee loading (Chapter 6). This finding is consistent with previous research examining individuals with knee OA who experienced a pain flare during 20-minutes of walking and individuals who did not[55]. These cumulative results suggest that the existing perception that gait symmetry is advantageous for individuals with knee OA may not be fully supported by this thesis.

The overall results of this thesis also support that an inter-limb symmetry index may have clinical utility as a screening tool for identifying individuals who may be at risk for bilateral disease; however, further research is needed to better understand symmetry

analyses and develop clinically applicable strategies for its assessment. Currently, it is not known how, or whether, symmetry changes over the course of knee OA progression. Cappozzo (1982)[261] argued that all individuals adopt a locomotive strategy based upon the functional and structural constraints accompanied by a disease[261]. This theory is echoed by Solit (1962)[262] who proposed that every individual's gait represents the most efficient strategy of their own body and situation[262]. As mobility compensations are implemented by individuals with knee OA to minimize symptoms and optimize function, structural impairments consistent with the disease, including joint space narrowing, osteophyte formation, cartilage degradation, muscular impairments, synovitis or bone marrow lesions[74] are likely present. Once these structural manifestations take place, the affected knee may not achieve movement patterns consistent with a non-diseased knee, resulting in contralateral movement adaptations that suggest regression of the contralateral knee toward an OA functional state thus reflecting symmetrical knee loading. Whether inter-limb asymmetry can be altered through intervention has not been investigated. In this thesis, a 30-minute walking intervention did not elicit large inter-limb changes at the group-level for individuals with symmetrical or asymmetrical knee loading (Chapter 6); however, a subgroup of individuals did appear to demonstrate large TJM symmetry changes (>10%)[263] following the 30-minute walk (Figure 6-9). Research examining potential differences in responders (>10% symmetry change) and non-responders (<10% symmetry change) following 30-minutes of walking, and inter-limb asymmetries across disease severities may give further insights into the acute and longitudinal dynamic or static nature of symmetry within this population.

Research has reported that only 13% of men and 8% of women with knee OA achieve the guideline recommendations for physical activity[53]. In the latest 2019 guidelines by The American College of Rheumatology, strong recommendations encouraged researchers to establish a knowledge-base for physical activity prescription for individuals with knee OA[21]. Recommendations called for research to examine differences in activity duration, frequency and intensity, while taking disease severity into consideration[21]. Aligning with these recommendations, this thesis expanded on the current literature by investigating the effects of 30-minutes of continuous walking (Chapter 6), a universally recommended duration of walking[195], in individuals with knee OA who displayed unilateral (asymmetrical knee loading) and bilateral (symmetrical knee loading) biomechanical characteristics of the disease (Chapter 5), each representing approximately 50% of the sample population (Chapter 4).

Individuals with symmetrical knee loading reported increases in knee pain over 30-minutes of walking that exceeded a clinically meaningful threshold of 2-points on an 11-point numeric pain rating scale (NPRS)[256]. Despite increased pain, individuals with symmetrical knee loading did not display large changes in TJM asymmetry. Increased knee pain is a common physical activity deterrent among individuals with knee OA[54], suggesting that this duration of physical activity may not be sustainable for long-term physical activity adherence. Despite worse patient-reported function at baseline reported by individuals with symmetrical knee loading (Chapter 5), biomechanical outcomes following 30-minutes of walking represented a more dynamic loading pattern, suggesting that the duration of walking had minimal-to-no negative consequences on mobility (Chapter 6). Similarly, the increase in knee pain did not impact gait speed, suggesting that functional performance

neither improved nor worsened. Based on the results, a single 30-minute walking session doesn't appear to impact function in individuals with symmetrical knee loading; however, it did increase pain. Therefore, if individuals with knee OA and symmetrical knee loading have difficulty engaging in longer duration activity, recommendations could encourage shorter duration activity (10-15-minutes)[257] to gradually build the capacity for longer durations. This stepwise approach to physical activity aligns well with current best practice recommendations[264], and may help with physical activity adherence for individuals unable to achieve longer activity durations.

In contrast to individuals with knee OA and symmetrical knee loading, the 30-minute walk did not result in a clinically meaningful increase in pain for individuals with asymmetrical knee loading. However, both affected and contralateral knees had increases in peak loading magnitudes combined with a more dynamic loading pattern. Although increases in first peak KAM have been associated with increased risk for structural knee OA progression[33], previous research supports that similar increases in peak knee loads following 30-minutes of walking were not associated with acute changes in cartilage thickness[195], suggesting that the changes in loading magnitude experienced by individuals with asymmetrical knee loading were unlikely to simulate structural adaptations[195]. Despite better patient-reported function at baseline (Chapter 5) individuals with asymmetrical knee loading saw similar increases in objective functional performance (gait speed) compared to individuals with symmetrical knee loading after 30-minutes of walking. These results corroborate that 30-minutes of walking does not negatively influence objectively measured functional performance (gait speed), patient-reported symptoms (pain), biomechanical characteristics, or inter-limb asymmetry for individuals with asymmetrical knee loading.

Combined with existing literature on the benefits of physical activity[265–267], these findings support that 30-minutes should be encouraged for these individuals.

7.3 Research Limitations and Future Directions

Cross-sectional analyses have been instrumental in gaining knowledge surrounding differences between individuals with knee OA and asymptomatic individuals; however, only through longitudinal analyses can we fully appreciate the natural progression of the disease. In the context of asymmetry, while findings suggest distinct differences between individuals with symmetrical and asymmetrical knee loading, it was not possible to assess how these gait strategies developed. On average, asymptomatic individuals walked with symmetrical knee loading while individuals with knee OA were found to walk with asymmetrical knee loading (Chapter 4), suggesting that the proposed association between symmetry and physiologically healthy gait may not be entirely incorrect but rather that symmetrical walking patterns exist prior to knee OA development. Unilateral knee OA onset may then contribute to a breakdown of inter-limb symmetry resulting in asymmetrical walking patterns, which further suggests that inter-limb asymmetry may be a risk factor for disease onset in the contralateral knee as a component of the unilateral-bilateral knee OA continuum. A theoretical spectrum of inter-limb asymmetry the knee OA disease continuum is presented in (Figure 7-1). The presence of asymmetry based on spatial-temporal walking characteristics have been associated with a significant increase in the likelihood of contralateral TKA following unilateral TKA[199]. Biomechanically TKA has been shown to significantly reduce peak KAM values, which can be viewed as a beneficial outcome[268]; however, many other gait outcomes such as peak KFM, or initial

contact to peak knee flexion angles (ICPF) show minimal changes after surgery, or are in line with individuals with moderate knee OA[268]. Whether or not these individuals reverted back to symmetrical spatial-temporal variables once knee OA development occurred in the contralateral knee is unknown. Study designs to examine inter-limb asymmetries more comprehensively in individuals with unilateral and bilateral knee OA, as well as across knee OA severities may further clarify how, or if, an inter-limb symmetry-asymmetry continuum parallels knee OA disease progression.

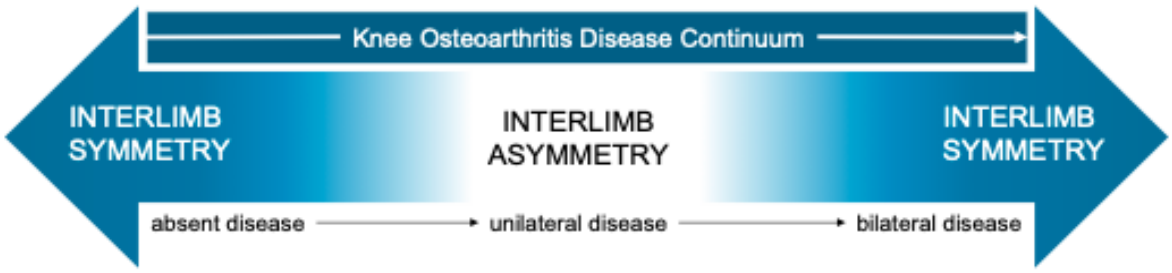


Figure 7-1: Theoretical spectrum of inter-limb asymmetry across the knee osteoarthritis disease continuum.

The results of this thesis preliminarily support the use of an inter-limb asymmetry index as a screening tool to assess potential knee OA severity or monitor responsiveness to interventions; however, the methodological needs for calculating symmetry prevent direct clinical implementation due to their limited access to the technologies employed in this thesis. One less technologically demanding method for measuring asymmetry during walking uses spatial-temporal parameters. These measures are readily available to clinicians through spatial-temporal gait mats, or inertial measurement units, and both have shown good-to-excellent reliability in assessing spatial-temporal parameters during gait

(ICC = 0.60-0.95)[269,270]. Thus, investigating spatial-temporal asymmetry could be used as a surrogate to the methodology used in this thesis and, offer clinicians readily available metrics that could be used to screen individuals more likely to progress to bilateral knee OA. Spatial-temporal asymmetry assessment has shown promise in identifying individuals with knee OA more at risk of contralateral TKA[199], with findings suggesting that every 1cm increase in step-length asymmetry (i.e., longer step length for the affected knee and shorter step length for the contralateral knee) increased the odds of contralateral TKA two-fold[199]. However, results from the Multicenter Osteoarthritis (MOST) Study demonstrated that elevated stance time asymmetry (i.e., more time spent on the contralateral limb) was associated with a decreased odds of contralateral knee pain over 2-years[198]. Further research examining whether inter-limb asymmetry thresholds for spatial-temporal variables are consistent with results from this thesis may give clinicians an easily accessible tool for monitoring individualized disease progression.

Overall, this thesis suggests that TJM asymmetry indices in individuals dichotomized as having either symmetrical or asymmetrical knee loading varied in response to 30-minutes of walking (i.e., increase, decrease or no change). Although the average TJM symmetry change does not appear clinically relevant, individuals with symmetrical knee loading increased their TJM asymmetry index (5% more asymmetric) in contrast to individuals with asymmetrical knee loading who decreased their TJM asymmetry index (2% more symmetric). However, the individual TJM responses to 30-minutes of walking in either group were varied, and distinct patterns emerged but were not tested in the current study (Figure 6-9). Previous research has calculated a minimal detectable change (MDC) cut-off of 10% for a Limb Symmetry Index[263], that was

calculated for a single leg hop as $\left(\frac{X_A}{X_c}\right) * 100$, where X_A represents the affected limb and X_c represents the contralateral limb. Applying this cut-off to the current participant sample, a total of 23 individuals with knee OA (53%) had a >10% change in TJM symmetry and 20 individuals (47%) had no change in TJM symmetry (<10% change) following 30-minutes of walking. Preliminary exploration of individualized inter-limb TJM responsiveness suggests likely differences in clinical (all KOOS and ICOAP measures) (Figure 7-2 & Figure 7-3) and functional (gait speed after 30-min walk) outcomes between individuals exceeding the MDC or not (Table 7-1). Integrating the biomechanical elements of this thesis into this proposed research direction remains to be explored. Additional responsiveness testing at the group- and individual-level is needed to further inform the utility of this symmetry metric and its role in OA mechanics. Further investigation into the static and dynamic nature of symmetry during walking may further help identify individuals demonstrating characteristics of increased knee OA severity, and further targeted rehabilitation and optimize patient outcomes.

Table 7-1: Participant demographics and clinical characteristics for individuals who demonstrated no change in symmetry versus those who changed symmetry after 30-minutes of walking (n=43)

	No Symmetry Change (n=23)	Symmetry Change (n=20)	Mean Difference (95%CI)
Age	60 ± 8	58 ± 12	2.00 [-4.27: 8.26]
Sex. no. of females (%)	14 (61)	8 (40)	-
Baseline Symmetric (%)	13 (56)	7 (35)	-
no. increased symmetry	-	13 (65)	-
TJM Asymmetry Before	31.6 ± 55.8	41.8 ± 32.4	-10.2 [-34.4: 20.7]
TJM Asymmetry After	31.0 ± 56.9	44.9 ± 34.7	-13.9 [-39.3: 17.0]
BMI, kg/m^2	30.5 ± 6.00	26.4 ± 7.32	4.12 [-0.04: 8.17]
Gait Speed Before, m/s	1.22 ± 0.17	1.32 ± 0.18	-0.10 [-0.21: 0.02]
Gait Speed After, m/s	1.24 ± 0.16	1.37 ± 0.22	**-0.13 [-0.24: -0.01]**
KOOS Total	59.4 ± 12.5	74.1 ± 10.9	**-14.6 [-21.9: -7.38]**
KOOS Symptoms	65.1 ± 11.8	75.1 ± 12.3	**-10.0 [-17.4: -2.54]**
KOOS Pain	61.6 ± 15.2	75.8 ± 13.3	**-14.3 [-23.1: -5.42]**
KOOS ADL	72.2 ± 14.2	86.4 ± 11.3	**-14.2 [-22.2: -6.24]**
KOOS Sport	40.4 ± 18.6	60.5 ± 22.5	**-20.1 [-32.7: -7.42]**
KOOS QoL	42.4 ± 15.2	57.8 ± 13.0	**-15.4 [-24.2: -6.65]**
ICOAP Total	70.7 ± 15.5	84.7 ± 13.4	**-14.0 [-23.0: -5.06]**
ICOAP Constant	76.1 ± 18.5	89.0 ± 14.5	**-12.9 [-23.3: -2.55]**
ICOAP Intermittent	66.1 ± 17.4	81.5 ± 15.1	**-15.3 [-25.4: -5.30]**

Note: Values are listed as mean and standard deviation unless otherwise indicated. TJM = total joint moment. KOOS = Knee Injury and Osteoarthritis Outcome Score. ADL = activities of daily living. QoL = Quality of life. ICOAP = Intermittent and Constant Osteoarthritis Pain. Mean differences are presented as no symmetry change minus symmetry change, where a positive value indicates that no symmetry change is greater than symmetry change, and a negative value indicates that symmetry change is greater than no symmetry change. Bolded values indicate significant between-group differences as the 95% CI does not cross zero.

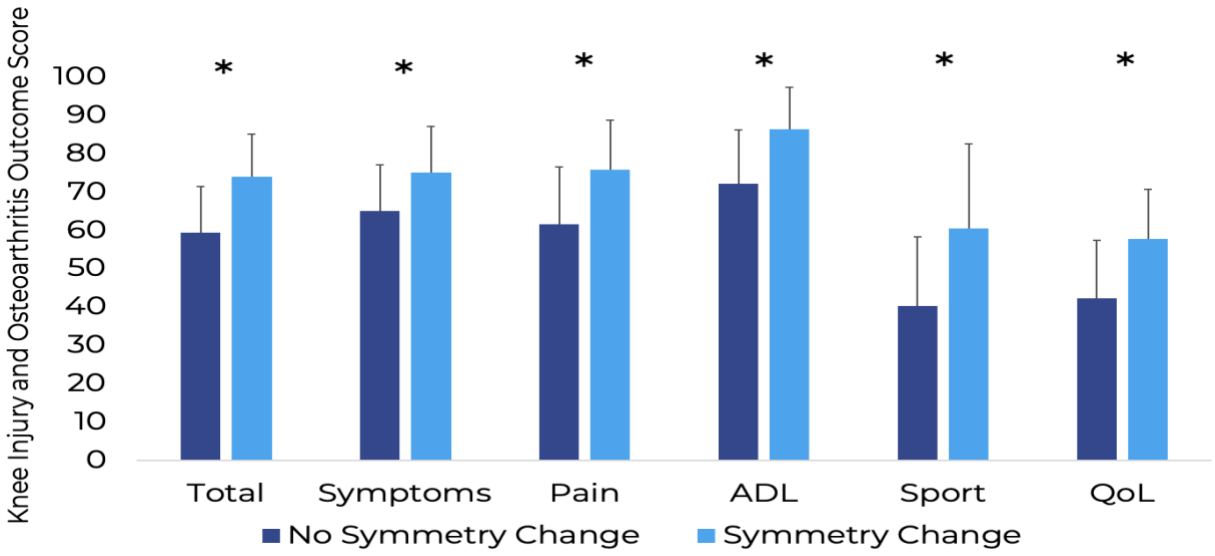


Figure 7-2: Means and standard deviations for total and subscale scores of the Knee Injury and Osteoarthritis Outcome Score for individuals with knee OA who demonstrated no change in TJM symmetry versus individuals who changed TJM symmetry after 30-minutes of walking. ADL = activities of daily living. QoL = quality of life. Asterisks (*) indicate significant between group differences ($p<0.05$).

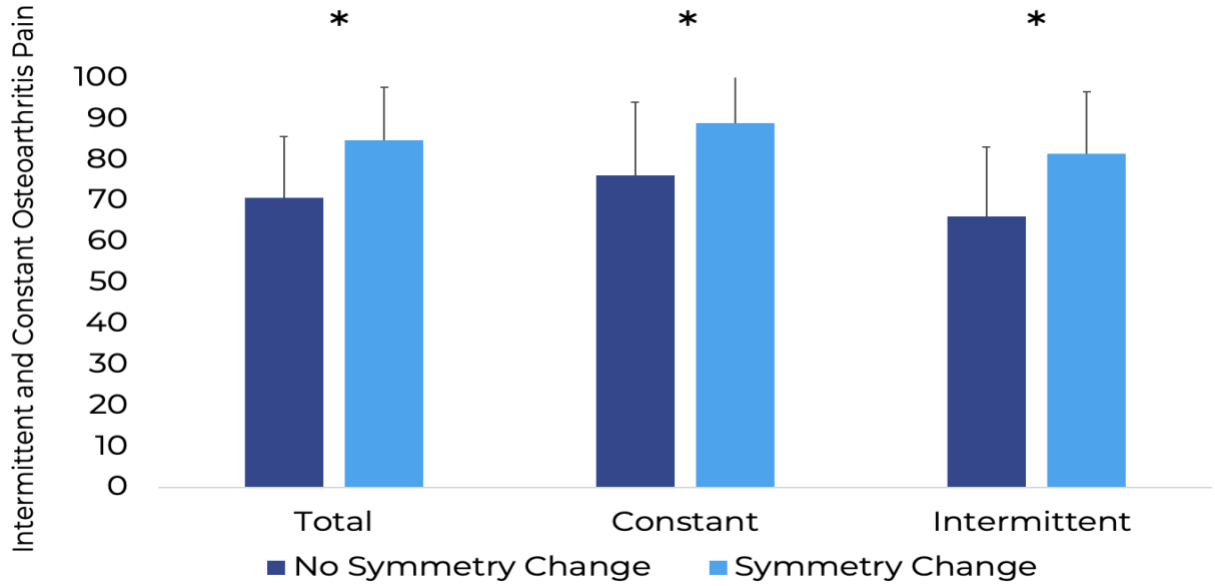


Figure 7-3: Means and standard deviations for total and subscale scores of the Intermittent and Constant Knee Osteoarthritis Pain Score for individuals with knee OA who demonstrated no change in TJM symmetry versus individuals who changed TJM symmetry after 30-minutes of walking. ADL = activities of daily living. QoL = quality of life. Asterisks (*) indicate significant between group differences ($p<0.05$).

Lastly, the results of Chapter 6 suggest that 30-minutes of continuous walking for individuals with symmetrical knee loading may lead to increased pain, and recommendations may suggest shorter bouts to either build capacity for longer duration activities or achieve the recommended 30-minute duration by using a multiple bout strategy. Limited research has investigated the impact of one continuous 45-minute walk versus multiple bouts of three 15-minute walks spaced one hour apart, showing promising results for symptom maintenance in knee OA[271]. Results demonstrated that once the accumulation of 30-minutes of walking was achieved (either continuously or through two 15-minute intervals), first peak knee contact forces were significantly increased; however, only continuous walking resulted in significant increases in pain[271]. Individuals with symmetrical knee loading in the current study reported a significant increase in pain from baseline to the first 10-minute interval; however, this was not a clinically meaningful increase (Chapter 6) and may still be a tolerable walking duration. Understanding whether accumulating the recommended daily physical activity in intervals of 10-15-minutes leads to an acute reduction in pain compared to 30-minutes of continuous walking for individuals with symmetrical knee loading may be beneficial to better understand how knee biomechanics and pain interact during shorter more frequent walking bouts. This information would help to elucidate realistic physical activity prescription for individuals who may not be able to walk continuously for longer durations without meaningful increases in pain.

7.4 Conclusion

The findings from this thesis indicate that community based, self-reported knee OA recruitment strategies may result in a biomechanically more severe knee OA sample compared to clinically diagnosed recruitment. Regardless of recruitment strategy, the prevalence of asymmetry was similar between groups, suggesting that approximately 50% of individuals with knee OA walk with symmetrical versus asymmetrical knee loading. This thesis provided promising evidence that symmetrical knee loading may align with bilateral knee OA as well as generated novel insights into contralateral knee OA development and progression. Mechanistically, the contralateral knee in individuals with symmetrical knee loading may have regressed to a functional state equivalent to that of the affected knee, and individuals with asymmetrical knee loading may benefit from earlier, targeted intervention for their contralateral knee to prevent functional decline and possibly disease onset. A single continuous 30-minute walking bout did not appear to negatively influence mobility regardless of symmetry status; however, undesirable pain responses may indicate that individuals with symmetrical knee loading could benefit from shorter bouts of walking. Clinically, a symmetry index may hold utility as a screening tool to assess potential knee OA severity or monitor responsiveness to interventions; however, further research assessing more clinically applicable tools are warranted. Research assessing symmetry across disease severities and investigating the severity of the contralateral knee are needed to help better interpret symmetry in this population.

References

1. Safiri S, Kolahi AA, Smith E, et al. Global, regional and national burden of osteoarthritis 1990-2017: a systematic analysis of the Global Burden of Disease Study 2017. *Ann Rheum Dis*. 2020;79(6):819-828. doi:10.1136/annrheumdis-2019-216515

2. Murray CJL, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet*. 2012;380(9859):2197-2223. doi:10.1016/S0140-6736(12)61689-4

3. Hunter DJ, Nevitt M, Losina E, Kraus V. Biomarkers for osteoarthritis: Current position and steps towards further validation. *Best Pract Res Clin Rheumatol*. 2014;28(1):61-71. doi:10.1016/j.berh.2014.01.007

4. 20111022_2200_impact_of_arthritis.pdf. Accessed June 10, 2022. https://www.arthritisalliance.ca/images/PDF/eng/Initiatives/20111022_2200_impact_of_arthritis.pdf

5. Hubertsson J, Petersson IF, Thorstensson CA, Englund M. Risk of sick leave and disability pension in working-age women and men with knee osteoarthritis. *Ann Rheum Dis*. 2013;72(3):401-405. doi:10.1136/annrheumdis-2012-201472

6. Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. *Nat Rev Rheumatol*. 2014;10(7):437-441. doi:10.1038/nrrheum.2014.44

7. Muchmore L, Lynch WD, Gardner HH, Williamson T, Burke T. Prevalence of arthritis and associated joint disorders in an employed population and the associated healthcare, sick leave, disability, and workers' compensation benefits cost and productivity loss for employers. *J Occup Environ Med*. 2003;45(4):369-378.

8. Bieleman HJ, Bierma-Zeinstra SMA, Oosterveld FGJ, Reneman MF, Verhagen AP, Groothoff JW. The effect of osteoarthritis of the hip or knee on work participation. *J Rheumatol*. 2011;38(9):1835-1843. doi:10.3899/jrheum.101210

9. Johnson VL, Hunter DJ. The epidemiology of osteoarthritis. *Best Pract Res Clin Rheumatol*. 2014;28(1):5-15. doi:10.1016/j.berh.2014.01.004

10. Khan M, Kobayashi K, Lee S, Vang Z. (In)visible minorities in canadian health data and research. *Popul Change Lifecourse Strateg Knowl Clust Discuss Pap Ser Un Réseau Strat Connaiss Chang Popul Parcours Vie Doc Trav*. 2015;3(1). https://ir.lib.uwo.ca/pclc/vol3/iss1/5

11. Le D, Almaw RD, Rinaldi D, et al. Barriers and strategies for recruiting participants who identify as racial minorities in musculoskeletal health research: a scoping review. *Front Public Health*. 2023;11. doi:10.3389/fpubh.2023.1211520

12. Egerton T, Lawford BJ, Campbell PK, et al. Expert-moderated peer-to-peer online support group for people with knee osteoarthritis: mixed methods randomized controlled pilot and feasibility study. *JMIR Form Res*. 2022;6(1):e32627. doi:10.2196/32627

13. Chen H, Zheng X, Huang H, Liu C, Wan Q, Shang S. The effects of a home-based exercise intervention on elderly patients with knee osteoarthritis: a quasi-experimental study. *BMC Musculoskelet Disord*. 2019;20(1):160. doi:10.1186/s12891-019-2521-4

14. Holden MA, Callaghan M, Felson D, et al. Clinical and cost-effectiveness of bracing in symptomatic knee osteoarthritis management: protocol for a multicentre, primary care, randomised, parallel-group, superiority trial. *BMJ Open*. 2021;11(3):e048196. doi:10.1136/bmjopen-2020-048196

15. Nelligan RK, Hinman RS, Kasza J, Bennell KL. Effectiveness of internet-delivered education and home exercise supported by behaviour change SMS on pain and function for people with knee osteoarthritis: a randomised controlled trial protocol. *BMC Musculoskelet Disord*. 2019;20(1):342. doi:10.1186/s12891-019-2714-x

16. Nelligan RK, Hinman RS, Teo PL, Bennell KL. Exploring attitudes and experiences of people with knee osteoarthritis toward a self-directed ehealth intervention to support exercise: qualitative study. *JMIR Rehabil Assist Technol*. 2020;7(2):e18860. doi:10.2196/18860

17. Nelligan RK, Hinman RS, McManus F, Lamb KE, Bennell KL. Moderators of the Effect of a Self-directed Digitally Delivered Exercise Program for People With Knee Osteoarthritis: Exploratory Analysis of a Randomized Controlled Trial. *J Med Internet Res*. 2021;23(10):e30768. doi:10.2196/30768

18. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis: Classification of osteoarthritis of the knee. *Arthritis Rheum*. 1986;29(8):1039-1049. doi:10.1002/art.1780290816

19. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage*. 2019;27(11):1578-1589. doi:10.1016/j.joca.2019.06.011

20. Moseng T, Vlieland TPMV, Battista S, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis: 2023 update. *Ann Rheum Dis*. Published online January 11, 2024. doi:10.1136/ard-2023-225041

21. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Rheumatol*. 2020;72(2):220-233. doi:10.1002/art.41142

22. van Doormaal MCM, Meerhoff GA, Vliet Vlieland TPM, Peter WF. A clinical practice guideline for physical therapy in patients with hip or knee osteoarthritis. *Musculoskeletal Care*. 2020;18(4):575-595. doi:10.1002/msc.1492

23. Gay C, Eschalier B, Levyckyj C, Bonnin A, Coudeyre E. Motivators for and barriers to physical activity in people with knee osteoarthritis: A qualitative study. *Joint Bone Spine*. 2018;85(4):481-486. doi:10.1016/j.jbspin.2017.07.007

24. Park E, Park HR, Choi ES. Barriers to and facilitators of physical activity among korean female adults with knee osteoarthritis and comorbidity: a qualitative study. *Healthcare*. 2020;8(3):226. doi:10.3390/healthcare8030226

25. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet Lond Engl*. 2019;393(10182):1745-1759. doi:10.1016/S0140-6736(19)30417-9

26. Astephen Wilson JL, Deluzio KJ, Dunbar MJ, Caldwell GE, Hubley-Kozey CL. The association between knee joint biomechanics and neuromuscular control and moderate knee osteoarthritis radiographic and pain severity. *Osteoarthritis Cartilage*. 2011;19(2):186-193. doi:10.1016/j.joca.2010.10.020

27. Rutherford DJ, Hubley-Kozey CL, Stanish WD. Changes in knee joint muscle activation patterns during walking associated with increased structural severity in knee osteoarthritis. *J Electromyogr Kinesiol*. 2013;23(3):704-711. doi:10.1016/j.jelekin.2013.01.003

28. Hubley-Kozey CL, Deluzio KJ, Landry SC, McNutt JS, Stanish WD. Neuromuscular alterations during walking in persons with moderate knee osteoarthritis. *J Electromyogr Kinesiol*. 2006;16(4):365-378. doi:10.1016/j.jelekin.2005.07.014

29. Andriacchi TP, Mündermann A, Smith RL, Alexander EJ, Dyrby CO, Koo S. A Framework for the in vivo pathomechanics of osteoarthritis at the knee. *Ann Biomed Eng*. 2004;32(3):447-457. doi:10.1023/B:ABME.0000017541.82498.37

30. Hurwitz DE, Sumner DR, Andriacchi TP, Sugar DA. Dynamic knee loads during gait predict proximal tibial bone distribution. *J Biomech*. 1998;31(5):423-430. doi:10.1016/S0021-9290(98)00028-1

31. Thorp LE, Wimmer MA, Block JA, et al. Bone mineral density in the proximal tibia varies as a function of static alignment and knee adduction angular momentum in individuals with medial knee osteoarthritis. *Bone*. 2006;39(5):1116-1122. doi:10.1016/j.bone.2006.05.001

32. Wada M, Maezawa Y, Baba H, Shimada S, Sasaki S, Nose Y. Relationships among bone mineral densities, static alignment and dynamic load in patients with medial compartment knee osteoarthritis. *Rheumatology*. 2001;40(5):499-505. doi:10.1093/rheumatology/40.5.499

33. D'Souza N, Charlton J, Grayson J, 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 Cartilage*. 2022;30(3):381-394. doi:10.1016/j.joca.2021.10.010

34. Maly MR, Acker SM, Totterman S, et al. Knee adduction moment relates to medial femoral and tibial cartilage morphology in clinical knee osteoarthritis. *J Biomech*. 2015;48(12):3495-3501. doi:10.1016/j.jbiomech.2015.04.039

35. Teoli A, Cloutier-Gendron M, Ho SYK, et al. The relationship between knee loading during gait and cartilage thickness in nontraumatic and posttraumatic knee osteoarthritis. *J Orthop Res Off Publ Orthop Res Soc*. Published online November 18, 2021. doi:10.1002/jor.25219

36. Brisson NM, Wiebenga EG, Stratford PW, 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. *J Orthop Res Off Publ Orthop Res Soc*. 2017;35(11):2476-2483. doi:10.1002/jor.23564

37. Chang AH, Moisio KC, Chmiel JS, et al. External knee adduction and flexion moments during gait and medial tibiofemoral disease progression in knee osteoarthritis. *Osteoarthritis Cartilage*. 2015;23(7):1099-1106. doi:10.1016/j.joca.2015.02.005

38. Bennell KL, Creaby MW, Wrigley TV, et al. Bone marrow lesions are related to dynamic knee loading in medial knee osteoarthritis. *Ann Rheum Dis*. 2010;69(6):1151-1154. doi:10.1136/ard.2009.118182

39. Hatfield GL, Stanish WD, Hubley-Kozey CL. Three-dimensional biomechanical gait characteristics at baseline are associated with progression to total knee arthroplasty. *Arthritis Care Res*. 2015;67(7):1004-1014. doi:10.1002/acr.22564

40. Rutherford D, Baker M, Wong I, Stanish W. The effect of age and knee osteoarthritis on muscle activation patterns and knee joint biomechanics during dual belt treadmill gait. *J Electromyogr Kinesiol*. 2017;34:58-64. doi:10.1016/j.jelekin.2017.04.001

41. Favre J, Jolles BM. Gait analysis of patients with knee osteoarthritis highlights a pathological mechanical pathway and provides a basis for therapeutic interventions. *EFORT Open Rev*. 2016;1(10):368-374. doi:10.1302/2058-5241.1.000051

42. 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. *J Orthop Res*. 2008;26(3):332-341. doi:10.1002/jor.20496

43. Siebers HL, Alrawashdeh W, Betsch M, Migliorini F, Hildebrand F, Eschweiler J. Comparison of different symmetry indices for the quantification of dynamic joint angles. *BMC Sports Sci Med Rehabil*. 2021;13(1):130. doi:10.1186/s13102-021-00355-4

44. Alrawashdeh W, Siebers HL, Reim J, Rath B, Tingart M, Eschweiler J. Gait symmetry - A valid parameter for pre and post planning for total knee arthroplasty. *J Musculoskelet Neuronal Interact*. 2022;22(1):102-112.

45. Patterson KK, Gage WH, Brooks D, Black SE, McIlroy WE. Evaluation of gait symmetry after stroke: A comparison of current methods and recommendations for standardization. *Gait Posture*. 2010;31(2):241-246. doi:10.1016/j.gaitpost.2009.10.014

46. Huang X, Mahoney JM, Lewis MM, Guangwei Du, Piazza SJ, Cusumano JP. Both coordination and symmetry of arm swing are reduced in Parkinson's disease. *Gait Posture*. 2012;35(3):373-377. doi:10.1016/j.gaitpost.2011.10.180

47. Collins AT, Richardson RT, Higginson JS. Interlimb symmetry of dynamic knee joint stiffness and co-contraction is maintained in early stage knee osteoarthritis. *J Electromyogr Kinesiol*. 2014;24(4):497-501. doi:10.1016/j.jelekin.2014.03.010

48. Zeni J, Snyder-Mackler L. Baseline differences between individuals who did and did not have contralateral symptomatic OA progression after TKA. *Osteoarthritis Cartilage*. 2016;24:S103. doi:10.1016/j.joca.2016.01.209

49. Aljehani MS, Christensen JC, Snyder-Mackler L, Crenshaw J, Brown A, Zeni JA. Knee biomechanics and contralateral knee osteoarthritis progression after total knee arthroplasty. *Gait Posture*. 2022;91:266-275. doi:10.1016/j.gaitpost.2021.10.020

50. Mills K, Hettinga BA, Pohl MB, Ferber R. Between-limb kinematic asymmetry during gait in unilateral and bilateral mild to moderate knee osteoarthritis. *Arch Phys Med Rehabil*. 2013;94(11):2241-2247. doi:10.1016/j.apmr.2013.05.010

51. Creaby MW, Bennell KL, Hunt MA. Gait differs between unilateral and bilateral knee osteoarthritis. *Arch Phys Med Rehabil*. 2012;93(5):822-827. doi:10.1016/j.apmr.2011.11.029

52. Adults 18-64 – 24-Hour Movement Guidelines. Accessed August 8, 2022. https://csepguidelines.ca/guidelines/adults-18-64/

53. Dunlop DD, Song J, Semanik PA, et al. Objective physical activity measurement in the osteoarthritis initiative: Are guidelines being met? *Arthritis Rheum*. 2011;63(11):3372-3382. doi:10.1002/art.30562

54. Kanavaki AM, Rushton A, Efstathiou N, 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. doi:10.1136/bmjopen-2017-017042

55. Boyer KA, Hafer JF. Gait mechanics contribute to exercise induced pain flares in knee osteoarthritis. *BMC Musculoskelet Disord*. 2019;20(1):107. doi:10.1186/s12891-019-2493-4

56. Osteoarthritis Symptoms and Diagnosis. Accessed June 13, 2022. https://arthritis.ca/about-arthritis/arthritis-types-(a-z)/types/osteoarthritis/osteoarthritis-symptoms-and-diagnosis

57. Osteoarthritis: Care for adults with osteoarthritis of the knee, Hip, or Hand. :63.

58. OATOOL_FINAL_Sept14_ENG.pdf. Accessed June 13, 2022. https://www.cfpc.ca/CFPC/media/Resources/Education/OATOOL_FINAL_Sept14_ENG.pdf

59. Arden NK, Perry TA, Bannuru RR, et al. Non-surgical management of knee osteoarthritis: comparison of ESCEO and OARSI 2019 guidelines. *Nat Rev Rheumatol*. 2021;17(1):59-66. doi:10.1038/s41584-020-00523-9

60. Katz JN, Arant KR, Loeser RF. Diagnosis and treatment of hip and knee osteoarthritis: a review. *JAMA*. 2021;325(6):568-578. doi:10.1001/jama.2020.22171

61. Iijima H, Inoue M, Suzuki Y, et al. Contralateral limb effect on gait asymmetry and ipsilateral pain in a patient with knee osteoarthritis: a proof-of-concept case report. *JBJS Case Connect*. 2020;10(1):e0418. doi:10.2106/JBJS.CC.19.00418

62. Iijima H, Eguchi R, Aoyama T, Takahashi M. Trunk movement asymmetry associated with pain, disability, and quadriceps strength asymmetry in individuals with knee osteoarthritis: a cross-sectional study. *Osteoarthritis Cartilage*. 2019;27(2):248-256. doi:10.1016/j.joca.2018.10.012

63. Messier SP, Beavers DP, Herman C, Hunter DJ, DeVita P. Are unilateral and bilateral knee osteoarthritis patients unique subsets of knee osteoarthritis? A biomechanical perspective. *Osteoarthritis Cartilage*. 2016;24(5):807-813. doi:10.1016/j.joca.2015.12.005

64. Bull FC, Al-Ansari SS, Biddle S, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med*. 2020;54(24):1451-1462. doi:10.1136/bjsports-2020-102955

65. Allen KD, Woolson S, Hoenig HM, et al. Stepped Exercise Program for Patients With Knee Osteoarthritis. *Ann Intern Med*. 2021;174(3):298-307. doi:10.7326/M20-4447

66. Sliepen M, Mauricio E, Lipperts M, Grimm B, Rosenbaum D. Objective assessment of physical activity and sedentary behaviour in knee osteoarthritis patients – beyond daily steps and total sedentary time. *BMC Musculoskelet Disord*. 2018;19(1):64. doi:10.1186/s12891-018-1980-3

67. Song J, Dunlop DD, Semanik PA, et al. Reallocating time spent in sleep, sedentary behavior and physical activity and its association with pain: a pilot sleep study from the Osteoarthritis Initiative. *Osteoarthritis Cartilage*. 2018;26(12):1595-1603. doi:10.1016/j.joca.2018.07.002

68. Kassebaum NJ, Arora M, Barber RM, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*. 2016;388(10053):1603-1658. doi:10.1016/S0140-6736(16)31460-X

69. Ackerman IN, Kemp JL, Crossley KM, Culvenor AG, Hinman RS. Hip and knee osteoarthritis affects younger people, too. *J Orthop Sports Phys Ther*. 2017;47(2):67-79. doi:10.2519/jospt.2017.7286

70. Hawker GA. Osteoarthritis is a serious disease. *Clin Exp Rheumatol*. 2019;37 Suppl 120(5):3-6.

71. Hawker GA, King LK. The Burden of Osteoarthritis in Older Adults. *Clin Geriatr Med*. 2022;38(2):181-192. doi:10.1016/j.cger.2021.11.005

72. Hunter DJ, March L, Chew M. Osteoarthritis in 2020 and beyond: a Lancet Commission. *Lancet Lond Engl*. 2020;396(10264):1711-1712. doi:10.1016/S0140-6736(20)32230-3

73. Kraus VB, Blanco FJ, Englund M, Karsdal MA, Lohmander LS. Call for standardized definitions of osteoarthritis and risk stratification for clinical trials and clinical use. *Osteoarthritis Cartilage*. 2015;23(8):1233-1241. doi:10.1016/j.joca.2015.03.036

74. Poole AR. Osteoarthritis as a whole joint disease. *HSS J Musculoskelet J Hosp Spec Surg*. 2012;8(1):4-6. doi:10.1007/s11420-011-9248-6

75. Lane NE, Brandt K, Hawker G, et al. OARSI-FDA initiative: defining the disease state of osteoarthritis. *Osteoarthritis Cartilage*. 2011;19(5):478-482. doi:10.1016/j.joca.2010.09.013

76. Kellgren JH, Lawrence JS. Radiological Assessment of Osteo-Arthrosis. *Ann Rheum Dis*. 1957;16(4):494-502.

77. Eckstein F, Collins JE, Nevitt MC, et al. Cartilage thickness change as an imaging biomarker of knee osteoarthritis progression – data from the finish OA biomarkers consortium. *Arthritis Rheumatol Hoboken NJ*. 2015;67(12):3184-3189. doi:10.1002/art.39324

78. Liem Y, Judge A, Li Y, Sharif M. Biochemical, clinical, demographic and imaging biomarkers for disease progression in knee osteoarthritis. *Biomark Med*. 2022;16(8):633-645. doi:10.2217/bmm-2021-0579

79. Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: A systematic search and summary of the literature. *BMC Musculoskelet Disord*. 2008;9(1):116. doi:10.1186/1471-2474-9-116

80. Creamer P. Osteoarthritis pain and its treatment. *Curr Opin Rheumatol*. 2000;12(5):450-455.

81. DiBonaventura M daCosta, Gupta S, McDonald M, Sadosky A, Pettitt D, Silverman S. Impact of self-rated osteoarthritis severity in an employed population: Cross-sectional analysis of data from the national health and wellness survey. *Health Qual Life Outcomes*. 2012;10(1):30. doi:10.1186/1477-7525-10-30

82. Sharif B, Kopec J, Bansback N, et al. Projecting the direct cost burden of osteoarthritis in Canada using a microsimulation model. *Osteoarthritis Cartilage*. 2015;23(10):1654-1663. doi:10.1016/j.joca.2015.05.029

83. Wharton S, Lau DCW, Vallis M, et al. Obesity in adults: a clinical practice guideline. *CMAJ*. 2020;192(31):E875-E891. doi:10.1503/cmaj.191707

84. Explore wait times for priority procedures across Canada | CIHI. Accessed March 25, 2024. https://www.cihi.ca/en/explore-wait-times-for-priority-procedures-across-canada

85. Li M, Nie Y, Zeng Y, et al. The trajectories of depression symptoms and comorbidity in knee osteoarthritis subjects. *Clin Rheumatol*. 2022;41(1):235-243. doi:10.1007/s10067-021-05847-9

86. Menon J, Mishra P. Health care resource use, health care expenditures and absenteeism costs associated with osteoarthritis in US healthcare system. *Osteoarthritis Cartilage*. 2018;26(4):480-484. doi:10.1016/j.joca.2017.12.007

87. Puig-Junoy J, Ruiz Zamora A. Socio-economic costs of osteoarthritis: A systematic review of cost-of-illness studies. *Semin Arthritis Rheum*. 2015;44(5):531-541. doi:10.1016/j.semarthrit.2014.10.012

88. Pencharz JN, MacLean CH. Measuring quality in arthritis care: The Arthritis Foundation's Quality Indicator set for osteoarthritis. *Arthritis Care Res*. 2004;51(4):538-548. doi:10.1002/art.20521

89. Mazzei DR, Ademola A, Abbott JH, Sajobi T, Hildebrand K, Marshall DA. Are education, exercise and diet interventions a cost-effective treatment to manage hip and knee osteoarthritis? A systematic review. *Osteoarthritis Cartilage*. 2021;29(4):456-470. doi:10.1016/j.joca.2020.10.002

90. Li LC, Sayre EC, Kopec JA, Esdaile JM, Bar S, Cibere J. Quality of nonpharmacological care in the community for people with knee and hip osteoarthritis. *J Rheumatol*. 2011;38(10):2230-2237. doi:10.3899/jrheum.110264

91. Turner MN, Hernandez DO, Cade W, Emerson CP, Reynolds JM, Best TM. The role of resistance training dosing on pain and physical function in individuals with knee osteoarthritis: a systematic review. *Sports Health*. 2020;12(2):200-206. doi:10.1177/1941738119887183

92. Park HM, Kim HS, Lee YJ. Knee osteoarthritis and its association with mental health and health-related quality of life: A nationwide cross-sectional study. *Geriatr Gerontol Int*. 2020;20(4):379-383. doi:10.1111/ggi.13879

93. Siviero P, Veronese N, Smith T, et al. Association between osteoarthritis and social isolation: data from the eposa study. *J Am Geriatr Soc*. 2020;68(1):87-95. doi:10.1111/jgs.16159

94. International Classification of Functioning, Disability and Health (ICF). Accessed June 10, 2022. https://www.who.int/standards/classifications/international-classification-of-functioning-disability-and-health

95. Wallace IJ, Worthington S, Felson DT, et al. Knee osteoarthritis has doubled in prevalence since the mid-20th century. *Proc Natl Acad Sci U S A*. 2017;114(35):9332-9336. doi:10.1073/pnas.1703856114

96. Prince SA, Melvin A, Roberts KC, Butler GP, Thompson W. Sedentary behaviour surveillance in Canada: trends, challenges and lessons learned. *Int J Behav Nutr Phys Act*. 2020;17(1):34. doi:10.1186/s12966-020-00925-8

97. Obesity in rural and urban Canada - Data Blog - Public Health Infobase | Public Health Agency of Canada. Accessed June 10, 2022. https://health-infobase.canada.ca/datalab/canadian-risk-factor-atlas-obesity-blog.html?=undefined&wbdisable=true

98. Vongsirinavarat M, Nilmart P, Somprasong S, Apinonkul B. Identification of knee osteoarthritis disability phenotypes regarding activity limitation: a cluster analysis. *BMC Musculoskelet Disord*. 2020;21(1):237. doi:10.1186/s12891-020-03260-y

99. King LK, Kendzerska T, Waugh EJ, Hawker GA. Impact of osteoarthritis on difficulty walking: a population-based study. *Arthritis Care Res*. 2018;70(1):71-79. doi:10.1002/acr.23250

100. Langlois JA, Keyl PM, Guralnik JM, Foley DJ, Marottoli RA, Wallace RB. Characteristics of older pedestrians who have difficulty crossing the street. *Am J Public Health*. 1997;87(3):393-397. doi:10.2105/AJPH.87.3.393

101. Andrews AW, Chinworth SA, Bourassa M, Garvin M, Benton D, Tanner S. Update on distance and velocity requirements for community ambulation. *J Geriatr Phys Ther*. 2010;33(3):128-134. doi:10.1097/JPT.0b013e3181eda321

102. Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. *JAMA*. 2011;305(1):50-58. doi:10.1001/jama.2010.1923

103. Ornetti P, Maillefert JF, Laroche D, Morisset C, Dougados M, Gossec L. Gait analysis as a quantifiable outcome measure in hip or knee osteoarthritis: A systematic review. *Joint Bone Spine*. 2010;77(5):421-425. doi:10.1016/j.jbspin.2009.12.009

104. Adults 18-64 – 24-Hour Movement Guidelines. Accessed June 13, 2022. https://csepguidelines.ca/guidelines/adults-18-64/

105. Fernandopulle S, Perry M, Manlapaz D, Jayakaran P. Effect of land-based generic physical activity interventions on pain, physical function, and physical performance in hip and knee osteoarthritis: a systematic review and meta-analysis. *Am J Phys Med Rehabil*. 2017;96(11):773-792. doi:10.1097/PHM.0000000000000736

106. Chmelo E, Nicklas B, Davis C, Miller GD, Legault C, Messier S. Physical activity and physical function in older adults with knee osteoarthritis. *J Phys Act Health*. 2013;10(6):777-783.

107. Zampogna B, Papalia R, Papalia GF, et al. The role of physical activity as conservative treatment for hip and knee osteoarthritis in older people: a systematic review and meta-analysis. *J Clin Med*. 2020;9(4):1167. doi:10.3390/jcm9041167

108. White DK, Lee J, Song J, Chang RW, Dunlop D. Potential functional benefit from light intensity physical activity in knee osteoarthritis. *Am J Prev Med*. 2017;53(5):689-696. doi:10.1016/j.amepre.2017.07.008

109. Hawke LJ, Taylor NF, Dowsey MM, Choong PFM, Shields N. In the dark about physical activity – exploring patient perceptions of physical activity after elective total knee joint replacement: a qualitative study. *Arthritis Care Res*. 2022;74(6):965-974. doi:10.1002/acr.24718

110. 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 Cartilage*. 2014;22(11):1833-1839. doi:10.1016/j.joca.2014.08.009

111. Hubley-Kozey CL, Costello KE, Hatfield GL, Astephen-Wilson J, Stanish WD. Baseline three-dimensional knee joint biomechanics and muscle activation patterns differ between those with moderate OA who have radiographic progression versus those who do not. *Osteoarthritis Cartilage*. 2014;22:S83. doi:10.1016/j.joca.2014.02.165

112. Hodges PW, van den Hoorn W, Wrigley TV, et al. Increased duration of co-contraction of medial knee muscles is associated with greater progression of knee osteoarthritis. *Man Ther*. 2016;21:151-158. doi:10.1016/j.math.2015.07.004

113. Kohn MD, Sassoon AA, Fernando ND. Classifications in brief: Kellgren-Lawrence classification of osteoarthritis. *Clin Orthop Relat Res*. 2016;474(8):1886-1893. doi:10.1007/s11999-016-4732-4

114. Culvenor AG, Engen CN, Øiestad BE, Engebretsen L, Risberg MA. Defining the presence of radiographic knee osteoarthritis: a comparison between the Kellgren and Lawrence system and OARSI atlas criteria. *Knee Surg Sports Traumatol Arthrosc*. 2015;23(12):3532-3539. doi:10.1007/s00167-014-3205-0

115. Joo PY, Borjali A, Chen AF, Muratoglu OK, Varadarajan KM. Defining and predicting radiographic knee osteoarthritis progression: a systematic review of findings from the osteoarthritis initiative. *Knee Surg Sports Traumatol Arthrosc*. Published online February 3, 2022. doi:10.1007/s00167-021-06768-5

116. Wright RW, Ross JR, Haas AK, et al. Osteoarthritis classification scales: interobserver reliability and arthroscopic correlation. *J Bone Joint Surg Am*. 2014;96(14):1145-1151. doi:10.2106/JBJS.M.00929

117. Scott WW, Lethbridge-Cejku M, Reichle R, Wigley FM, Tobin JD, Hochberg MC. Reliability of grading scales for individual radiographic features of osteoarthritis of the knee. The Baltimore longitudinal study of aging atlas of knee osteoarthritis. *Invest Radiol*. 1993;28(6):497-501.

118. Kinds MB, Welsing PMJ, Vignon EP, et al. A systematic review of the association between radiographic and clinical osteoarthritis of hip and knee. *Osteoarthritis Cartilage*. 2011;19(7):768-778. doi:10.1016/j.joca.2011.01.015

119. Ribeiro IC, Coimbra AMV, Costallat BL, Coimbra IB. Relationship between radiological severity and physical and mental health in elderly individuals with knee osteoarthritis. *Arthritis Res Ther*. 2020;22(1):187. doi:10.1186/s13075-020-02280-2

120. Davis EM, Hubley-Kozey CL, Landry SC, Ikeda DM, Stanish WD, Astephen Wilson JL. Longitudinal evidence links joint level mechanics and muscle activation patterns to 3-year medial joint space narrowing. *Clin Biomech*. 2019;61:233-239. doi:10.1016/j.clinbiomech.2018.12.016

121. Hunter DJ, Altman RD, Cicuttini F, et al. OARSI Clinical Trials Recommendations: Knee imaging in clinical trials in osteoarthritis. *Osteoarthritis Cartilage*. 2015;23(5):698-715. doi:10.1016/j.joca.2015.03.012

122. Hawker GA, Badley EM, Borkhoff CM, et al. Which patients are most likely to benefit from total joint arthroplasty? *Arthritis Rheum*. 2013;65(5):1243-1252. doi:10.1002/art.37901

123. Hunter DJ, Zhang YQ, Tu X, et al. Change in joint space width: Hyaline articular cartilage loss or alteration in meniscus? *Arthritis Rheum*. 2006;54(8):2488-2495. doi:10.1002/art.22016

124. Adams JG, McaLindon T, Dimasi M, Carey J, Eustace S. Contribution of meniscal extrusion and cartilage loss to joint space narrowing in osteoarthritis. *Clin Radiol*. 1999;54(8):502-506. doi:10.1016/S0009-9260(99)90846-2

125. Peterfy C, Woodworth T, Altman R. Workshop for Consensus on Osteoarthritis Imaging: MRI of the knee. *Osteoarthritis Cartilage*. 2006;14:44-45. doi:10.1016/j.joca.2006.02.025

126. Mosher TJ, Dardzinski BJ. Cartilage mri t2 relaxation time mapping: overview and applications. *Semin Musculoskelet Radiol*. 2004;08(04):355-368. doi:10.1055/s-2004-861764

127. Oo WM, Linklater JM, Hunter DJ. Imaging in knee osteoarthritis. *Curr Opin Rheumatol*. 2017;29(1):86-95. doi:10.1097/BOR.0000000000000350

128. Taylor C, Carballido-Gamio J, Majumdar S, Li X. Comparison of quantitative imaging of cartilage for osteoarthritis: T2, T1ρ, dGEMRIC and contrast-enhanced computed tomography. *Magn Reson Imaging*. 2009;27(6):779-784. doi:10.1016/j.mri.2009.01.016

129. Crema MD, Roemer FW, Marra MD, et al. Articular cartilage in the knee: current MRI imaging techniques and applications in clinical practice and research. *Radiographics*. 2011;31(1):37-61. doi:10.1148/rg.311105084

130. Liess C, Lüsse S, Karger N, Heller M, Glüer CC. Detection of changes in cartilage water content using MRI T2-mapping in vivo. *Osteoarthritis Cartilage*. 2002;10(12):907-913. doi:10.1053/joca.2002.0847

131. Pan J, Pialat JB, Joseph T, et al. Knee Cartilage T2 Characteristics and Evolution in Relation to Morphologic Abnormalities Detected at 3-T MR Imaging: A Longitudinal Study of the Normal Control Cohort from the Osteoarthritis Initiative. *Radiology*. 2011;261(2):507-515. doi:10.1148/radiol.11102234

132. Baum T, Joseph GB, Karampinos DC, Jungmann PM, Link TM, Bauer JS. Cartilage and meniscal T2 relaxation time as non-invasive biomarker for knee osteoarthritis and cartilage repair procedures. *Osteoarthritis Cartilage*. 2013;21(10):1474-1484. doi:10.1016/j.joca.2013.07.012

133. Li X, Benjamin Ma C, Link TM, et al. In vivo T1ρ and T2 mapping of articular cartilage in osteoarthritis of the knee using 3T MRI. *Osteoarthritis Cartilage*. 2007;15(7):789-797. doi:10.1016/j.joca.2007.01.011

134. MacKay JW, Low SBL, Smith TO, Toms AP, McCaskie AW, Gilbert FJ. Systematic review and meta-analysis of the reliability and discriminative validity of cartilage compositional MRI in knee osteoarthritis. *Osteoarthritis Cartilage*. 2018;26(9):1140-1152. doi:10.1016/j.joca.2017.11.018

135. Hunter DJ, Guermazi A, Lo GH, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). *Osteoarthritis Cartilage*. 2011;19(8):990-1002. doi:10.1016/j.joca.2011.05.004

136. Peterfy CG, Guermazi A, Zaim S, et al. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. *Osteoarthritis Cartilage*. 2004;12(3):177-190. doi:10.1016/j.joca.2003.11.003

137. Lynch JA, Roemer FW, Nevitt MC, et al. Comparison of BLOKS and WORMS scoring systems part I. Cross sectional comparison of methods to assess cartilage morphology, meniscal damage and bone marrow lesions on knee MRI: data from the osteoarthritis initiative. *Osteoarthritis Cartilage*. 2010;18(11):1393-1401. doi:10.1016/j.joca.2010.08.017

138. Hunter DJ, Lo GH, Gale D, Grainger AJ, Guermazi A, Conaghan PG. The reliability of a new scoring system for knee osteoarthritis MRI and the validity of bone marrow lesion assessment: BLOKS (Boston–Leeds Osteoarthritis Knee Score). *Ann Rheum Dis*. 2008;67(2):206-211. doi:10.1136/ard.2006.066183

139. Sakellariou G, Conaghan PG, Zhang W, et al. EULAR recommendations for the use of imaging in the clinical management of peripheral joint osteoarthritis. *Ann Rheum Dis*. 2017;76(9):1484-1494. doi:10.1136/annrheumdis-2016-210815

140. McAlindon TE, Driban JB, Henrotin Y, et al. OARSI Clinical Trials Recommendations: Design, conduct, and reporting of clinical trials for knee osteoarthritis. *Osteoarthritis Cartilage*. 2015;23(5):747-760. doi:10.1016/j.joca.2015.03.005

141. Davis AM, King LK, Stanaitis I, Hawker GA. Fundamentals of osteoarthritis: outcome evaluation with patient-reported measures and functional tests. *Osteoarthritis Cartilage*. 2022;30(6):775-785. doi:10.1016/j.joca.2021.07.016

142. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: A health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol*. 1988;15:1833-1840.

143. Irrgang JJ, Snyder-Mackler L, Wainner RS, Fu FH, Harner CD. Development of a patient-reported measure of function of the knee*. *JBJS*. 1998;80(8):1132.

144. Dawson J, Fitzpatrick R, Murray D, Carr A. Questionnaire on the perceptions of patients about total knee replacement. *J Bone Joint Surg Br*. 1998;80-B(1):63-69. doi:10.1302/0301-620X.80B1.0800063

145. Roos EM, Lohmander LS. The Knee Injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes*. 2003;1(1):64. doi:10.1186/1477-7525-1-64

146. Hawker GA, Davis AM, French MR, et al. Development and preliminary psychometric testing of a new OA pain measure – an OARSI/OMERACT initiative. *Osteoarthritis Cartilage*. 2008;16(4):409-414. doi:10.1016/j.joca.2007.12.015

147. Wang Y, Yin M, Zhu S, Chen X, Zhou H, Qian W. Patient-reported outcome measures used in patients undergoing total knee arthroplasty: a COSMIN systematic review. *Bone Jt Res*. 2021;10(3):203-217. doi:10.1302/2046-3758.103.BJR-2020-0268.R1

148. Sasaki R, Honda Y, Oga S, et al. Effect of exercise and/or educational interventions on physical activity and pain in patients with hip/knee osteoarthritis: A systematic review with meta-analysis. *PLOS ONE*. 2022;17(11):e0275591. doi:10.1371/journal.pone.0275591

149. Collins NJ, Prinsen CAC, Christensen R, Bartels EM, Terwee CB, Roos EM. Knee Injury and Osteoarthritis Outcome Score (KOOS): systematic review and meta-analysis of measurement properties. *Osteoarthritis Cartilage*. 2016;24(8):1317-1329. doi:10.1016/j.joca.2016.03.010

150. Nishimoto J, Tanaka S, Inoue Y, Tanaka R. Minimal clinically important differences in short-term postoperative Knee injury and Osteoarthritis Outcome Score (KOOS) after total knee arthroplasty: A prospective cohort study. *J Orthop Trauma Rehabil*. Published online June 30, 2023:22104917231181644. doi:10.1177/22104917231181644

151. Singh JA, Luo R, Landon GC, Suarez-Almazor M. Reliability and clinically important improvement thresholds for osteoarthritis pain and function scales: a multicenter study. *J Rheumatol*. 2014;41(3):509-515. doi:10.3899/jrheum.130609

152. Carlesso LC, Hawker GA, Torner J, et al. Association of intermittent and constant knee pain patterns with knee pain severity and with radiographic knee osteoarthritis duration and severity. *Arthritis Care Res*. 2021;73(6):788-793. doi:10.1002/acr.24194

153. Baker R. Gait analysis methods in rehabilitation. *J NeuroEngineering Rehabil*. 2006;3(1):4. doi:10.1186/1743-0003-3-4

154. Brand RA. Can biomechanics contribute to clinical orthopaedic assessments? *Iowa Orthop J*. 1989;9:61-64.

155. Research Methods in Biomechanics-2nd Edition. Human Kinetics. Accessed July 15, 2022. https://us.humankinetics.com/products/research-methods-in-biomechanics-2nd-edition

156. Mills K, Hunt MA, Ferber R. Biomechanical deviations during level walking associated with knee osteoarthritis: a systematic review and meta-analysis. *Arthritis Care Res*. 2013;65(10):1643-1665. doi:10.1002/acr.22015

157. Childs JD, Sparto PJ, Fitzgerald GK, Bizzini M, Irrgang JJ. Alterations in lower extremity movement and muscle activation patterns in individuals with knee osteoarthritis. *Clin Biomech*. 2004;19(1):44-49. doi:10.1016/j.clinbiomech.2003.08.007

158. SchmitT LC, Rudolph KS. Influences on knee movement strategies during walking in persons with medial knee osteoarthritis. *Arthritis Care Res*. 2007;57(6):1018-1026. doi:10.1002/art.22889

159. Henriksen M, Graven-Nielsen T, Aaboe J, Andriacchi TP, Bliddal H. Gait changes in patients with knee osteoarthritis are replicated by experimental knee pain. *Arthritis Care Res*. 2010;62(4):501-509. doi:10.1002/acr.20033

160. 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 Cartilage*. 2014;22(3):464-471. doi:10.1016/j.joca.2013.12.014

161. Heiden TL, Lloyd DG, Ackland TR. Knee joint kinematics, kinetics and muscle co-contraction in knee osteoarthritis patient gait. *Clin Biomech*. 2009;24(10):833-841. doi:10.1016/j.clinbiomech.2009.08.005

162. Favre J, Erhart-Hledik JC, Chehab EF, Andriacchi TP. Baseline ambulatory knee kinematics are associated with changes in cartilage thickness in osteoarthritic patients over 5 years. *J Biomech*. 2016;49(9):1859-1864. doi:10.1016/j.jbiomech.2016.04.029

163. Maly MR, Costigan PA, Olney SJ. Mechanical factors relate to pain in knee osteoarthritis. *Clin Biomech*. 2008;23(6):796-805. doi:10.1016/j.clinbiomech.2008.01.014

164. Schnitzer TJ, Popovich JM, Andersson GBJ, Andriacchi TP. Effect of piroxicam on gait in patients with osteoarthritis of the knee. *Arthritis Rheum*. 1993;36(9):1207-1213. doi:10.1002/art.1780360905

165. Panjabi MM. The stabilizing system of the spine. part i. function, dysfunction, adaptation, and enhancement: *J Spinal Disord*. 1992;5(4):383-389. doi:10.1097/00002517-199212000-00001

166. Mills K, Hunt MA, Leigh R, Ferber R. A systematic review and meta-analysis of lower limb neuromuscular alterations associated with knee osteoarthritis during level walking. *Clin Biomech*. 2013;28(7):713-724. doi:10.1016/j.clinbiomech.2013.07.008

167. Rutherford DJ, Hubley-Kozey CL, Stanish WD, Dunbar MJ. Neuromuscular alterations exist with knee osteoarthritis presence and severity despite walking velocity similarities. *Clin Biomech*. 2011;26(4):377-383. doi:10.1016/j.clinbiomech.2010.11.018

168. Bytyqi D, Shabani B, Lustig S, Cheze L, Karahoda Gjurgjeala N, Neyret P. Gait knee kinematic alterations in medial osteoarthritis: three dimensional assessment. *Int Orthop*. 2014;38(6):1191-1198. doi:10.1007/s00264-014-2312-3

169. Fukaya T, Mutsuzaki H, Nakano W, Mori K. Characteristics of frontal plane lower limb movement during walking in patients with knee osteoarthritis of varying severity. *J Orthop Surg Hong Kong*. 2019;27(2):2309499019848085. doi:10.1177/2309499019848085

170. Briem K, Snyder-Mackler L. Proximal gait adaptations in medial knee OA. *J Orthop Res*. 2009;27(1):78-83. doi:10.1002/jor.20718

171. Butler RJ, Barrios JA, Royer T, Davis IS. Frontal-plane gait mechanics in people with medial knee osteoarthritis are different from those in people with lateral knee osteoarthritis. *Phys Ther*. 2011;91(8):1235-1243. doi:10.2522/ptj.20100324

172. Kumar D, Manal KT, Rudolph KS. Knee joint loading during gait in healthy controls and individuals with knee osteoarthritis. *Osteoarthritis Cartilage*. 2013;21(2):298-305. doi:10.1016/j.joca.2012.11.008

173. 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 Res*. 2009;61(4):459-467. doi:10.1002/art.24336

174. Yang NH, Nayeb-Hashemi H, Canavan PK, Vaziri A. Effect of frontal plane tibiofemoral angle on the stress and strain at the knee cartilage during the stance phase of gait. *J Orthop Res Off Publ Orthop Res Soc*. 2010;28(12):1539-1547. doi:10.1002/jor.21174

175. Chang AH, Chmiel JS, Moisio KC, et al. Varus thrust and knee frontal plane dynamic motion in persons with knee osteoarthritis. *Osteoarthritis Cartilage*. 2013;21(11):1668-1673. doi:10.1016/j.joca.2013.08.007

176. Chang A, Hayes K, Dunlop D, et al. Thrust during ambulation and the progression of knee osteoarthritis. *Arthritis Rheum*. 2004;50(12):3897-3903. doi:10.1002/art.20657

177. Schipplein OD, Andriacchi TP. Interaction between active and passive knee stabilizers during level walking. *J Orthop Res*. 1991;9(1):113-119. doi:10.1002/jor.1100090114

178. Mahmoudian A, van Dieen JH, Bruijn SM, et al. Varus thrust in women with early medial knee osteoarthritis and its relation with the external knee adduction moment. *Clin Biomech*. 2016;39:109-114. doi:10.1016/j.clinbiomech.2016.10.006

179. Kuroyanagi Y, Nagura T, Kiriyama Y, et al. A quantitative assessment of varus thrust in patients with medial knee osteoarthritis. *The Knee*. 2012;19(2):130-134. doi:10.1016/j.knee.2010.12.007

180. Wink AE, Gross KD, Brown CA, et al. Association of varus knee thrust during walking with worsening Western Ontario and McMaster Universities Osteoarthritis index knee pain: a prospective cohort study. *Arthritis Care Res*. 2019;71(10):1353-1359. doi:10.1002/acr.23766

181. Birmingham TB, Hunt MA, Jones IC, Jenkyn TR, Giffin JR. Test–retest reliability of the peak knee adduction moment during walking in patients with medial compartment knee osteoarthritis. *Arthritis Care Res*. 2007;57(6):1012-1017. doi:10.1002/art.22899

182. Meyer AJ, D'Lima DD, Besier TF, Lloyd DG, Colwell Jr. CW, Fregly BJ. Are external knee load and EMG measures accurate indicators of internal knee contact forces during gait? *J Orthop Res*. 2013;31(6):921-929. doi:10.1002/jor.22304

183. Thorp LE, Wimmer MA, Block JA, et al. Bone mineral density in the proximal tibia varies as a function of static alignment and knee adduction angular momentum in individuals with medial knee osteoarthritis. *Bone*. 2006;39(5):1116-1122. doi:10.1016/j.bone.2006.05.001

184. 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. *Ann Rheum Dis*. 2002;61(7):617-622. doi:10.1136/ard.61.7.617

185. Foroughi N, Smith R, Vanwanseele B. The association of external knee adduction moment with biomechanical variables in osteoarthritis: A systematic review. *The Knee*. 2009;16(5):303-309. doi:10.1016/j.knee.2008.12.007

186. Astephen JL, Deluzio KJ, Caldwell GE, Dunbar MJ, Hubley-Kozey CL. Gait and neuromuscular pattern changes are associated with differences in knee osteoarthritis severity levels. *J Biomech*. 2008;41(4):868-876. doi:10.1016/j.jbiomech.2007.10.016

187. Maly MR, Robbins SM, Stratford PW, Birmingham TB, Callaghan JP. Cumulative knee adductor load distinguishes between healthy and osteoarthritic knees–A proof of principle study. *Gait Posture*. 2013;37(3):397-401. doi:10.1016/j.gaitpost.2012.08.013

188. Robbins SMK, Birmingham TB, Jones GR, Callaghan JP, Maly MR. Developing an estimate of daily cumulative loading for the knee: Examining test–retest reliability. *Gait Posture*. 2009;30(4):497-501. doi:10.1016/j.gaitpost.2009.07.118

189. Astephen Wilson JL, Stanish WD, Hubley-Kozey CL. Asymptomatic and symptomatic individuals with the same radiographic evidence of knee osteoarthritis walk with different knee moments and muscle activity. *J Orthop Res*. 2017;35(8):1661-1670. doi:10.1002/jor.23465

190. Asay JL, Erhart-Hledik JC, Andriacchi TP. Changes in the total knee joint moment in patients with medial compartment knee osteoarthritis over 5 years. *J Orthop Res*. 2018;36(9):2373-2379. doi:10.1002/jor.23908

191. Moyer RF, Birmingham TB, Bryant DM, Giffin JR, Marriott KA, Leitch KM. Biomechanical effects of valgus knee bracing: a systematic review and meta-analysis. *Osteoarthritis Cartilage*. 2015;23(2):178-188. doi:10.1016/j.joca.2014.11.018

192. Gholami S, Torkaman G, Bahrami F, Bayat N. Gait modification with subject-specific foot progression angle in people with moderate knee osteoarthritis: Investigation of knee adduction moment and muscle activity. *The Knee*. 2022;35:124-132. doi:10.1016/j.knee.2022.03.001

193. Alghadir AH, Anwer S, Iqbal A, Iqbal ZA. Test-retest reliability, validity, and minimum detectable change of visual analog, numerical rating, and verbal rating scales for measurement of osteoarthritic knee pain. *J Pain Res*. 2018;11:851-856. doi:10.2147/JPR.S158847

194. McCann B. Sex differences in knee osteoarthritis processes: the role of muscle strength in explaining acute pain intensity, pain sensitization, knee joint moment and muscle activation responses to a standard continuous walk. Published online December 16, 2022. Accessed March 14, 2024. https://DalSpace.library.dal.ca//handle/10222/82178

195. Budarick A. Physical Activity and the Role of Walking in Knee Osteoarthritis. Published online November 10, 2023. Accessed March 7, 2024. https://DalSpace.library.dal.ca//handle/10222/83125

196. Rutherford D, Baker M, Urquhart N, Stanish W. The effect of a frontal plane gait perturbation bout on knee biomechanics and muscle activation in older adults and individuals with knee osteoarthritis. *Clin Biomech*. 2022;92:105574. doi:10.1016/j.clinbiomech.2022.105574

197. Kraus VB, Sprow K, Powell KE, et al. Effects of physical activity in knee and hip osteoarthritis: a systematic umbrella review. *Med Sci Sports Exerc*. 2019;51(6):1324-1339. doi:10.1249/MSS.0000000000001944

198. Corrigan P, Felson DT, Lewis CL, et al. Relation of temporal asymmetry during walking to 2-year knee pain outcomes in those with mild-to-moderate unilateral knee pain: an exploratory analysis from the Multicenter Osteoarthritis (MOST) Study. *Arthritis Care Res*. n/a(n/a). doi:10.1002/acr.25050

199. Kim J, Felson DT, LaValley M, et al. Association of gait asymmetry with risk of a contralateral total knee arthroplasty in people with unilateral total knee arthroplasty: the multicenter osteoarthritis study. *Osteoarthritis Cartilage*. 2023;31:S123-S124. doi:10.1016/j.joca.2023.01.077

200. Queen R, Dickerson L, Ranganathan S, Schmitt D. A novel method for measuring asymmetry in kinematic and kinetic variables: The normalized symmetry index. *J Biomech*. 2020;99:109531. doi:10.1016/j.jbiomech.2019.109531

201. Herzog W, Nigg BM, Read LJ, Olsson E. Asymmetries in ground reaction force patterns in normal human gait: *Med Sci Sports Exerc*. 1989;21(1):110-114. doi:10.1249/00005768-198902000-00020

202. Gouwanda D. Further validation of Normalized Symmetry Index and normalized cross-correlation in identifying gait asymmetry on restricted knee and ankle movement. In: *2012 IEEE-EMBS Conference on Biomedical Engineering and Sciences*. IEEE; 2012:423-427. doi:10.1109/IECBES.2012.6498167

203. Robinson RO, Herzog W, Nigg BM. Use of force platform variables to quantify the effects of chiropractic manipulation on gait symmetry. *J Manipulative Physiol Ther*. 1987;10(4):172-176.

204. Błażkiewicz M, Wiszomirska I, Wit A. Comparison of four methods of calculating the symmetry of spatial-temporal parameters of gait. *Acta Bioeng Biomech*. 2014;16(1):29-35.

205. Kaufman KR, Frittoli S, Frigo CA. Gait asymmetry of transfemoral amputees using mechanical and microprocessor-controlled prosthetic knees. *Clin Biomech*. 2012;27(5):460-465. doi:10.1016/j.clinbiomech.2011.11.011

206. Mantashloo Z, Letafatkar A, Moradi M. Vertical ground reaction force and knee muscle activation asymmetries in patients with ACL reconstruction compared to healthy individuals. *Knee Surg Sports Traumatol Arthrosc Off J ESSKA*. 2020;28(6):2009-2014. doi:10.1007/s00167-019-05743-5

207. Hadizadeh M, Amri S, Mohafez H, Roohi SA, Mokhtar AH. Gait analysis of national athletes after anterior cruciate ligament reconstruction following three stages of rehabilitation program: Symmetrical perspective. *Gait Posture*. 2016;48:152-158. doi:10.1016/j.gaitpost.2016.05.002

208. Felson DT. Osteoarthritis as a disease of mechanics. *Osteoarthritis Cartilage*. 2013;21(1):10-15. doi:10.1016/j.joca.2012.09.012

209. Shakoor N, Block JA, Shott S, Case JP. Nonrandom evolution of end-stage osteoarthritis of the lower limbs. *Arthritis Rheum*. 2002;46(12):3185-3189. doi:10.1002/art.10649

210. Pozzi F, Snyder-Mackler L, Zeni J. Relationship between biomechanical asymmetries during a step up and over task and stair climbing after total knee arthroplasty. *Clin Biomech*. 2015;30(1):78-85. doi:10.1016/j.clinbiomech.2014.11.001

211. Alnahdi AH, Zeni JA, Snyder-Mackler L. Gait after unilateral total knee arthroplasty: Frontal plane analysis. *J Orthop Res*. 2011;29(5):647-652. doi:10.1002/jor.21323

212. Farquhar SJ, Kaufman KR, Snyder-Mackler L. Sit-to-Stand 3 months after unilateral total knee arthroplasty: Comparison of self-selected and constrained conditions. *Gait Posture*. 2009;30(2):187-191. doi:10.1016/j.gaitpost.2009.04.007

213. Kobsar D, Barden JM, Clermont C, Wilson JLA, Ferber R. Sex differences in the regularity and symmetry of gait in older adults with and without knee osteoarthritis. *Gait Posture*. 2022;95:192-197. doi:10.1016/j.gaitpost.2022.04.023

214. Peixoto JG, de Souza Moreira B, Diz JBM, Timoteo EF, Kirkwood RN, Teixeira-Salmela LF. Analysis of symmetry between lower limbs during gait of older women with bilateral knee osteoarthritis. *Aging Clin Exp Res*. 2019;31(1):67-73. doi:10.1007/s40520-018-0942-9

215. Bilek F, Deniz G, Esmez O, Belhan O. Spatiotemporal parameters of the operated and non-operated knees before and after unilateral total knee arthroplasty. *Gait Posture*. 2022;91:192-197. doi:10.1016/j.gaitpost.2021.10.033

216. Collins NJ, Misra D, Felson DT, Crossley KM, Roos EM. Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). *Arthritis Care Res*. 2011;63(S11):S208-S228. doi:10.1002/acr.20632

217. Borg G. Psychophysical scaling with applications in physical work and the perception of exertion. *Scand J Work Environ Health*. 1990;16:55-58.

218. Rutherford DJ, Moyer R, Baker M, Saleh S. High day-to-day repeatability of lower extremity muscle activation patterns and joint biomechanics of dual-belt treadmill gait: A reliability study in healthy young adults. *J Electromyogr Kinesiol*. 2020;51:102401. doi:10.1016/j.jelekin.2020.102401

219. McNair PJ, Depledge J, Brettkelly M, Stanley SN. Verbal encouragement: effects on maximum effort voluntary muscle: action. *Br J Sports Med*. 1996;30(3):243-245. doi:10.1136/bjsm.30.3.243

220. Wu G, Cavanagh PR. ISB recommendations for standardization in the reporting of kinematic data. *J Biomech*. 1995;28(10):1257-1261. doi:10.1016/0021-9290(95)00017-c

221. Grood ES, Suntay WJ. A Joint coordinate system for the clinical description of three-dimensional motions: application to the knee. *J Biomech Eng*. 1983;105(2):136-144. doi:10.1115/1.3138397

222. Zeni JA, Richards JG, Higginson JS. Two simple methods for determining gait events during treadmill and overground walking using kinematic data. *Gait Posture*. 2008;27(4):710-714. doi:10.1016/j.gaitpost.2007.07.007

223. Robbins SM, Astephen Wilson JL, 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):421-427. doi:10.1016/j.gaitpost.2013.01.001

224. Vaughan CL, Vaughan CL, Vaughan CL, Vaughan CL. *GaitCD*. Kiboho Publishers; 1999.

225. McCarthy CJ, Callaghan MJ, Oldham JA. The reliability of isometric strength and fatigue measures in patients with knee osteoarthritis. *Man Ther*. 2008;13(2):159-164. doi:10.1016/j.math.2006.12.003

226. Pataky TC, Robinson MA, Vanrenterghem J. Region-of-interest analyses of one-dimensional biomechanical trajectories: bridging 0D and 1D theory, augmenting statistical power. *PeerJ*. 2016;4:e2652. doi:10.7717/peerj.2652

227. Wang J, Hu Q, Wu C, et al. Gait asymmetry variation in kinematics, kinetics, and muscle force along with the severity levels of knee osteoarthritis. *Orthop Surg*. 2023;15(5):1384-1391. doi:10.1111/os.13721

228. Kang H. Sample size determination and power analysis using the G*Power software. *J Educ Eval Health Prof*. 2021;18:17. doi:10.3352/jeehp.2021.18.17

229. Cui A, Li H, Wang D, Zhong J, Chen Y, Lu H. Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. *eClinicalMedicine*. 2020;29. doi:10.1016/j.eclinm.2020.100587

230. Huang CH, James K, Lanois C, Corrigan P, Yen SC, Stefanik J. Inter-joint coordination variability is associated with pain severity and joint loading in persons with knee osteoarthritis. *J Orthop Res*. 2023;41(12):2610-2616. doi:10.1002/jor.25592

231. Finan PH, Buenaver LF, Bounds SC, et al. Discordance between pain and radiographic severity in knee osteoarthritis: findings from quantitative sensory testing of central sensitization. *Arthritis Rheum*. 2013;65(2):363-372. doi:10.1002/art.34646

232. Hatfield GL, Costello KE, Astephen Wilson JL, Stanish WD, Hubley-Kozey CL. Baseline gait muscle activation patterns differ for osteoarthritis patients who undergo total knee arthroplasty five to eight years later from those who do not. *Arthritis Care Res*. 2021;73(4):549-558. doi:10.1002/acr.24143

233. Costello KE, Wilson JLA, Stanish WD, Urquhart N, Hubley-Kozey CL. Differences in baseline joint moments and muscle activation patterns associated with knee osteoarthritis progression when defined using a clinical versus a structural outcome. *J Appl Biomech*. 2020;36(1):39-51. doi:10.1123/jab.2019-0127

234. Metcalfe AJ, Andersson ML, Goodfellow R, Thorstensson CA. Is knee osteoarthritis a symmetrical disease? Analysis of a 12 year prospective cohort study. *BMC Musculoskelet Disord*. 2012;13(1):153. doi:10.1186/1471-2474-13-153

235. Remedios S, Rutherford D. Lower extremity muscle patterns and frontal plane biomechanics are altered in the contralateral knee of adults with osteoarthritis compared to asymptomatic adults. *J Electromyogr Kinesiol*. 2024;75:102865. doi:10.1016/j.jelekin.2024.102865

236. Robbins SMK, Maly MR. The effect of gait speed on the knee adduction moment depends on waveform summary measures. *Gait Posture*. 2009;30(4):543-546. doi:10.1016/j.gaitpost.2009.08.236

237. 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. *Clin Biomech*. 2012;27(5):520-523. doi:10.1016/j.clinbiomech.2011.12.007

238. Darlow B, Krägeloh C, Abbott JH, et al. The osteoarthritis knowledge scale. *Musculoskeletal Care*. 2023;21(2):516-526. doi:10.1002/msc.1727

239. Astephen Wilson JL, Dunbar MJ, Hubley-Kozey CL. Knee joint biomechanics and neuromuscular control during gait before and after total knee arthroplasty are sex-specific. *J Arthroplasty*. 2015;30(1):118-125. doi:10.1016/j.arth.2014.07.028

240. Glass N, Segal NA, Sluka KA, et al. Examining sex differences in knee pain: the Multicenter Osteoarthritis Study. *Osteoarthritis Cartilage*. 2014;22(8):1100-1106. doi:10.1016/j.joca.2014.06.030

241. Kumar D, Souza RB, Subburaj K, et al. Are there sex differences in knee cartilage composition and walking mechanics in healthy and osteoarthritis populations? *Clin Orthop Relat Res*. 2015;473(8):2548. doi:10.1007/s11999-015-4212-2

242. Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis Cartilage*. 2005;13(9):769-781. doi:10.1016/j.joca.2005.04.014

243. de Rooij M, van der Leeden M, Heymans MW, et al. Prognosis of pain and physical functioning in patients with knee osteoarthritis: a systematic review and meta-analysis. *Arthritis Care Res*. 2016;68(4):481-492. doi:10.1002/acr.22693

244. Bindawas SM, Vennu V, Al Snih S. Differences in health-related quality of life among subjects with frequent bilateral or unilateral knee pain: data from the osteoarthritis initiative study. *J Orthop Sports Phys Ther*. 2015;45(2):128-136. doi:10.2519/jospt.2015.5123

245. Pietrosimone B, Blackburn JT, Padua DA, et al. Walking gait asymmetries 6 months following anterior cruciate ligament reconstruction predict 12-month patient-reported outcomes. *J Orthop Res*. 2018;36(11):2932-2940. doi:10.1002/jor.24056

246. Rutherford DJ, Moreside J, Wong I. Differences in hip joint biomechanics and muscle activation in individuals with femoroacetabular impingement compared with healthy, asymptomatic individuals: is level-ground gait analysis enough? *Orthop J Sports Med*. 2018;6(5):2325967118769829. doi:10.1177/2325967118769829

247. Chui K, Hood E, Klima D. Meaningful change in walking speed. *Top Geriatr Rehabil*. 2012;28(2):97. doi:10.1097/TGR.0b013e3182510195

248. Landry SC, McKean KA, Hubley-Kozey CL, Stanish WD, Deluzio KJ. Knee biomechanics of moderate OA patients measured during gait at a self-selected and fast walking speed. *J Biomech*. 2007;40(8):1754-1761. doi:10.1016/j.jbiomech.2006.08.010

249. Canada H. Canadian Guidelines for Body Weight Classification in Adults. Published March 21, 2003. Accessed March 22, 2024. https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/healthy-weights/canadian-guidelines-body-weight-classification-adults/questions-answers-public.html

250. Harding GT, Hubley-Kozey CL, Dunbar MJ, Stanish WD, Astephen Wilson JL. Body mass index affects knee joint mechanics during gait differently with and without moderate knee osteoarthritis. *Osteoarthritis Cartilage*. 2012;20(11):1234-1242. doi:10.1016/j.joca.2012.08.004

251. Bensalma F, Hagemeister N, Cagnin A, et al. Biomechanical markers associations with pain, symptoms, and disability compared to radiographic severity in knee osteoarthritis patients: a secondary analysis from a cluster randomized controlled trial. *BMC Musculoskelet Disord*. 2022;23(1):896. doi:10.1186/s12891-022-05845-1

252. Van Rossom S, Emmerzaal J, van der Straaten R, et al. The biomechanical fingerprint of hip and knee osteoarthritis patients during activities of daily living. *Clin Biomech*. 2023;101:105858. doi:10.1016/j.clinbiomech.2022.105858

253. Duffell LD, Gulati V, Southgate DFL, McGregor AH. Measuring body weight distribution during sit-to-stand in patients with early knee osteoarthritis. *Gait Posture*. 2013;38(4):745-750. doi:10.1016/j.gaitpost.2013.03.015

254. Dobson F, Hinman RS, Roos EM, et al. OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. *Osteoarthritis Cartilage*. 2013;21(8):1042-1052. doi:10.1016/j.joca.2013.05.002

255. Wallis JA, Webster KE, Levinger P, Taylor NF. What proportion of people with hip and knee osteoarthritis meet physical activity guidelines? A systematic review and meta-analysis. *Osteoarthritis Cartilage*. 2013;21(11):1648-1659. doi:10.1016/j.joca.2013.08.003

256. Salaffi F, Stancati A, Alberto Silvestri C, Ciapetti A, Grassi W. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. *Eur J Pain*. 2004;8(4):283-291. doi:10.1016/j.ejpain.2003.09.004

257. Jakiela JT, Waugh EJ, White DK. Walk at least 10 minutes a day for adults with knee osteoarthritis: recommendation for minimal activity during the covid-19 pandemic. *J Rheumatol*. 2021;48(2):157-159. doi:10.3899/jrheum.200914

258. Badley EM, Wilfong JM, Zahid S, Perruccio AV. The status of arthritis in Canada: national report.

259. Park K, Roemmich RT, Elrod JM, Hass CJ, Hsiao-Wecksler ET. Effects of aging and Parkinson's disease on joint coupling, symmetry, complexity and variability of lower limb movements during gait. *Clin Biomech*. 2016;33:92-97. doi:10.1016/j.clinbiomech.2016.02.012

260. Selzer F, Zarra MB, MacFarlane LA, et al. Objective performance tests assess aspects of function not captured by self-report in knee osteoarthritis. *Osteoarthr Cartil Open*. 2022;4(4):100311. doi:10.1016/j.ocarto.2022.100311

261. Cappozzo A. Considerations on clinical gait evaluation. *J Biomech*. 1983;16(4):302. doi:10.1016/0021-9290(83)90202-6

262. Solit M. A study in structural dynamics. *J Am Osteopath Assoc*. 1962;62:30-40.

263. Patterson BE, Crossley KM, Perraton LG, et al. Limb symmetry index on a functional test battery improves between one and five years after anterior cruciate ligament reconstruction, primarily due to worsening contralateral limb function. *Phys Ther Sport*. 2020;44:67-74. doi:10.1016/j.ptsp.2020.04.031

264. Dogra S, Copeland JL, Altenburg TM, Heyland DK, Owen N, Dunstan DW. Start with reducing sedentary behavior: A stepwise approach to physical activity counseling in clinical practice. *Patient Educ Couns*. 2022;105(6):1353-1361. doi:10.1016/j.pec.2021.09.019

265. Grgic J, Dumuid D, Bengoechea EG, et al. Health outcomes associated with reallocations of time between sleep, sedentary behaviour, and physical activity: a systematic scoping review of isotemporal substitution studies. *Int J Behav Nutr Phys Act*. 2018;15(1):69. doi:10.1186/s12966-018-0691-3

266. Warburton DER, Bredin SSD. Health benefits of physical activity: a systematic review of current systematic reviews. *Curr Opin Cardiol*. 2017;32(5):541. doi:10.1097/HCO.0000000000000437

267. Pearce M, Garcia L, Abbas A, et al. Association between physical activity and risk of depression. *JAMA Psychiatry*. 2022;79(6):550-559. doi:10.1001/jamapsychiatry.2022.0609

268. Outerleys JB, Dunbar MJ, Richardson G, Hubley-Kozey CL, Wilson JLA. Quantifying achievable levels of improvement in knee joint biomechanics during gait after total knee arthroplasty relative to osteoarthritis severity. *J Appl Biomech*. 2021;37(2):130-138. doi:10.1123/jab.2020-0051

269. Bravi M, Gallotta E, Morrone M, et al. Concurrent validity and inter trial reliability of a single inertial measurement unit for spatial-temporal gait parameter analysis in patients with recent total hip or total knee arthroplasty. *Gait Posture*. 2020;76:175-181. doi:10.1016/j.gaitpost.2019.12.014

270. Menz HB, Latt MD, Tiedemann A, Mun San Kwan M, Lord SR. Reliability of the GAITRite® walkway system for the quantification of temporo-spatial parameters of gait in young and older people. *Gait Posture*. 2004;20(1):20-25. doi:10.1016/S0966-6362(03)00068-7

271. Farrokhi S, Jayabalan P, Gustafson JA, Klatt BA, Sowa GA, Piva SR. The influence of continuous versus interval walking exercise on knee joint loading and pain in patients with knee osteoarthritis. *Gait Posture*. 2017;56:129-133. doi:10.1016/j.gaitpost.2017.05.015

Appendix A: Study Research Ethics Board Approval (File #: 2022-6340)

Health Sciences Research Ethics Board Letter of Approval
January 18, 2023 Rebecca Moyer
Health\School of Physiotherapy

Dear Rebecca,

REB #:2022-6340

Project Title: Characterizing Gait Asymmetries in Individuals with Knee Osteoarthritis

Effective Date: January 18, 2023
Expiry Date: January 18, 2024

The Health Sciences Research Ethics Board has reviewed your application for research involving humans and found the proposed research to be in accordance with the Tri-Council Policy Statement on *Ethical Conduct for Research Involving Humans*. This approval will be in effect for 12 months as indicated above. This approval is subject to the conditions listed below which constitute your on-going responsibilities with respect to the ethical conduct of this research.

Sincerely,

Dr. Jennifer Isenor
Chair, Health Sciences Research Ethics Board Dalhousie University

FUNDED:
PhD Salary Award 22-0000000152

Post REB Approval: On-going Responsibilities of Researchers

After receiving ethical approval for the conduct of research involving humans, there are several ongoing responsibilities that researchers must meet to remain in compliance with University and Tri-Council policies.

Additional Research Ethics approval

Prior to conducting any research, researchers must ensure that all required research ethics approvals are secured (in addition to Dalhousie approval). This includes, but is not limited to, securing appropriate research ethics approvals from: other institutions with whom the PI is affiliated; the institutions of research team members; the institution at which participants may be recruited or from which data may be collected; organizations or groups

(e.g. school boards, Indigenous communities, correctional services, long-term care facilities, service agencies and community groups) and from any other responsible review body or bodies at the research site.

Reporting adverse events

Any significant adverse events experienced by research participants must be reported in writing to Research Ethics within 24 hours of their occurrence. Examples of what might be considered "significant" include: a negative physical reaction by a participant (e.g. fainting, nausea, unexpected pain, allergic reaction), an emotional breakdown of a participant during an interview, report by a participant of some sort of negative repercussion from their participation (e.g. reaction of spouse or employer) or complaint by a participant with respect to their participation, report of neglect or abuse of a child or adult in need of protection, or a privacy breach. The above list is indicative but not all-inclusive. The written report must include details of the situation and actions taken (or proposed) by the researcher in response to the incident.

Seeking approval for changes to research

Prior to implementing any changes to your research plan, whether to the risk assessment, methods, analysis, study instruments or recruitment/consent material, researchers must submit them to the Research Ethics Board for review and approval. This is done by completing the amendment request process (described on the website) and submitting an updated ethics submission that includes and explains the proposed changes. Please note that reviews are not conducted in August.

Continuing ethical review - annual reports

Research involving humans is subject to continuing REB review and oversight. REB approvals are valid for up to 12 months at a time (per the Tri-Council Policy Statement (TCPS) article 6.14). Prior to the REB approval expiry date, researchers may apply to extend REB approval by completing an Annual Report (available on the website). The report should be submitted 3 weeks in advance of the REB approval expiry date to allow time for REB review and to prevent a lapse of ethics approval for the research. Researchers should note that no research involving humans may be conducted in the absence of a valid ethical approval and that allowing REB approval to lapse is a violation of the University Scholarly Misconduct Policy, inconsistent with the TCPS and may result in the suspension of research and research funding, as required by the funding agency.

Final review - final reports

When the researcher is confident that all research-related interventions or interactions with participants have been completed (for prospective research) and/or that all data acquisition is complete, there will be no further access to participant records or collection of biological materials (for secondary use of information research), a Final Report (available on the

website) must be submitted to Research Ethics. After review and acknowledgement of the Final Report, the Research Ethics file will be closed.

Retaining records in a secure manner

Researchers must ensure that records and data associated with their research are managed consistent with their approved research plans both during and after the project. Research information must be confidentially and securely retained and/or disposed of in such a manner as to comply with confidentiality provisions specified in the protocol and consent forms. This may involve destruction of the records, or continued arrangements for secure storage.

It is the researcher's responsibility to keep a copy of the REB approval letters. This can be important to demonstrate that research was undertaken with Board approval. Please note that the University will securely store your REB project file for 5 years after the REB approval end date at which point the file records may be permanently destroyed.

Current contact information and university affiliation

The lead researchers must inform the Research Ethics office of any changes to contact information for the PI (and supervisor, if appropriate), especially the electronic mail address, for the duration of the REB approval. The PI must inform Research Ethics if there is a termination or interruption of their affiliation with Dalhousie University.

Legal Counsel

The Principal Investigator agrees to comply with all legislative and regulatory requirements that apply to the project. The Principal Investigator agrees to notify the University Legal Counsel office in the event that they receive a notice of non-compliance, complaint or other proceeding relating to such requirements.

Supervision of students

Faculty must ensure that students conducting research under their supervision are aware of their responsibilities as described above and have adequate support to conduct their research in a safe and ethical manner.

Appendix B: Heatmaps Outlining Individual Responses for Non-significant KOOS or ICOAP subscales

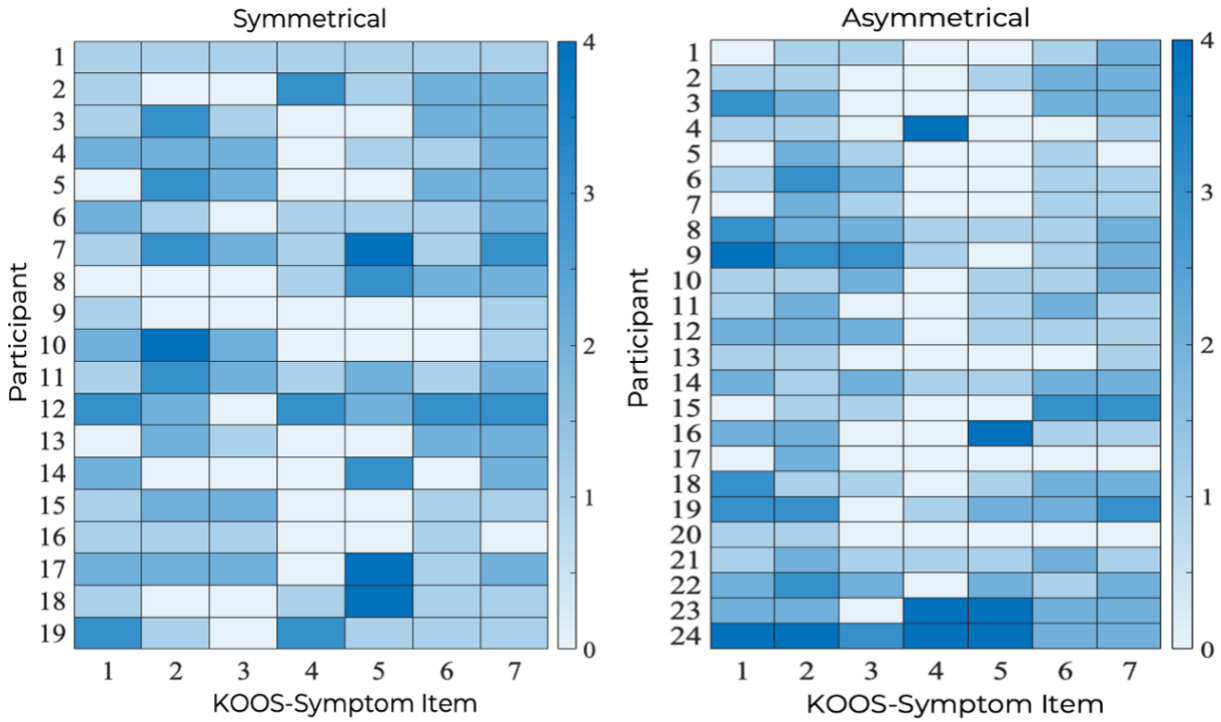


Figure B-1: Heatmap depicting the distribution of Likert scale responses for the Knee injury and Osteoarthritis Outcome Score (KOOS) - Symptoms sub-scale. The heatmap displays the responses for each item within the KOOS-Symptoms sub-scale across all respondents. Color intensity represents degree of difficulty, with darker shades indicating higher worse difficulty. The left subplot shows responses from individuals with symmetrical knee loading, while the right subplot displays responses from individuals with asymmetrical knee loading. Each row represents a respondent, and each column represents an item within the KOOS-Symptoms sub-scale.

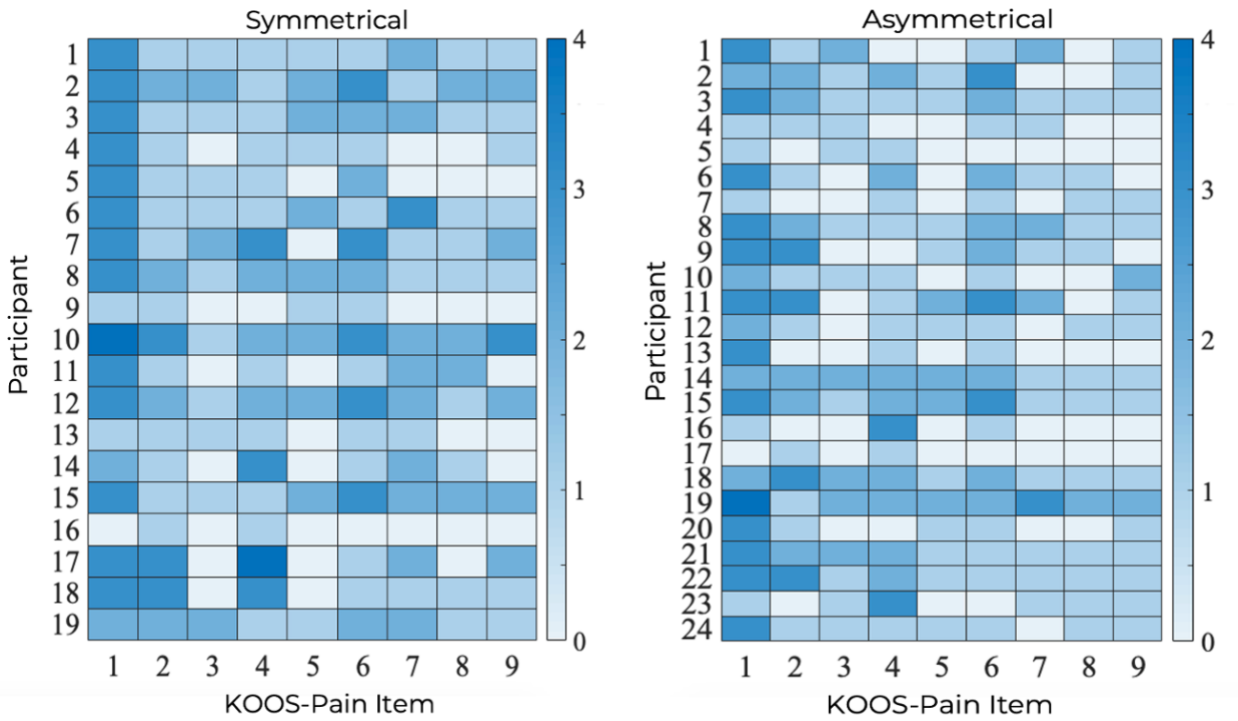


Figure B-2: Heatmap depicting the distribution of Likert scale responses for the Knee injury and Osteoarthritis Outcome Score (KOOS) - Pain sub-scale. The heatmap displays the responses for each item within the KOOS-Pain sub-scale across all respondents. Color intensity represents degree of difficulty, with darker shades indicating higher worse difficulty. The left subplot shows responses from individuals with symmetrical knee loading, while the right subplot displays responses from individuals with asymmetrical knee loading. Each row represents a respondent, and each column represents an item within the KOOS-Pain sub-scale.

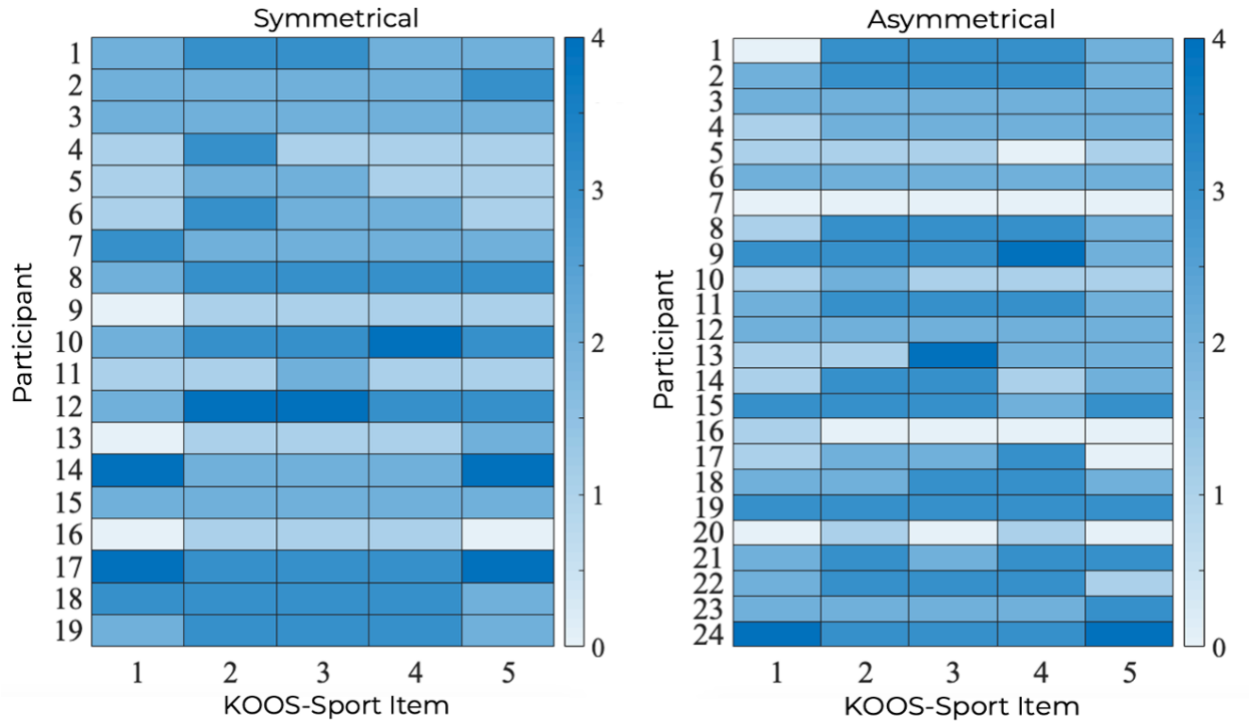


Figure B-3: Heatmap depicting the distribution of Likert scale responses for the Knee injury and Osteoarthritis Outcome Score (KOOS) – Function, Sports and Recreational Activities (Sport) sub-scale. The heatmap displays the responses for each item within the KOOS-Sport sub-scale across all respondents. Color intensity represents degree of difficulty, with darker shades indicating higher worse difficulty. The left subplot shows responses from individuals with symmetrical knee loading, while the right subplot displays responses from individuals with asymmetrical knee loading. Each row represents a respondent, and each column represents an item within the KOOS-Sport sub-scale.

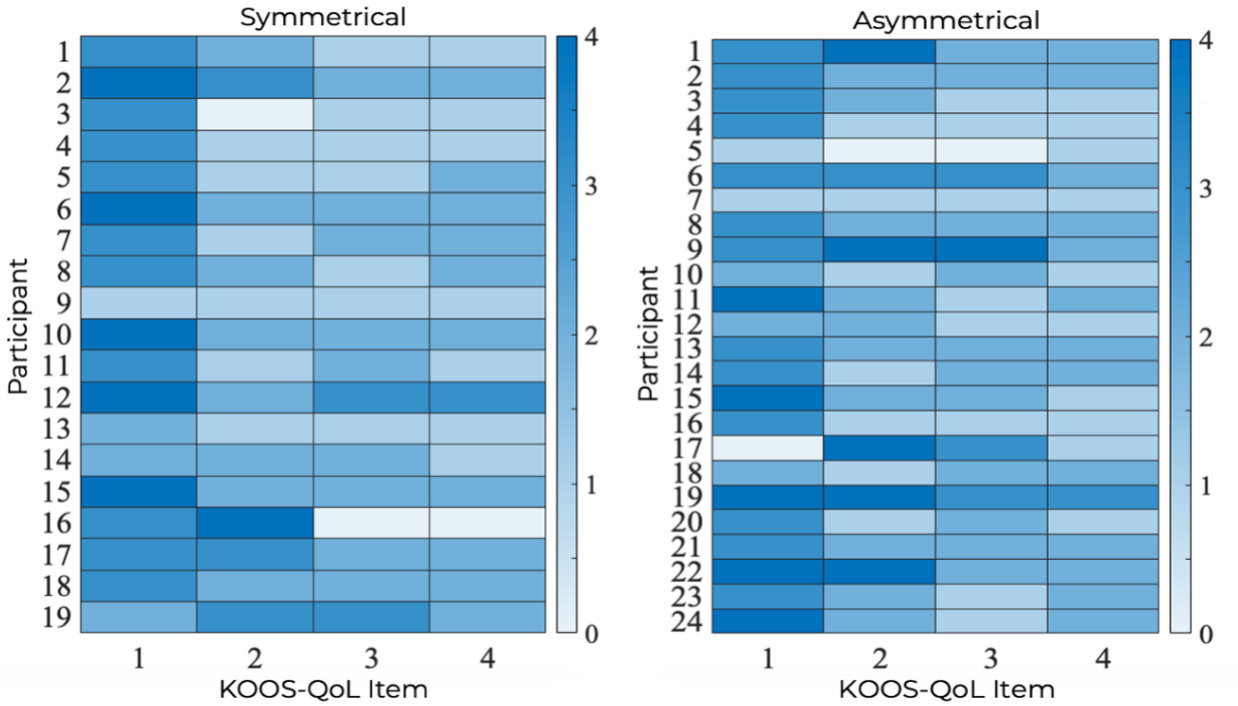


Figure B-4: Heatmaps depicting the distribution of Likert scale responses for the Knee injury and Osteoarthritis Outcome Score (KOOS) – Quality of Life (QoL) sub-scale. The heatmap displays the responses for each item within the KOOS-QoL sub-scale across all respondents. Color intensity represents degree of difficulty, with darker shades indicating higher worse difficulty. The left subplot shows responses from individuals with symmetrical knee loading, while the right subplot displays responses from individuals with asymmetrical knee loading. Each row represents a respondent, and each column represents an item within the KOOS-QoL sub-scale.

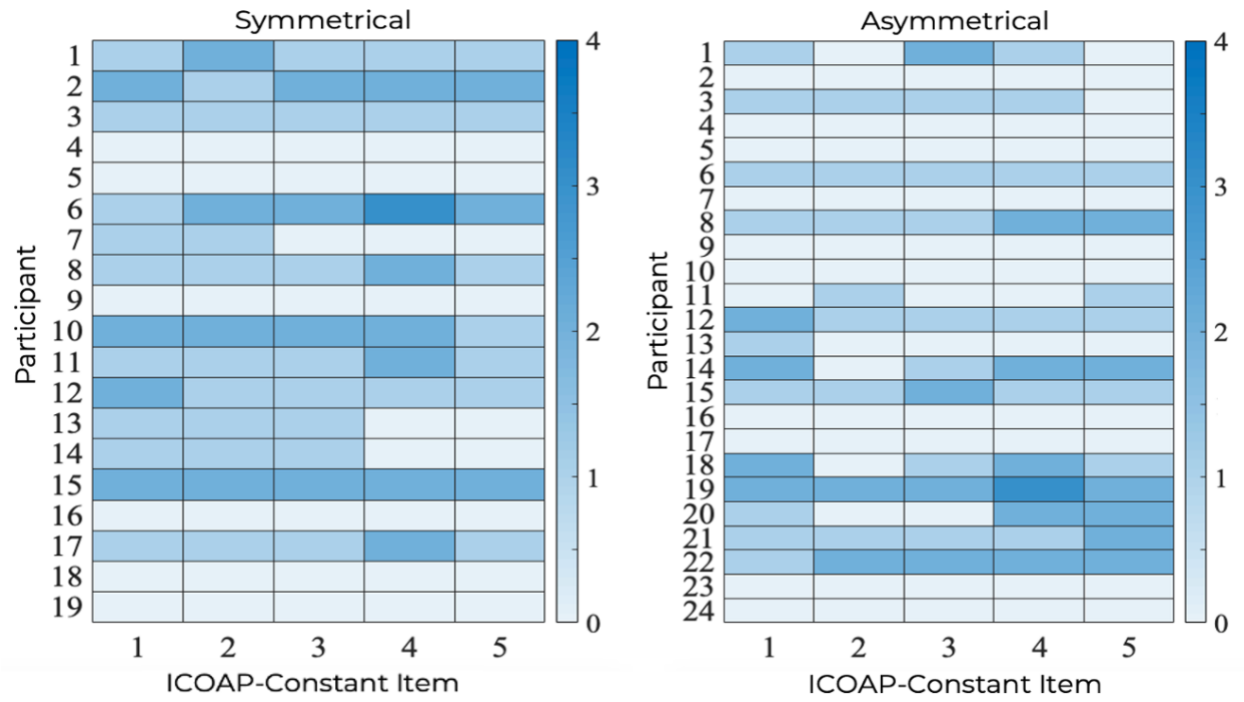


Figure B-5: Heatmap depicting the distribution of Likert scale responses for the Intermittent and Constant Osteoarthritis Pain (ICOAP) score - Constant sub-scale. The heatmap displays the responses for each item within the ICOAP -Constant sub-scale across all respondents. Color intensity represents degree of difficulty, with darker shades indicating higher worse difficulty. The left subplot shows responses from individuals with symmetrical knee loading, while the right subplot displays responses from individuals with asymmetrical knee loading. Each row represents a respondent, and each column represents an item within the ICOAP - Constant sub-scale.

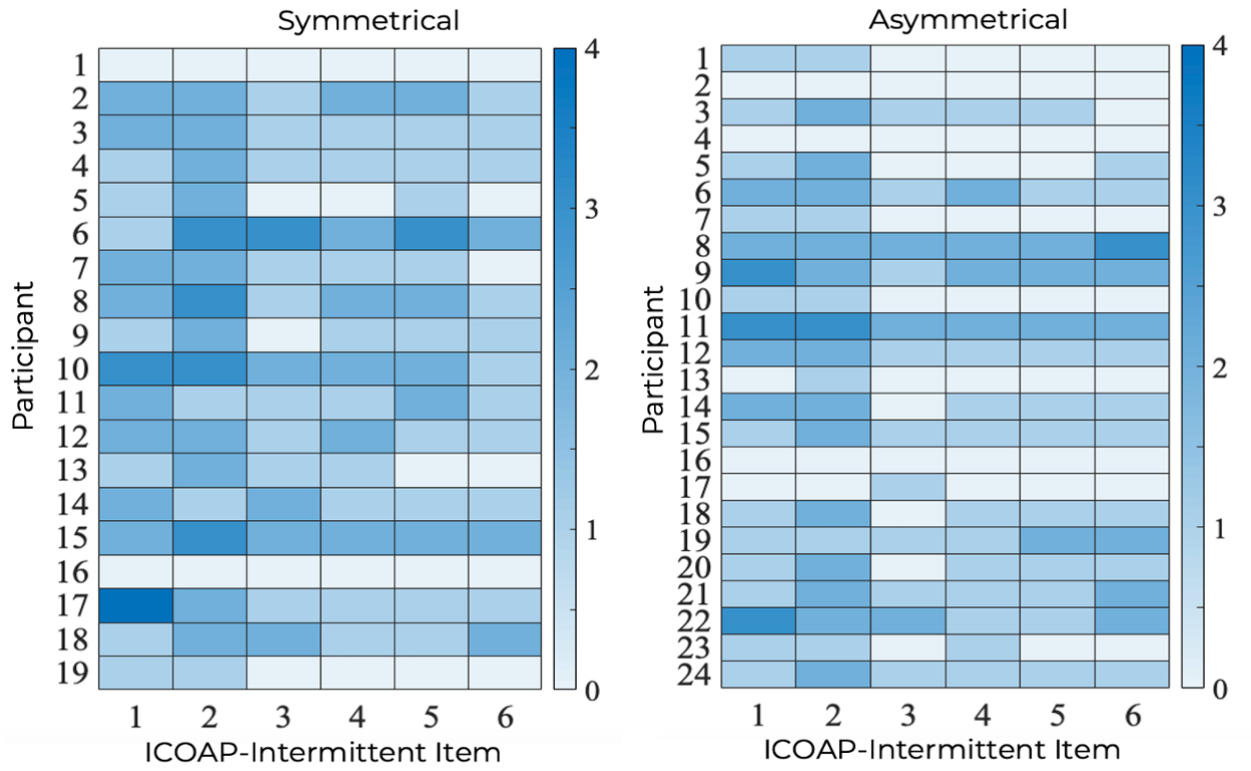
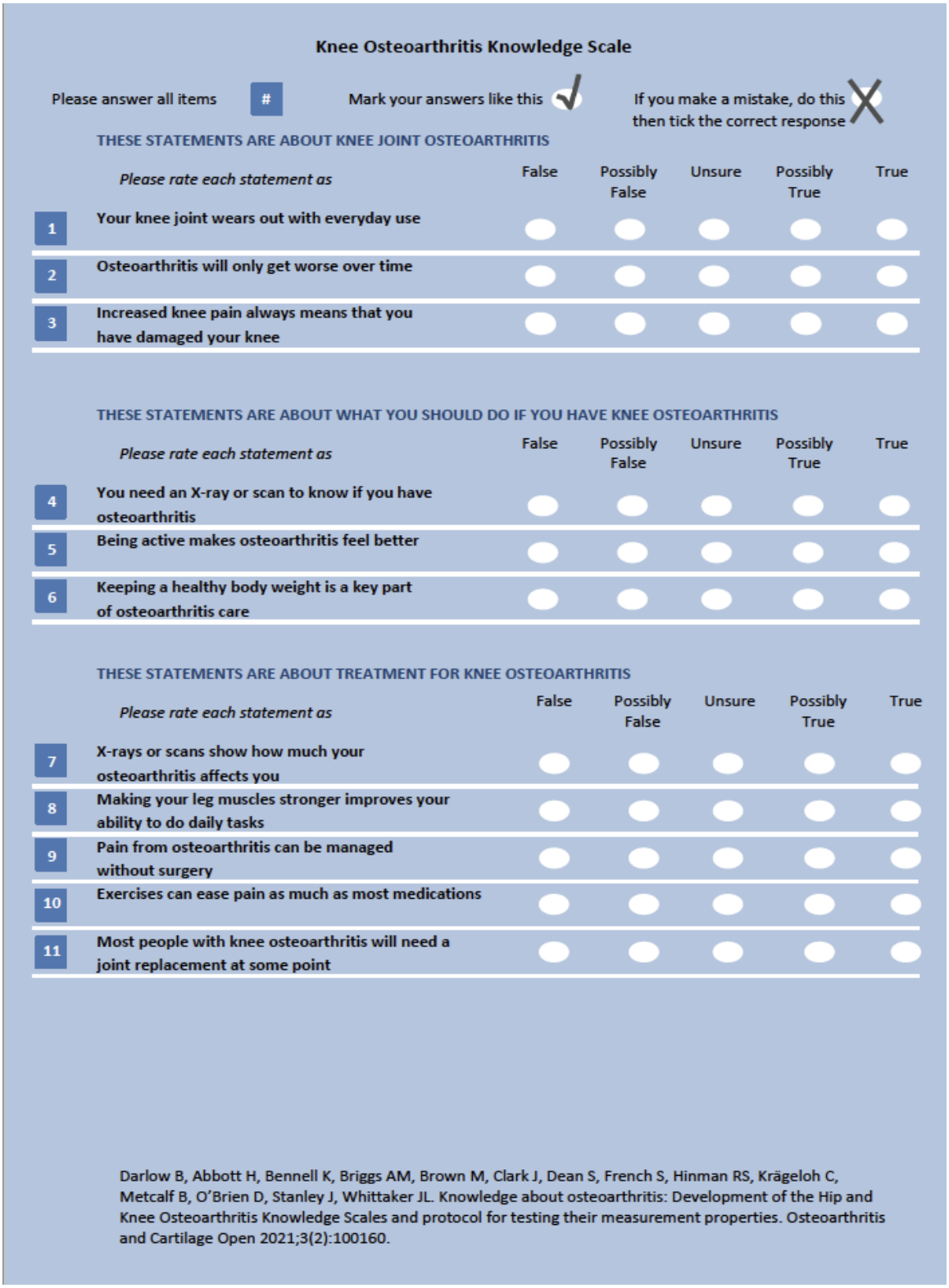


Figure B-6: Heatmap depicting the distribution of Likert scale responses for the Intermittent and Constant Osteoarthritis Pain (ICOAP) score - Intermittent sub-scale. The heatmap displays the responses for each item within the ICOAP - Intermittent sub-scale across all respondents. Color intensity represents degree of difficulty, with darker shades indicating higher worse difficulty. The left subplot shows responses from individuals with symmetrical knee loading, while the right subplot displays responses from individuals with asymmetrical knee loading. Each row represents a respondent, and each column represents an item within the ICOAP - Intermittent sub-scale.

Appendix C: Copy of The Osteoarthritis Knowledge Scale (OAKS)



Knee Osteoarthritis Knowledge Scale

Please answer all items # Mark your answers like this ✓ If you make a mistake, do this ✗ then tick the correct response

THESE STATEMENTS ARE ABOUT KNEE JOINT OSTEOARTHRITIS

	Please rate each statement as	False	Possibly False	Unsure	Possibly True	True
1	Your knee joint wears out with everyday use	○	○	○	○	○
2	Osteoarthritis will only get worse over time	○	○	○	○	○
3	Increased knee pain always means that you have damaged your knee	○	○	○	○	○

THESE STATEMENTS ARE ABOUT WHAT YOU SHOULD DO IF YOU HAVE KNEE OSTEOARTHRITIS

	Please rate each statement as	False	Possibly False	Unsure	Possibly True	True
4	You need an X-ray or scan to know if you have osteoarthritis	○	○	○	○	○
5	Being active makes osteoarthritis feel better	○	○	○	○	○
6	Keeping a healthy body weight is a key part of osteoarthritis care	○	○	○	○	○

THESE STATEMENTS ARE ABOUT TREATMENT FOR KNEE OSTEOARTHRITIS

	Please rate each statement as	False	Possibly False	Unsure	Possibly True	True
7	X-rays or scans show how much your osteoarthritis affects you	○	○	○	○	○
8	Making your leg muscles stronger improves your ability to do daily tasks	○	○	○	○	○
9	Pain from osteoarthritis can be managed without surgery	○	○	○	○	○
10	Exercises can ease pain as much as most medications	○	○	○	○	○
11	Most people with knee osteoarthritis will need a joint replacement at some point	○	○	○	○	○

Darlow B, Abbott H, Bennell K, Briggs AM, Brown M, Clark J, Dean S, French S, Hinman RS, Krägeloh C, Metcalf B, O'Brien D, Stanley J, Whittaker JL. Knowledge about osteoarthritis: Development of the Hip and Knee Osteoarthritis Knowledge Scales and protocol for testing their measurement properties. Osteoarthritis and Cartilage Open 2021;3(2):100160.

Knee Osteoarthritis Knowledge Scale

The Knee Osteoarthritis Knowledge Scale Scoring instructions

There are 11-items that contribute to the score. Each item presents a statement with a five-point Likert scale. Each item is scored on a scale from 1 to 5.

To compute the score, reverse score items 1,2, 3, 4, 7, and 11 and add these to items 5, 6, 8, 9, and 10. Total scores for the scale range from 11 to 55, and higher scores indicate greater knowledge about osteoarthritis.

Darlow B, Abbott H, Bennell K, Briggs AM, Brown M, Clark J, Dean S, French S, Hinman RS, Krägeloh C, Metcalf B, O'Brien D, Stanley J, Whittaker JL. Knowledge about osteoarthritis: Development of the Hip and Knee Osteoarthritis Knowledge Scales and protocol for testing their measurement properties. Osteoarthritis and Cartilage Open 2021;3(2):100160.