Physical Activity and the Role of Walking in Knee Osteoarthritis

by

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Dedicated to Jake,
who often knows me better than I know myself,
and to my parents.

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Abstract

Walking is recommended as a type of physical activity for individuals with knee osteoarthritis, yet this population is physically inactive. The quantitative effects of walking exercise on joint health to inform walking prescription remain poorly understood. The overall aim of this thesis was to better understand whether and how physical activity, particularly walking, is prescribed to manage knee osteoarthritis, and to add to our understanding of the effects of walking on quantitative joint health outcomes for individuals with knee osteoarthritis.

A healthcare quality survey of individuals with mild-to-moderate knee osteoarthritis (Chapter 3) revealed that less than half of participants received recommended care across four healthcare quality indicators, and approximately two-thirds received advice to exercise. Binary logistic regressions indicated no differences in healthcare quality based on participant demographic, social, or patient-reported factors. Within a systematic review and meta-analysis on the biomechanical and structural effects of walking interventions (Chapter 4), pooled data analysis from 33 articles indicated walking interventions elicit minimal-to-no change in discrete biomechanical metrics of joint loading, and moderately increase gait speed. Longer interventions were associated with lower peak knee flexion moments in meta-regressions. Descriptive analyses suggested walking exercise does not alter knee joint structure beyond natural history changes. A laboratory-based experimental study on the immediate biomechanical, structural, and patient-reported effects of a 30-minute walking bout (Chapter 5) indicated that continuous walking increases peak knee joint loading, elicits minimal-to-no increases in pain, and does not change cartilage thickness. Pain and structural imaging responder and non-responder sub-groups were identified and examined in exploratory analyses.

Low exercise prescription rates (Chapter 3) are unsurprising given the little quantitative evidence that currently exists to support walking exercise (Chapter 4); however, the effect of walking exercise on biomechanical, structural, and patient-reported outcomes (Chapters 4 and 5) support that more individuals with knee osteoarthritis should be advised to exercise. This thesis adds to growing evidence that exists to educate patients on the potential overall and joint health benefits of walking exercise, and absence of harms related to disease progression. Findings can be used to inform walking prescription parameters to increase physical activity for knee osteoarthritis populations.

List of Abbreviations and Symbols Used

3D	Three-Dimensional
ACR	American College of Rheumatology
BC OA	British Columbia Osteoarthritis
BLOKS	Boston-Leeds Osteoarthritis Knee Score
BMI	Body Mass Index
BML	Bone Marrow Lesion
CanPath	Canadian Partnership for Tomorrow's Health
CI	Confidence Interval
COMP	Cartilage Oligomeric Matrix Protein
EQ-5D-5L	5-level Euro-Qol 5-dimension
EULAR	European League Against Rheumatism
FIESTA	Fast Imaging Employing Steady-State Acquisition
FOV	Field of View
ICC	Intra-Class Correlation Coefficient
ICOAP	Intermittent and Constant Osteoarthritis Pain
IDEA	Intensive Diet and Exercise for Arthritis
IPAQ-SF	International Physical Activity Questionnaire – Short Form
IQR	Interquartile Range
KAM	Knee Adduction Moment
KFA	Knee Flexion Angle
KFM	Knee Flexion Moment
kg	Kilogram
kg/m^2	Kilograms per metres squared
KLG	Kellgren and Lawrence Grade
km/h	Kilometers per hour
KOOS	Knee injury and Osteoarthritis Outcome Score
m/s	Metres per second
MDC	Minimal Detectable Change
mm	Millimetre

MOAKS	Magnetic Resonance Imaging Osteoarthritis Knee Score
MRI	Magnetic Resonance Imaging
N	Newtons
Nm/kg	Newton metres per kilogram
NICE	National Institute for Clinical Excellence
NPRS	Numeric Pain Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OARSI	Osteoarthritis Research Society International
OR	Odds Ratio
PASE	Physical Activity Scale for the Elderly
PATH	Partnership for Tomorrow's Health
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
REDCap	Research Electronic Data Capture
SD	Standard Deviation
SMD	Standardized Mean Difference
TE	Echo Time
TR	Relaxation Time
US	Ultrasound
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

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Chapter 1 Introduction

1.1 Motivation

Osteoarthritis is a prevalent chronic and disabling musculoskeletal condition that affects one in every three adults aged 55 years or older, and is most commonly found in the knee (1,2). Knee osteoarthritis prevalence is rapidly increasing due to modifiable lifestyle factors that increase an individual's risk of developing knee osteoarthritis, including obesity and physical inactivity (3). Individuals with knee osteoarthritis experience an increased risk of all-cause mortality (4–6) and high rates of comorbidities (7–9). Thus, knee osteoarthritis and associated comorbidities substantially burden both the individual and healthcare system (10). Current etiological hypotheses postulate that knee osteoarthritis results from a combination of mechanical, inflammatory, and biological factors that interact to create structural joint changes (11–14). Knee osteoarthritis is characterized by structural disease characteristics, including damage to or disrepair of articular cartilage, subchondral bone, ligaments, menisci, and synovium, which are frequently accompanied by clinical characteristics, including pervasive knee joint pain, functional limitations, stiffness, instability, and decreased quality of life (15–17).

Evidence-based clinical practice guidelines have been developed to inform knee osteoarthritis care and improve clinical outcomes (18–25). Current evidence emphasizes that non-surgical and non-pharmacological treatment modalities should be used as core treatment, including education and self-management, physical activity, therapeutic exercise, and weight management (18–25). Traditional clinical management strategies focus on symptom relief using pharmacological treatment awaiting eventual end-stage joint replacement surgery (26); however, these treatments may be associated with negative consequences (27,28) and are not recommended for all individuals with knee osteoarthritis (18–25). Further, it is difficult to determine the individuals who are best suited for surgical or pharmacological treatment. Alternatively, core strategies are recommended for all individuals with knee osteoarthritis. There is limited evidence quantifying the quality and types of care individuals with knee osteoarthritis receive (29–39), and most studies focus on individuals with relatively late-stage knee osteoarthritis (30,33,34,37,40). However, earlier intervention allows more potential for core or other treatments to slow or prevent symptoms or structural knee osteoarthritis progression (41–44); therefore, treatments provided to individuals with earlier stages of knee osteoarthritis warrant evaluation when examining healthcare pathways. It remains unclear whether core strategies are implemented in clinical care and align with best-practice guidelines, particularly for individuals with knee osteoarthritis at earlier stages of the disease process.

One of the most widely recommended forms of non-surgical and non-pharmacological treatment for knee osteoarthritis is structured, land-based physical activity (18–25). Walking is a strongly recommended activity type (18,21,25,45–48) and is correspondingly the most performed physical activity by individuals with knee osteoarthritis (49,50). Unfortunately, many individuals with knee osteoarthritis are physically inactive (49,51–60), and do not receive advice to exercise from their healthcare providers (29–39). Exercise prescription may be limited by the lack of disease-specific physical activity guidelines (61,62); indeed, there is currently insufficient evidence to inform knee osteoarthritis physical activity prescription parameters (e.g., duration, intensity) (21,63–66). As such, physical activity and walking recommendations for knee osteoarthritis are widely adopted from general physical activity guidelines for older adults (45–47,67–70). However, these general guidelines are based on cardiovascular and general health benefits (71–74), and do not consider disease-specific outcomes including mechanical, structural or clinical features that characterise knee osteoarthritis (11–15). There is very little evidence quantifying the effects of continuous walking (75–78), or examining the effect of walking parameters (79–81), on disease-specific joint health outcomes. More evidence is required to understand the effects of continuous walking as a type of physical activity on disease-specific outcomes to optimize physical activity prescription for knee osteoarthritis populations.

Repetitive, aberrant joint loading can contribute to osteoarthritis disease processes (12,82). Individuals with, compared to without, knee osteoarthritis typically walk with altered loading magnitudes in the sagittal and frontal planes (83–86), and mechanical loading may contribute to structural changes in the joint (11,87). Indeed, walking mechanics have previously been associated with symptomatic (e.g., increased knee pain) (86,88,89), clinical (i.e., progression to total knee arthroplasty) (90), and structural (e.g., cartilage thinning) (91–95) knee osteoarthritis progression. Continuous walking increases knee joint loading frequency (i.e., number of steps), and in combination with aberrant loading magnitudes in knee osteoarthritis populations, may ultimately have implications for both symptoms and structural disease progression. The biomechanical effects of continuous walking for knee osteoarthritis has received little attention to date (75,78–81,96), and should be examined following single-bout and repeated walking exposures to understand the immediate and potentially cumulative effects of continuous walking on knee joint loading, symptoms, and structural progression.

Structural response to physical activity is typically measured longitudinally using radiographs or magnetic resonance imaging (MRI) (97–100); however, emerging structural imaging modalities and biomarkers, including MRI and ultrasound measures, can assess immediate changes in knee joint structure. Immediate changes in cartilage morphology in response to loading represent cartilage mechanical properties (101,102), have been proposed as surrogate markers of biochemical composition (103), and therefore may be related to longitudinal structural changes (104–106). Structural imaging assessment of healthy tissues has demonstrated that cartilage thickness decreases following an acute bout of walking (107,108), although research on osteoarthritic knees is lacking and suggests cartilage thickness may not decrease following a walking bout (109). More osteoarthritis-specific research is needed on immediate cartilage response following continuous walking since loading may influence healthy and pathological tissues differently (87).

Finally, multiple knee osteoarthritis outcomes are rarely reported together, including mechanical, structural, and clinical factors. Recent work has highlighted preliminary relationships between joint reaction forces and cartilage thickness deformation following continuous walking in knee osteoarthritis populations (110). Additionally, research has demonstrated associations between knee osteoarthritis walking mechanics or joint loading, and changes in knee pain or serum biomarkers indicative of cartilage health, in response to a continuous walking bout (79–81,111,112). This evidence collectively suggests that mechanical, structural, and pain response to continuous walking may be related. The acute effects of prolonged walking on interrelated knee osteoarthritis outcomes warrants further research to comprehensively understand the effects of continuous walking on knee joint health outcomes and inform walking prescription for knee osteoarthritis populations.

1.2 Thesis Aim and Objectives

The overall aim of this thesis was to better understand whether and how physical activity, particularly walking, is prescribed to manage knee osteoarthritis (Chapters 3 and 4), and to add to our understanding of the effects of walking on quantitative joint health outcomes for individuals with knee osteoarthritis (Chapters 4 and 5).

1.2.1 Thesis Objective 1

1.2.1.1 Rationale

Clinical practice guidelines for knee osteoarthritis management consistently recommend non-surgical and non-pharmacological treatment strategies to manage patient symptoms (18–25). However, evidence shows that surgical and pharmacological care pathways are more frequently implemented for individuals with knee osteoarthritis compared to non-surgical and non-pharmacological modalities (32,34,36,38). The quality of non-surgical and non-pharmacological osteoarthritis care is suboptimal (29–39), and has not shown a clear improvement over time (113). Specific core treatment quality varies based on geographic regions and healthcare systems (30,34,36,39), as well as social and demographic factors (30,34,36). Previous evidence quantifying the quality of osteoarthritis care has focused on relatively late-stage osteoarthritis populations (30,33,34,37,40), however, treatments at earlier stages of knee osteoarthritis are preferred because they permit earlier and continued intervention throughout the disease process (41–44). The quality of osteoarthritis care has rarely been quantified in less clinically severe knee osteoarthritis populations (114); this information will help identify gaps in recommended osteoarthritis care pathways to improve patient care and outcomes, informing objective 1.

1.2.1.2 Specific Objectives

Thesis objective 1 was to evaluate the quality and types of care individuals with mild-to-moderate knee osteoarthritis receive in the Maritime provinces of Canada (Nova Scotia, New Brunswick, Prince Edward Island).

Objective 1 was achieved through three sub-objectives:

i. Determine the quality of non-surgical and non-pharmacological care strategies prescribed to individuals with knee osteoarthritis in the Maritimes.

ii. Determine the association between the quality and types of care received with patient demographic (age, sex) and social (education, employment) factors.

iii. Determine the association between the quality and types of care received with patient-reported outcomes.

1.2.1.3 Summary

Chapter 3 is a cross-sectional, descriptive observational survey-based study that addresses thesis objective 1. This chapter contributes to the overall purpose of this thesis by examining whether physical activity, along with other types of core treatment, is prescribed for individuals with mild-to-moderate knee osteoarthritis.

1.2.2 Thesis Objective 2

1.2.2.1 Rationale

One of the most widely recommended forms of non-surgical and non-pharmacological treatment for knee osteoarthritis is physical activity (18–25). Structured, land-based aerobic physical activities, including walking, are strongly recommended across clinical practice and physical activity guidelines (18,21,25,45–48). However, increased joint loading, and the potential negative structural consequences of those loads (11,87), underscore the fear of disease worsening that is commonly expressed by individuals with knee osteoarthritis and their healthcare providers in relation to participating in or prescribing physical activity (61,115,116). Mechanical and structural responses to walking interventions have received little attention in the literature to date; therefore, it remains unclear how prolonged walking, within a single-bout or across repeated exposures, may influence disease-specific quantitative joint health outcomes for individuals with knee osteoarthritis. Additionally, disease-specific physical activity guidelines are lacking (21), and it is unknown whether knee osteoarthritis outcomes may be influenced by specific walking parameters. More information on the overall effects of walking for biomechanical and structural knee joint health outcomes and prescribed walking parameters will improve our understanding of the suitability of walking as a treatment approach for knee osteoarthritis, encompassing objective 2.

1.2.2.2 Specific Objectives

Thesis objective 2 was to review, synthesize, and evaluate the strength of the evidence quantifying the effects of walking interventions on quantitative biomechanical and structural knee osteoarthritis outcomes.

Objective 2 was achieved through three sub-objectives:

i. Determine the biomechanical and structural effects of walking interventions on quantitative knee osteoarthritis joint health.

ii. Summarize the walking parameters prescribed for individuals with knee osteoarthritis.

iii. Explore associations between quantitative knee osteoarthritis outcomes and walking parameters.

1.2.2.3 Summary

Chapter 4 is a systematic review and meta-analysis with meta-regressions that addresses thesis objective 2. This chapter contributes to the overall purpose of this thesis by examining how walking is currently prescribed for individuals with knee osteoarthritis and summarizes existing literature on the effects of walking on quantitative biomechanical and structural knee osteoarthritis outcomes.

1.2.3 Thesis Objective 3

1.2.3.1 Rationale

Walking involves knee joint loading, which is presumed to contribute to knee osteoarthritis disease processes (14,117). Continuous walking has been shown to increase joint contact and muscle forces, as well as knee joint pain, after 30 minutes (79,80,96). Despite gait biomechanics representing modifiable risk factors for knee osteoarthritis, biomechanical alterations following continuous walking have rarely been examined for individuals with knee osteoarthritis (79,81,111,112). Biomechanical changes following a walking bout may inform the appropriateness of walking exercise for knee osteoarthritis populations based on relationships between joint loading during gait and pain and joint-level structural response. Knee pain has been independently associated with knee joint moments (118), and biomechanical changes differentiated sub-groups of participants who did and did not report increased pain levels following a continuous walk (81). Further, continuous walking resulted in decreased cartilage thickness within healthy participants (107,108,119–121), and cartilage deformation may be related to mechanical factors (109) or associated with longitudinal structural disease progression (101,122). There is a paucity of research on cartilage thickness changes following continuous walking for individuals with knee osteoarthritis (109); yet, disease-specific responses are important to consider since loading influences healthy and pathological tissues differently (87). Morphological cartilage changes can be quantified using MRI or emerging imaging modalities including ultrasound; evidence comparing different imaging modalities in knee osteoarthritis populations is currently lacking (123). Additional information is required to understand how gait biomechanics, cartilage thickness, and pain change in response to a walking bout to provide a mechanistic investigation into interrelated knee osteoarthritis outcomes, and the suitability of walking exercise on these outcomes, leading to objective 3.

1.2.3.2 Specific Objectives

Thesis objective 3 was to determine the immediate effect of a 30-minute continuous walking bout on biomechanical, structural, and patient-reported outcomes in individuals with knee osteoarthritis.

Objective 3 was achieved through three sub-objectives:

i. Describe and quantify how gait biomechanics change in individuals with knee osteoarthritis following 30-minutes of continuous walking.

ii. Describe, quantify, and compare articular cartilage thickness changes following 30-minutes of continuous walking using MRI and ultrasound.

iii. Explore sub-groups of responders and non-responders based on structural (cartilage thickness) and patient-reported (pain) changes following walking to examine sub-group differences based on baseline metrics or biomechanical response to walking.

1.2.3.3 Summary

Chapter 5 is a laboratory-based experimental study that addresses thesis objective 3. This chapter contributes to the overall purpose of this thesis by examining the immediate effects of walking on biomechanical, structural, and patient-reported knee osteoarthritis outcomes, thus adding to our current understanding of the effects of walking on quantitative joint health.

1.3 Thesis Overview

Chapter 1 introduces this thesis and provides the overarching motivation for studying physical activity and the role of walking for knee osteoarthritis, with a focus on biomechanical, structural, and patient-reported features. It provides the overall aim of the thesis, as well as the three specific objectives with corresponding rationale, sub-objectives, and noted contribution to the overall thesis.

Chapter 2 provides a review of the relevant literature informing this thesis. The literature review identifies gaps in the current literature regarding the quality of knee osteoarthritis care and the effects of walking on knee osteoarthritis outcomes. The literature review provides a summary of the burden of knee osteoarthritis, factors contributing to the incidence and progression of knee osteoarthritis, knee osteoarthritis management guidelines, the quality of knee osteoarthritis care, and the effects of walking on knee osteoarthritis clinical, biomechanical, and structural outcomes.

Chapter 3 is a manuscript-style study chapter addressing thesis objective 1. This study is a descriptive observational survey-based study titled "Quality of Non-Surgical and Non-Pharmacological Knee Osteoarthritis Care in the Maritimes."

Chapter 4 is a manuscript-style study chapter addressing thesis objective 2. This study is a systematic review and meta-analysis titled "The Effect of Walking Interventions on Biomechanical and Structural Knee Osteoarthritis Outcomes: A Systematic Review and Meta-Analysis."

Chapter 5 is a manuscript-style study chapter addressing thesis objective 3. This study is a laboratory-based study titled “The Immediate Effect of a 30-minute Continuous Walking Bout on Biomechanical and Structural Imaging Outcomes in Knee Osteoarthritis.”

Chapter 6 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 study presented in Chapter 3.

Appendix B represents a supplemental analysis of Chapter 3 to replicate the original methodology of the British Columbia Osteoarthritis Survey.

Appendix C shows the detailed systematic review search strategy employed in Chapter 4.

Appendix D presents research ethics board approval for the study presented in Chapter 5.

Appendix E provides the Magnetic Resonance Imaging Screening questionnaire used during participant recruitment for the study presented in Chapter 5.

Chapter 2 Literature Review

2.1 Knee Osteoarthritis

2.1.1 Burden of Osteoarthritis

The global prevalence of osteoarthritis exceeds 500 million people (7% of the global population) (1). Prevalence of osteoarthritis is higher in high-income countries including Canada, where the prevalence is approaching 5 million people (14% of the Canadian population) (1,124). There is no cure for osteoarthritis; thus, osteoarthritis is currently the third most rapidly rising disabling condition worldwide (125), at least partially due to increasing life expectancies and changes in lifestyle factors including rapidly rising rates of obesity and physical inactivity (126). Osteoarthritis can occur in any joint, but is most frequently found in the knee joint, which accounts for over 350 million cases worldwide (5% of the global population) and nearly 2 million cases in Canada (5% of the Canadian population) (1,2). Knee osteoarthritis is therefore the most disabling form of osteoarthritis globally due to its high prevalence and weight-bearing function, which places a large and growing burden on the healthcare system (127).

Knee osteoarthritis and associated comorbidities contribute to high healthcare costs. Direct costs of knee osteoarthritis in Canada are expected to increase from \$2.9 billion in 2010 to \$7.6 billion in 2031 (10). Direct costs can be attributed to increasing proportions of individuals undergoing joint replacement surgery (128), more physician visits (129), and pharmaceutical costs (130). The proportion of Canadians receiving knee joint replacement surgery within the national benchmark timeframe of 182-days decreased from approximately 70% in 2016-2019 to approximately 50% in 2020-2022 (131), indicating that surgical demand exceeds the capacity of the Canadian healthcare system, particularly amidst and following the COVID-19 pandemic. Therefore, non-surgical management strategies are considerably more resource- and cost-effective than surgical interventions (132,133). Substantial indirect costs are also sustained. Productivity costs of work loss in the Canadian workforce are expected to increase from $12 billion in 2010 to $17.5 billion in 2031 (134). Indirect costs are driven by absenteeism (i.e., disease-related time off from work), presenteeism (i.e., disease-related loss of productivity while at work), and inability to work (i.e., early retirement) (135). Individuals with, compared to without, osteoarthritis are 1.8 times more likely to miss work (136), and osteoarthritis has been associated with early retirement due to pain and disability (137), which results in considerable personal (i.e., decreased income) and labour force costs (138).

Knee osteoarthritis also results in considerable patient burden. Knee osteoarthritis is characterized by joint pain, stiffness, physical dysfunction, and mobility limitations. Joint pain is the hallmark symptom of knee osteoarthritis. Knee osteoarthritis joint pain is commonly described as either a dull, aching, and constant pain, or an intense, unpredictable, and intermittent pain (139). As a result of these pain experiences, many individuals with knee osteoarthritis experience sleep disturbances (140,141), which are associated with fatigue (142,143). Pain can also contribute to mobility limitations and activity restrictions (140), which can lead to mood changes, including anxiety and depression (144). Together, these factors collectively contribute to decreased quality of life and overall wellbeing (145–147). Individuals with knee osteoarthritis also experience associated health risks. For example, individuals with, compared to without, knee osteoarthritis experience an increased risk of all-cause mortality (4–6). Additionally, knee osteoarthritis is frequently accompanied by comorbid conditions, including concomitant joint pain, diabetes, cardiovascular disease, osteoporosis, and lung disease, among others (7–9). These comorbidities burden the patient and contribute to worse prognosis of clinical osteoarthritis symptoms, including pain and performance-based physical function, for individuals with knee osteoarthritis (7). Effective knee osteoarthritis management strategies are required to reduce economic and personal burdens.

2.1.2 Defining Knee Osteoarthritis

Osteoarthritis is a chronic, progressive joint condition characterised by structural and clinical components. The etiology of osteoarthritis is complex, and accumulating evidence suggests that osteoarthritis likely develops through a combination of mechanical (14,148), biochemical (149,150), and genetic (151,152) mechanisms. The contributing structural and clinical components have been differentiated to provide a more comprehensive understanding of osteoarthritis, and have been defined as the disease (i.e., joint-level structural changes) and illness (i.e., patient-reported symptoms) states, respectively (15). Although disease and illness components often occur simultaneously, it is possible for each to occur independently (153); therefore, knowledge on how both structural and clinical features can be diagnosed and monitored for progression is required to provide a holistic understanding of knee osteoarthritis.

The disease state of osteoarthritis is defined as the presence (or absence) of structural changes within the joint. Although the focus of knee osteoarthritis is typically placed on damage to or disrepair of articular cartilage, osteoarthritis is a whole-joint disease affecting multiple structures within synovial joints including articular cartilage, subchondral bone, ligaments, menisci, muscles, nerves, and synovium (15). It has been proposed that structural changes in the joint occur primarily as a result of abnormal joint mechanics, including knee joint malalignment and increased knee joint loading (12,14,15,148). Osteoarthritis was previously classified as a “wear and tear” disease of the local joint; however, it is now regarded as a more systemic disease, influenced by molecular, biological, and inflammatory factors (13,154). Mechanical and inflammatory components likely interact resulting in structural changes (11); thus, an improved understanding of how mechanical and inflammatory factors collectively contribute to structural disease processes, and their effect on clinical components, is necessary to comprehensively understand knee joint health.

Structural disease characteristics may also contribute to osteoarthritis illness components. The illness state of osteoarthritis is defined as patient experiences or perceptions of ill health, which can occur in the presence or absence of disease (15,155). Common patient-reported symptoms include pervasive joint pain, stiffness, knee joint instability, functional disability, reduced knee joint range of motion, and mobility limitations (15–17). These symptoms consequently result in reduced activities of daily living, mood changes, sleep disturbances, fatigue, and decreased quality of life (140,144,146). Knee joint pain is the most common reason individuals with knee osteoarthritis seek clinical care (156,157); accordingly, pain relief is the primary focus of most knee osteoarthritis treatment strategies. Therefore, the importance of patient-reported symptomatic outcomes cannot be overstated, and the combination of structural and clinical components provides the most comprehensive understanding of knee osteoarthritis initiation and progression.

2.1.3 Risk Factors for Knee Osteoarthritis

There are several non-modifiable and modifiable factors that increase an individual's risk of developing knee osteoarthritis. The most widely reported non-modifiable risk factors for knee osteoarthritis development include sex, race, and age (158,159). Knee osteoarthritis is more prevalent in females than males (1), and in African Americans compared to whites (160). Although rates of knee osteoarthritis increase with age (1), prevalence is increasing in younger people, such that over half of new osteoarthritis diagnoses occur in individuals under the age of 65 years (161). This increase in prevalence overall and within younger age groups can likely be attributed to changes in lifestyle and other modifiable risk factors including obesity, physical inactivity, previous joint injury, and knee joint malalignment (3).

One of the best-established modifiable risk factors for knee osteoarthritis is obesity. Obesity is conventionally defined using body mass index (BMI), where a BMI of ≥ 25 kg/m^2 is deemed overweight, and a BMI of ≥ 30 kg/m^2 is deemed obese (162). Obesity is proposed to contribute to knee osteoarthritis via both mechanical (163) and metabolic (164) pathways. Mechanically speaking, increased body mass contributes to increased knee joint loading (163). Metabolically speaking, adiposity contributes to low-grade inflammation and promotes proinflammatory factors that negatively affect joint tissues (164). Risk of knee osteoarthritis doubles if an individual is overweight or obese (165), and most individuals with knee osteoarthritis are overweight or obese (166). Further, being overweight or obese is associated with physical inactivity in individuals with knee osteoarthritis (167), fueling a cycle that contributes to further weight gain.

Physical inactivity is closely linked with obesity and is also a distinct and well-documented risk factor for knee osteoarthritis. Physical inactivity is defined as not achieving recommended physical activity levels. Physical inactivity can contribute to quadriceps muscle weakness (168), which is a risk factor for knee osteoarthritis development (169). Additionally, increased physical activity can help mitigate undesirable age-related alterations in walking mechanics (170). Maintaining recommended physical activity levels may reduce the risk of developing radiographic or symptomatic knee osteoarthritis (171,172), or slow disease progression (100). Unfortunately, most individuals with knee osteoarthritis are physically inactive (49,51–60). The human musculoskeletal system is designed to respond to biophysical stimuli, and therefore mechanical joint loading is essential to maintain healthy tissue structure and strength (173,174). Thus, physical inactivity not only fosters worse overall health (175), but may provide insufficient mechanical stimuli, promoting joint dysfunction and increasing the risk of knee osteoarthritis. Conversely, although early evidence suggested high levels of physical activity, particularly high intensity sports, increased knee osteoarthritis risk (176,177), the relationship between physical activity and risk of osteoarthritis may be mediated by previous knee injuries (178,179).

Previous knee joint injury is another well-established risk factor for knee osteoarthritis development (158,165). Systematic reviews have concluded that individuals who sustained an anterior cruciate ligament injury, meniscal damage, or lower limb fracture, experienced a 4-to-6-fold higher risk of developing radiographic or clinical knee osteoarthritis (180,181). Additionally, it is estimated that 5% of incident knee pain can be explained by previous knee injury (165). Knee injuries are traumatic events that disrupt joint homeostasis, impair the joint's ability to heal, and can ultimately lead to joint dysfunction and failure (182). Arthroscopic investigations following an anterior cruciate ligament rupture concluded that approximately 90% of knees had sustained articular cartilage injuries (183). Cartilage degeneration following an anterior cruciate ligament injury can contribute to aberrant walking and cartilage loading patterns (184), and altered biological and mechanical components can contribute to knee osteoarthritis development.

Another mechanical risk factor for the development and progression of knee osteoarthritis is knee joint malalignment (185–187). Knee joint malalignment is identified in the frontal plane as either varus (i.e., bow-legged) or valgus (i.e., knock-kneed) alignment. Malalignment shifts the contact forces within the knee joint and results in abnormal static and dynamic knee joint loading (188). Altered load distribution and resultant changes in joint geometry may influence cartilage composition (189), making the joint more susceptible to further structural or mechanical changes. It has also been proposed that malalignment mediates the relationship between obesity and disease progression (190–192). While obesity increases total compressive knee joint forces, malalignment increases peak external knee adduction moment (193), which differentiates individuals with knee osteoarthritis from asymptomatic counterparts (83). The individual and combined contributions of mechanical, metabolic, and biological factors increase an individual's risk for developing knee osteoarthritis.

2.1.4 Knee Osteoarthritis Diagnosis

Osteoarthritis can be diagnosed using structural or clinical features, aligning with the respective disease and illness states. Radiographic knee osteoarthritis diagnosis considers isolated structural findings, and is frequently defined as a Kellgren and Lawrence grade (KLG) of 2 or greater (194). The KLG scale rates the presence and severity of osteoarthritis ranging from 0 (none) to 4 (severe) based on the presence of osteophytes and joint space narrowing (194). Osteophytes are bony outgrowths typically associated with the degeneration of articular cartilage, and joint space narrowing is defined as a decrease in the smallest distance between the femoral condyle and tibial plateau. A KLG of 2 or greater therefore indicates definite osteoarthritis (presence of osteophytes and joint space narrowing) with minimal severity (194). However, radiographic findings are poorly associated with patient symptoms (195,196). Accordingly, other osteoarthritis diagnostic criteria combine both structural and clinical components to better reflect patient burden.

Symptomatic knee osteoarthritis diagnostic criteria consider both radiographic and clinical components. Symptomatic knee osteoarthritis is defined as concurrent radiographic (i.e., KLG ≥ 2) and clinical findings, particularly knee pain. An example of classification criteria for clinical research that considers both radiographic and symptomatic findings are the American College of Rheumatology (ACR) classification criteria (197). The ACR criteria state a standardized definition of knee osteoarthritis that includes knee pain and at least one additional symptom or risk factor, including 50 years of age or older, morning stiffness lasting less than 30 minutes, or crepitus, as well as radiographic osteophytes (197). Osteophytes were deemed the criterion measure to differentiate osteoarthritis from other rheumatic conditions. The ACR clinical and radiographic knee osteoarthritis classification criteria are sensitive (91%) and specific (86%) (197). The ACR criteria are widely implemented across clinical trials; however, radiographs experience a slow rate of change and the ACR criteria may reflect more advanced stages of the disease (198). To identify earlier disease-related changes, knee osteoarthritis is increasingly diagnosed and classified in clinical and research contexts, respectively, using clinical criteria that rely on patient symptoms rather than structural imaging.

It is now generally accepted that imaging is not required to diagnose knee osteoarthritis (199,200). Therefore, clinical definitions of knee osteoarthritis have been developed by the ACR (197), European League Against Rheumatism (EULAR) (201), and National Institute for Clinical Excellence (NICE) (23), which are based on patient symptoms and/or clinical exam findings (23,201). According to the ACR criteria, clinical findings can be used to classify knee osteoarthritis in the absence of radiographs if the patient experiences knee pain and at least three additional symptoms or risk factors, including 50 years of age or older, morning stiffness that lasts less than 30 minutes, crepitus, bony tenderness or enlargement, and no palpable warmth (197). The EULAR diagnostic criteria state that knee osteoarthritis can be diagnosed clinically if the patient is 40 years of age or older, has usage-related knee joint pain, short-lived (i.e., <30 minute) morning stiffness, functional limitation, and one or more signs on clinical examination, including crepitus, restricted movement, or bony enlargement (201). The NICE clinical diagnostic criteria state that knee osteoarthritis can be diagnosed clinically if the patient is 45 years of age or older, has activity-related joint pain, and has no morning joint-related stiffness or morning stiffness that lasts no longer than 30 minutes (23). The EULAR and NICE clinical diagnostic criteria have been deemed the most specific and sensitive criteria, respectively, whereas the clinical ACR criteria were the most consistent compared to other clinical criteria over 5-to-10 year follow-up (202), suggesting it may be the best-suited clinical criteria across both clinical practice and research contexts.

2.1.5 Knee Osteoarthritis Progression

Following a knee osteoarthritis diagnosis, it is important to monitor patient-reported, clinical, and structural changes to determine how the individual, and their knee joint, respond to interventions and progress over time. Knee osteoarthritis progression is defined as worsening severity in terms of either clinical illness or structural disease components, or a combination. There are several different methods to assess knee osteoarthritis progression, namely symptomatic (e.g., knee pain), clinical (e.g., total knee arthroplasty), and structural (e.g., cartilage thickness loss) progression.

2.1.5.1 Symptomatic Knee Osteoarthritis Progression

It is vitally important to evaluate the progression of symptoms, particularly knee pain, to determine how knee osteoarthritis influences patient perceptions of overall wellbeing. Symptomatic knee osteoarthritis progression are frequently evaluated using a multitude of patient-reported outcome measures, including the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), which contains sub-scales for pain, stiffness, and physical function (203), and the Knee injury and Osteoarthritis Outcome Score (KOOS), which is an extension of the WOMAC and contains sub-scales for pain, symptoms, function in activities of daily living, function in sports and recreation, and knee-related quality of life (204). Although knee osteoarthritis may be better characterized by persistent, rather than continuously worsening, knee pain and symptoms (205), symptomatic knee osteoarthritis progression, and specifically trajectories of worsening knee pain, may be promoted by patient-specific factors including lower education and higher BMI, comorbidity, activity limitation, and joint space tenderness (206). Patient-reported metrics can be influenced by psychological factors including anxiety, depression, fear of movement, poor coping, or low self-efficacy (144,156); nevertheless, it is imperative to consider patient symptoms when evaluating knee osteoarthritis progression to assess how patients perceive their health.

2.1.5.2 Clinical Knee Osteoarthritis Progression

While symptomatic knee osteoarthritis progression is useful to examine changes in patient symptoms, structural changes are not considered within this approach; therefore, other metrics have been used in the literature to denote clinical knee osteoarthritis progression. For example, total knee arthroplasty is an informative clinical end point that is influenced by both patient symptoms and end-stage structural changes (207,208). Based on clinical indications, progression to total knee arthroplasty is intended for individuals with late-stage structural joint changes who did not achieve the acceptable symptom state with non-surgical treatment options (18,208). Therefore, although progression to total knee arthroplasty is a valuable end-stage clinical knee osteoarthritis progression metric, other structural imaging metrics may be more useful in identifying earlier or smaller structural changes indicative of knee osteoarthritis progression.

2.1.5.3 Structural Knee Osteoarthritis Progression

Structural knee osteoarthritis progression examines joint-level structural changes and is best evaluated using non-invasive imaging techniques. Although imaging is generally not required to diagnose knee osteoarthritis, it is a valuable tool to diagnose atypical clinical presentations of osteoarthritis, augment treatment or interventions including surgical planning or guided intra-articular injections, and monitor knee osteoarthritis structural disease progression (199,200). Imaging techniques including radiography, magnetic resonance imaging (MRI), and ultrasound permit visualization of the internal knee joint structures and their acute or longitudinal response to interventions.

Radiographic osteoarthritis disease progression can be assessed longitudinally using measures of joint space narrowing or KLG (194). The complete loss of radiographic joint space width is denoted as end-stage disease and is a common precursor to total knee replacement surgery (209). However, radiographs are not sensitive to change, experience a slow rate of change, and are not able to differentiate changes within soft tissues that may contribute to osteoarthritis symptoms and disease progression (210,211). Therefore, with recent technological advancements, knee osteoarthritis progression is now frequently assessed using more comprehensive imaging modalities including MRI and ultrasound, both of which can visualize additional joint structures and acute structural changes.

MRI is the current gold standard non-invasive imaging modality for monitoring knee osteoarthritis disease progression because it simultaneously visualizes all tissues within the joint and can comprehensively assess both longitudinal and acute changes in the whole joint in three-dimensions. Structural pathologies related to knee osteoarthritis, including cartilage composition (e.g., inflammatory biomarkers) and morphology (e.g., volume, thickness), bone marrow lesions, subchondral cysts, osteophytes, and effusion and synovitis, are concurrently visualized using MRI. Longitudinal structural disease progression is typically denoted as cartilage thickness loss using MRI (212,213); however, MRI also affords the unique opportunity to evaluate changes in cartilage morphology acutely in response to loading (109,214,215). Cartilage deformation represents the change in cartilage thickness in response to load, and has been proposed as a surrogate measure of cartilage composition (101). Cartilage composition changes denote physiological changes, indicate the quality of articular cartilage, and are associated with longitudinal structural disease progression (104,105). Thus, changes in MRI structural outcomes provide a comprehensive understanding of the entire knee osteoarthritis disease process from pre-morphological compositional changes to end-stage structural deterioration.

Acute changes in cartilage morphology can also be assessed using ultrasound imaging. Ultrasound directly identifies inflammatory and structural features of the knee including articular cartilage, tendons, ligaments, bursae, menisci, and synovium, which may promote early detection or an improved understanding of subtle osteoarthritis disease progression (216). Additionally, ultrasound can visualize superficial bone structures including osteophytes or irregular bony contours. Ultrasound is typically used to measure cartilage morphology for knee osteoarthritis, including cartilage thickness, volume, and surface area. Ultrasound is sensitive for measuring cartilage morphology and inflammatory markers, including osteophytes, synovitis, and effusion (107,217). The use of ultrasound imaging is an emerging area of research in the knee osteoarthritis literature (218), presenting a promising new pathway to investigate structural outcomes.

2.1.6 Factors Associated with Knee Osteoarthritis Progression

While symptoms and structural changes are essential markers of knee osteoarthritis progression, it remains unclear whether structural disease progression relates to patient-reported symptoms. For example, presence of radiographic knee osteoarthritis has limited association to knee pain or other patient-reported features (195,196,219,220), although radiographic progression has been strongly associated to symptom worsening prior to total knee arthroplasty (221). Additionally, many studies indicate agreement between knee pain and MRI outcomes including effusion and synovitis (222–225), osteophytes (224), cartilage volume (226), cartilage lesions (223,227), bone marrow lesions (222,225), meniscal tears (223), and composition measures (227), while other studies report weak-to-no associations between pain or physical function and MRI features (228). Finally, there is disagreement of whether ultrasound findings do (229,230) or do not (123,231) correspond with patient symptoms. Together, these findings highlight a disconnect between structural change and patient symptoms. More research is therefore needed to determine whether structural outcomes are associated with patient-reported and symptomatic outcomes.

Biomechanical factors have been associated with knee osteoarthritis progression. Gait analyses are frequently used to examine mechanical contributions to or consequences of knee osteoarthritis, including kinematic (i.e., joint angles) and kinetic (i.e., joint moments) components. Kinematics describe movement patterns without consideration of the forces causing motion, whereas kinetics describe movement with the associated forces. Kinetics, particularly external joint moments, are typically regarded as surrogate measures of joint contact forces (232,233) and are frequently used to describe knee joint loading.

Evidence from gait analyses highlight that individuals with knee osteoarthritis walk with characteristic gait patterns, particularly in the sagittal and frontal planes. In the sagittal plane, individuals with knee osteoarthritis, compared to asymptomatic counterparts, walk with lower knee flexion angle peaks and ranges (85), and exhibit lower knee flexion moment peaks and overall magnitudes (83–86), which has been described as a "stiff-knee" gait pattern. These sagittal plane changes progressively increase with knee osteoarthritis severity (84,234,235), and lower peak knee flexion moments have been independently associated with increased knee pain (118). Alterations in sagittal plane moments have also been associated with clinical and structural knee osteoarthritis progression, where higher peak knee flexion moment was associated with decreased tibial medial-to-lateral thickness change over 5-years (91), and lower knee flexion-extension moment difference was associated with progression to total knee arthroplasty after 5-to-8-years (90). However, other work has reported no association between peak knee flexion moment and medial knee osteoarthritis disease progression (95). Knee flexion moments reflect muscular contribution to movement and overall joint loading (236,237). This evidence collectively suggests sagittal plane gait mechanics may be related to knee osteoarthritis progression.

Considering knee osteoarthritis is commonly found in the medial tibiofemoral joint compartment (238), an emphasis has been placed on investigating frontal plane mechanics in knee osteoarthritis populations. Compared to asymptomatic counterparts, individuals with knee osteoarthritis typically walk with higher first and second peak knee adduction moments (83,84,239), higher knee adduction moment impulse (89,240), and higher overall knee adduction moment magnitude with less mid-stance unloading (85,86). Characteristic frontal plane changes increase with knee osteoarthritis severity (234,235). Knee adduction moment reflects medial-to-lateral tibiofemoral compartmental loading (87), where the impulse considers both the magnitude and duration of loading (240). Higher peak knee adduction moment and impulse have been associated with increased knee pain in knee osteoarthritis populations (118,241), indicating an association between biomechanical and patient-reported factors. Further, frontal plane biomechanics have been associated with clinical and structural knee osteoarthritis progression (90–95). For example, knee adduction moment features, including higher peaks, impulse, and overall magnitudes, have been associated with greater tibiofemoral osteoarthritis progression (92), lower femoral medial-to-lateral cartilage thickness ratio (91), higher medial tibial cartilage volume loss

(94), worsening bone marrow lesions and cartilage thickness loss (95), radiographic progression (93), as well as progression to total knee arthroplasty (90). Knee adduction moment features are therefore key biomechanical metrics to consider within interventions as they are consistently connected with various metrics of knee osteoarthritis progression.

2.1.7 Knee Osteoarthritis Summary

Knee osteoarthritis presents a substantial burden to the healthcare system (10) and greatly influences the overall health and quality of life of affected individuals (145–147). Knee osteoarthritis is a complex disease process based on interactions from mechanical, inflammatory, and biological factors, as well as modifiable risk factors (3,14,154). The disease and illness components are each important to consider throughout the knee osteoarthritis disease process since they may occur independently or together, and collectively represent joint-level to patient-level outcomes as the condition progresses (15). To minimize the burdens of knee osteoarthritis and improve patient outcomes, treatment strategies are required to slow, or ideally stop, disease progression. Optimal treatment strategies would improve both structural and clinical components, and potentially contribute to the prevention of knee osteoarthritis by addressing risk factors for disease incidence (242). Implementing knee osteoarthritis treatment at early stages of the disease would allow the highest potential to slow or potentially halt knee osteoarthritis progression by affording earlier and continued intervention, which may prevent symptomatic, clinical, or structural changes (41–44). Successful treatment strategies would have the potential to improve patient overall health and symptoms and reduce the large personal and societal burdens of knee osteoarthritis.

2.2 Knee Osteoarthritis Management

2.2.1 Knee Osteoarthritis Treatment Guidelines

There is no cure for knee osteoarthritis; therefore, disease and symptom management strategies are required to improve clinical and structural outcomes and reduce individual and societal burdens (242). Clinical practice guidelines for knee osteoarthritis have been developed for clinicians, policy makers, and patients to enhance decision-making for appropriate osteoarthritis care pathways and optimize healthcare delivery (18–25). These evidence-based recommendations have been systematically developed using consensus-based approaches by multidisciplinary teams of experienced researchers, clinicians, and other stakeholders, including patients. Clinical practice guidelines prioritize treatment options to manage knee osteoarthritis outcomes including reducing pain and improving physical function and quality of life (18). Based on current literature and the efficacy and cost-effectiveness of non-surgical treatments for knee osteoarthritis, recent clinical practice guidelines focus on various non-surgical care pathways.

Several international entities exist for osteoarthritis care that have created distinct sets of knee osteoarthritis treatment guidelines. These entities include: the American Academy of Orthopaedic Surgeons (20), ACR (21), EULAR (24), European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases (19), NICE (23), Osteoarthritis Society International (OARSI) (18), Royal Australian College of General Practitioners (25), and the United States Department of Veterans Affairs and Department of Defense (22).

2.2.1.1 Core Treatment

Across clinical practice guidelines, there is international consensus on recommended core treatment for knee osteoarthritis. Core treatments are safe, effective, low cost, and highly accessible, and are therefore deemed suitable for nearly any individual with knee osteoarthritis, regardless of disease severity or most comorbidities. Recommended core treatments include education and self-management, physical activity, therapeutic exercise, and weight loss when medically indicated (i.e., BMI ≥ 25 kg/m^2) (18–25). These core strategies should be implemented for virtually every person with knee osteoarthritis and should be combined with other first- and second-line treatment approaches for optimal care (18,25).

Education and Self-Management. Patient education and self-management are considered the standard-of-care and remain the recommended first step for knee osteoarthritis treatment. This approach should provide information on osteoarthritis, including disease progression, self-efficacy and self-care techniques, and an explanation of potential benefits, risks, and potential outcomes of each treatment option (18–25). Education and self-management programs do not directly or meaningfully influence knee osteoarthritis symptoms or quality of life, although they pose minimal risk and may improve self-efficacy for knee osteoarthritis self-management, particularly when coupled with other forms of treatment (243).

Physical Activity. Physical activity encapsulates all physical movement and activities of daily living, both structured and unstructured. Achieving recommended physical activity levels is necessary for individuals with knee osteoarthritis to maintain overall health. General physical activity guidelines for older adults have been deemed safe for individuals with knee osteoarthritis (20,24). For instance, EULAR recommends that individuals with knee osteoarthritis should achieve 30 minutes of moderate intensity physical activity at least 5 days per week, or 20 minutes of vigorous intensity physical activity at least 3 days per week (24). Clinical practice guidelines agree that physical activity is associated with reduced pain, improved physical function, and improved cardiovascular and overall health (18–25). However, physical activity increases the loads placed on the joint, which may induce osteoarthritis disease processes (87,117). Although physical activity improves overall and cardiovascular health, more knowledge on joint-health outcomes (e.g., mechanical joint loading, structural changes) is required.

Therapeutic Exercise. Therapeutic exercise is defined as any type of exercise prescribed to target knee osteoarthritis symptoms. Despite recommending therapeutic exercise as core treatment for knee osteoarthritis, clinical practice guidelines have noted that the optimal exercise dosage (e.g., frequency, intensity, duration) remains unknown (21,63,64), and that there is no clear preference between different types of exercises (e.g., aerobic vs. strengthening programs) for improving pain and function (19,22,65,244). Types of therapeutic exercise most widely and strongly recommended across clinical practice guidelines include land-based aerobic and/or strengthening exercises, including walking, tai chi, and muscle strengthening (18,20,23–25). Other forms of exercise, including aquatic exercise, cycling, balance activities, and yoga are conditionally recommended (18,21,25). Nevertheless, a broad range of exercise types and doses are effective for knee osteoarthritis management, and exercise prescription should consider patient preferences, physical ability, and exercise accessibility to promote adherence (21). Additional evidence is required to determine optimal exercise prescription parameters for knee osteoarthritis.

Weight Loss. Maintaining a healthy body weight is critical for individuals with knee osteoarthritis. Therefore, weight loss is recommended across all clinical practice guidelines for individuals who are overweight or obese (i.e., BMI ≥ 25 kg/m^2) (18–25). Specific recommendations for weight loss targets are 5% to 7.5% of overall body weight (18,25). Relatively low magnitudes of weight loss (0.25% body weight per week) decrease pain and disability (245), whereas higher magnitudes (5 to 10% body weight) further reduce knee joint contact forces and inflammation (246–249). Moreover, there is a dose-response relationship between weight loss and improved clinical outcomes in individuals with knee osteoarthritis, including pain, physical function and performance, quality of life, knee joint forces, and inflammation (250). Therefore, weight loss reduces joint loading and inflammation, both of which contribute to osteoarthritis disease processes (163,251).

2.2.1.2 Adjunct Therapies

Adjunctive therapies are also recommended across clinical practice guidelines to supplement core treatments; however, these approaches vary across guidelines and are not recommended for all individuals with knee osteoarthritis. For example, non-surgical and non-pharmacological adjunctive therapies include acupuncture, walking aids (e.g., canes), psychological interventions, braces, taping, modified footwear, thermal interventions, massage, or transcutaneous electrical nerve stimulation (18–25). To determine whether these therapies would be suitable for specific patients, it is important to continually assess patient-reported pain and physical function, among other clinical factors. The strength of this evidence varies, and as such, recommendations are inconsistent across clinical practice guidelines. These treatments should therefore be individualized based on clinical need, with a clear description of potential benefits or costs associated with treatment.

2.2.1.3 Pharmacological Treatment

Several clinical practice guidelines recommend the use of pain-relieving medications to supplement core treatment. However, this advice is inconsistent across guidelines. The most widely recommended pharmacologic treatments include topical or oral non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen or paracetamol, chondroitin, or topical capsaicin (18–25). Further, some pharmacological therapies are recommended against, including opioids, glucosamine, hyaluronic acid injections, fish oil, and vitamin D supplements (18,19,21–23,25). Pharmacological therapies can provide negative consequences including gastrointestinal complications, renal toxicities, and heightened cardiovascular risk and are therefore not recommended for all individuals with osteoarthritis (27). Guidelines state that pharmacological therapy requires a full explanation of possible benefits and harms, and the "good clinical practice statement" from OARSI suggests that patients who are safe to use pharmacological treatment should use these treatments at the lowest possible dose for the shortest possible treatment duration (18). All pharmacological treatment should be used in conjunction with other core treatments, including physical activity or therapeutic exercise.

2.2.1.4 Surgical Treatment

Although osteoarthritis clinical practice guidelines focus on non-surgical treatment, joint replacement surgery is a treatment option intended to improve symptoms and restore joint function. It is now widely accepted that a referral for joint replacement surgery should be end-stage treatment (18,19,22,23). The NICE guidelines state that joint replacement should only be considered if the patient experiences joint symptoms that have a substantial impact on their quality of life and they have not responded to core or other non-surgical treatments (23). Although joint replacement surgery can improve physical function (252), it is also associated with adverse outcomes (28). The Canadian healthcare system is experiencing a backlog of knee joint replacement surgeries (131); therefore, non-surgical treatment modalities have more potential to reduce the burden on the healthcare system by reducing comorbidities and targeting knee osteoarthritis earlier in the disease process.

2.2.2 Quality Indicators of Osteoarthritis Care

With international consensus on core management strategies for knee osteoarthritis, it is important to determine whether individuals with knee osteoarthritis receive evidence-based care in practice. Osteoarthritis care pathways must be clearly defined and routinely evaluated to determine the types and quality of care received and assess whether clinical guidelines are implemented in practice. A strategy to evaluate the quality of care is to use osteoarthritis quality indicators that evaluate clinician-delivered care processes.

Osteoarthritis quality indicators represent the minimally acceptable standard of care and are intended to measure the degree to which health services are consistent with current clinical practice guidelines. Quality indicators are constructed as IF-THEN-BECAUSE statements to identify the care process and rationale (253,254). The “IF” statement represents the eligibility criterion for a care process to be performed. The “THEN” statement identifies the specific care process to be performed. The “BECAUSE” statement provides rationale and describes potential health outcomes. The quality of care is assessed using pass-rates for each quality indicator. Pass rates are calculated by dividing the number of individuals who received the care process (i.e., achieved the “THEN” statement) by the total number of individuals eligible for the care process (i.e., achieved the “IF” statement). Pass rates indicate the proportion of eligible individuals who received recommended care.

The Arthritis Foundation Quality Indicator Project was an initiative conducted to develop a set of care process indicators to assess the quality of osteoarthritis care, as well as rheumatoid arthritis care and analgesic use (254). Quality indicators were developed using a three-step process: (1) conduct a comprehensive literature search to identify existing quality indicators, (2) select care processes that would significantly impact outcomes and were widely recommended, and (3) define each quality indicator, including the expected impact on health outcomes. This process resulted in 14 quality indicators for osteoarthritis across the following categories: physical examination, pain and functional assessment, education, exercise, weight loss, assistive devices, pharmacologic therapy, surgery, and radiographs (254). These quality indicators are presented in Table 2.1.

The Arthritis Foundation quality indicator set was originally intended to assess the quality of care from the clinician's perspective using medical records or healthcare provider questionnaires. However, medical records can be discordant with patient perceptions of care received (255). Therefore, patient self-reported quality indicator metrics are the preferred method to continuously monitor and evaluate osteoarthritis healthcare quality because they reflect the observed quality of care and can better identify changes in patient symptoms and outcomes (38). To date, few patient-reported tools designed to assess quality of osteoarthritis care have been developed and implemented. Examples of patient-reported tools include the British Columbia Osteoarthritis Survey (36) and the Osteoarthritis Quality Indicator questionnaire (38,256). Within these tools, quality indicator eligibility and achievement are derived from patient-reported survey responses (36,38,256). Overall quality scores are calculated based on the proportion of quality indicators achieved.

Table 2.1. Arthritis Foundation Osteoarthritis Quality Indicators.

Physical examination	1	If a patient is begun on a drug treatment for joint pain, arthritis, or arthralgia, then evidence that the affected joint was examined should be documented.
Pain and functional assessment	2	If a patient is diagnosed with symptomatic osteoarthritis of the knee or hip, then their pain should be assessed annually and when new to a practice.
	3	If a patient is diagnosed with symptomatic osteoarthritis of the knee or hip, then their functional status should be assessed annually and when new to a practice.
Education	4	If a patient has had a diagnosis of symptomatic osteoarthritis of the knee or hip for > 3 months, then education about the natural history, treatment, and self-management of osteoarthritis should have been given or recommended at least once.
Exercise	5	If an ambulatory patient has had a diagnosis of symptomatic osteoarthritis of the knee or hip for > 3 months and has no contraindication to exercise and is physically and mentally able to exercise, then a directed or supervised muscle strengthening, or aerobic exercise program should have been prescribed at least once and reviewed at least once per year.
Weight loss	6	If an individual is overweight (as defined by body mass index of ≥ 27 kg/m^2), then the individual should be advised to lose weight annually.
	7	If a patient has symptomatic osteoarthritis of the knee or hip and is overweight (as defined by body mass index of ≥ 27 kg/m^2), then the patient should be advised to lose weight at least annually and the benefit of weight loss on the symptoms of osteoarthritis should be explained to the patient.
	8	If a patient has symptomatic osteoarthritis of the knee or hip and has been overweight (as defined by body mass index of ≥ 27 kg/m^2) for > 3 years, then the patient should receive referral to a weight loss program.
Assistive devices	9	If a patient has had symptomatic osteoarthritis of the hip or knee and reports difficulty walking to accomplish activities of daily living for >3 months, then the patient's walking ability should be assessed for need of ambulatory assistive devices.
	10	If a patient has a diagnosis of osteoarthritis and reports difficulties with non-ambulatory activities of daily living, then the patient's functional ability with problem tasks should be assessed for need of non-ambulatory assistive devices to aid with problem tasks.
Pharmacologic therapy	11	If a nonnarcotic pharmacologic therapy is initiated to treat osteoarthritis pain of mild or moderate severity, then acetaminophen should be the first drug used, unless there is a documented contraindication to use.
	12	If oral pharmacologic therapy for osteoarthritis is changed from acetaminophen to a different oral agent, then there should be evidence that the patient has had a trial of maximum-dose acetaminophen (suitable for age/comorbidities).
Surgery	13	If a patient with severe symptomatic osteoarthritis of the knee or hip has failed to respond to nonpharmacologic and pharmacologic therapy, then the patient should be offered referral to an orthopedic surgeon.
Radiographs	14	If a patient has hip or knee osteoarthritis and has worsening complaints accompanied by a progressive decrease in activities and no previous radiograph during the preceding 3 months, then a knee or hip radiograph should be performed within 3 months.

2.2.3 Quality of Osteoarthritis Care

The implementation of patient-reported quality indicator assessment tools has evaluated the quality of osteoarthritis care within different countries and healthcare settings. Overall pass rates span a wide range from 22.4% to 61.6%, where the average value across the literature is approximately 50% (29–39). The reported overall quality of care is dependent on the specific set of quality indicators selected, country of origin, healthcare setting, and population examined. Globally, the quality of osteoarthritis care is suboptimal, and a knowledge-to-practice gap exists between clinical practice guidelines and patient perceptions of clinical care.

The non-pharmacological quality indicators with the highest pass rates relate to exercise. Providing “advice to exercise” is consistently highest achieved, with pass rates ranging from 25.2% to 84.0%, achieving an average of approximately 64% across the literature (29–39). Pass rates of “referral for exercise” were consistently lower than “providing information about exercise” (31–33,35,37–39), which may help explain why most individuals with knee osteoarthritis are physically inactive (49,51–60), particularly if they are uncomfortable exercising or are unsure how to begin an exercise regimen independently. The lack of evidence-based disease-specific exercise dosage parameters has been identified as a major barrier to exercise prescription in knee osteoarthritis populations (257,258), consequently affecting exercise participation. The ACR stated that advice to exercise should be as specific as possible, rather than a general recommendation to exercise (21); therefore, more research on advice to exercise and the effect of specific types and dosages of exercise on knee osteoarthritis is required to inform exercise prescription and encourage individuals with knee osteoarthritis to be more physically active.

The quality indicators with the lowest pass rates relate to weight loss. Pass rates for "advice to lose weight" ranged from 24.0% to 69.2%, achieving an average of approximately 44% across the literature (30–39). However, pass rates for "referral to lose weight" were substantially lower, ranging from 0% to 20%, achieving an average of approximately 9% across the literature (31–33,35,37–39). Low rates of weight-loss referrals may present a barrier to individuals with osteoarthritis who are informed they should lose weight but feel that they do not have adequate professional support to achieve meaningful weight loss (259). Considering even modest amounts of weight loss are associated with improved patient symptoms (245), overweight or obese patients should be encouraged to lose weight in a gradual and sustainable manner. More information on weight loss quality indicators is needed to identify potential gaps in these care pathways and provide targeted strategies to improve the mechanical and metabolic risk factors for knee osteoarthritis initiation and progression associated with obesity.

The quality of adjunctive therapies is the most variable of all quality indicators. For example, pass rates for "assessment of walking aids" (e.g., walker, crutch) ranged from 0% to 40%, with an average of approximately 27% across studies, and pass rates for "assessment for other appliances" (e.g., assistive technology, special chairs) ranged from 0% to 18.5%, with an average of approximately 15% across studies (31–33,35–39). It is likely that the variability within the quality of these outcomes stems from the variability across clinical practice guidelines for recommendations of adjunctive therapies; for instance, various walking aids or devices were recommended (21), conditionally recommended (23,24), or advised against (18,25) within different clinical practice guidelines. Since adjunctive therapies are not core treatment, more knowledge on these pass rates may be useful to understand which individuals are receiving adjunctive therapies compared to core treatment, and whether patient characteristics influence the quality or types of adjunctive care received.

The quality of non-pharmacological care is lower than that of pharmacological care (32,38). Pass rates for "acetaminophen" ranged from 46.0% to 80.0%, with an average of approximately 66% across the literature, which represents the highest average pass rate of all quality indicators (29,31–35,37–39). Pass rates for other pharmacological treatments were slightly lower, where "information about NSAIDs" ranged from 42.0% to 72.0% (average of approximately 56%) and "prescription of stronger painkillers" ranged from 31.4% to 66% (average of approximately 46%) (29,31–35,37–39). Finally, pass rates for "referral for surgery" ranged from 15.0% to 72.7%, achieving an average of approximately 47% across studies (29,31,32,35,37–39). These findings indicate that pharmacological and surgical treatment pathways are used more frequently compared to core and other non-surgical treatment options. Therefore, a larger emphasis must be placed on understanding the quality of non-surgical and non-pharmacological care pathways because they align with core treatment, are recommended for almost all individuals, and may be most beneficial for individuals with knee osteoarthritis.

Numerous trends emerged when examining the quality of osteoarthritis care. Specifically, quality indicator pass rates were dependent on patient-level factors, including demographic, social, healthcare history, and symptomatic factors, as well as regional factors and associated healthcare systems. Demographic and social factors associated with improved care quality include female sex (34,36), younger age (30,34,36), and higher education level (34,36). Healthcare factors associated with improved care include reported osteoarthritis in multiple joints, presence of comorbidities, or having undergone joint replacement surgery (36,37), as well as higher overall osteoarthritis treatment satisfaction (31,32) and interacting with multiple healthcare professionals (e.g., therapist and specialist) (30,37). Further, worse patient-reported symptoms (i.e., using the WOMAC) have been associated with better healthcare quality (36), which is consistent with evidence reporting that individuals with late-stage osteoarthritis (i.e., pre-total knee arthroplasty) receive high quality of care (34). Much of the previous quality indicator work has been completed on individuals with relatively late-stage osteoarthritis (30,33,34,37,40); therefore, it remains poorly understood whether individuals with less severe osteoarthritis receive optimal quality of care. It is necessary to consider patient-level factors when assessing the quality and types of osteoarthritis care to determine whether inequities exist in healthcare delivery, particularly amongst individuals with earlier stages of knee osteoarthritis.

In addition to patient-level factors, regional factors have also been shown to influence the quality of care. For instance, a multinational study across four European countries indicated that the quality and types of osteoarthritis care varied by country (39). Additionally, within Canada, the quality of osteoarthritis care was dependent on the provincial health systems (30,34,36). In British Columbia, Ontario, and Alberta, pass rates for advice to exercise were 25.2%, 62.8%, and 75.4%, respectively, and for advice to lose weight were 25.0%, 58.5%, and 69.2%, respectively (30,34,36). These individual pass rates should be interpreted with caution as each of these studies used a separate set of quality indicators to assess the quality of care; nevertheless, trends indicate that provincial healthcare systems influence the quality of osteoarthritis care. Quality of osteoarthritis care has yet to be assessed within the remaining seven Canadian provinces but would provide valuable information to improve the quality of osteoarthritis care across Canada. It is important to consider regional factors when assessing care quality because cultural norms or regional healthcare systems vary globally, and even within countries including Canada, which can influence the quality and types of care received for knee osteoarthritis.

2.2.4 Knee Osteoarthritis Management Summary

The translation of clinical guidelines into practice is essential to ensure clinical care aligns with current best evidence. Evidence quantifying the quality of osteoarthritis care globally suggests that pharmacological and surgical modalities are widely used, whereas non-surgical and non-pharmacological modalities, including core treatments, are implemented less often (29,31–35,37–39). Traditional care pathways of pharmacological treatment preceding end-stage joint replacement surgery are troubling considering these treatment modalities are associated with various complications and are not indicated for all patients (18–25). Indeed, it is difficult to determine the individuals with knee osteoarthritis who are the best candidates for knee joint replacement surgery, and as such, not all individuals receive meaningful clinical improvement following surgery (260,261). These challenges promote a cycle of longer surgical waitlists and worsening progression of knee osteoarthritis. Conversely, the mechanisms of and eligibility criteria for core management strategies are better understood. Core treatments have been deemed appropriate for virtually all individuals with knee osteoarthritis (18–25) and can be used to intervene earlier in the disease process in attempt to slow or stop disease progression. Therefore, an emphasis should be placed on quantifying non-surgical and non-pharmacological osteoarthritis quality indicators to identify gaps in patient care and develop targeted strategies to improve the quality of osteoarthritis care for all individuals.

2.3 Physical Activity and Knee Osteoarthritis

2.3.1 Physical Activity Guidelines

Physical activity and therapeutic exercise are internationally and unanimously recognized as core treatments for knee osteoarthritis, where clinical practice guidelines emphasize that these treatments are safe for all individuals with knee osteoarthritis, and can be used in conjunction with other first and second line treatments (18–25). In addition to general clinical practice guidelines, several entities have provided physical activity and exercise-specific recommendations that would be appropriate for individuals with knee osteoarthritis, including the American College of Sports Medicine (67), American Geriatrics Society (45), Canadian Society of Exercise Physiology (69), Ottawa Panel (46,68,262,263), Royal Dutch Society for Physical Therapy (47), and United States Department of Health and Human Services (48).

Evidence-based clinical practice and physical activity guidelines for individuals with knee osteoarthritis recommend general activity parameters (i.e., types and dosages) to improve pain, function, quality of life, and overall health. Types of activities most consistently recommended include aerobic, strengthening, land-based, aquatic, mind-body, balance or flexibility, and neuromuscular subdomains (18–25,45–48,67–69,262,263). Specific activities including walking and tai chi are strongly recommended, whereas aquatic exercise, cycling, and yoga are conditionally recommended (18,21,25,45–48). Physical activity prescription should consider patient preference, accessibility, and affordability when selecting the type of activity to promote optimal health benefits and improve adherence (21). For example, walking is feasible for most individuals considering it can be done independently in any location and does not require specialized equipment.

Additionally, walking has been deemed a safe, low cost aerobic activity for knee osteoarthritis (18,46,264), and is the most commonly performed physical activity type among individuals with knee osteoarthritis (49,50). Therefore, walking may be a suitable activity for individuals with knee osteoarthritis because it can be used as both a therapeutic exercise (e.g., within a structured walking session) and physical activity (e.g., during activities of daily living) treatment. Overall, physical activity prescriptions for individuals with knee osteoarthritis should be tailored to the individual and include the recommended activity type and dosage (e.g., frequency, intensity, and duration).

Physical activity guidelines for older adults provide recommendations for physical activity dosages across aerobic and strengthening domains. These guidelines recommend participating in aerobic activities at least 3-5 days per week at a moderate intensity (approximately 60% of maximal heart rate) for 30-60 minutes per day (24,45,47,48,67). They also note that individuals who are untrained should begin at lower training intensities and volumes (e.g., 40% maximal heart rate for at least 20 minutes per day) and progressively increase training parameters as their fitness improves (24,45,47,48,67). Walking is the most common form of aerobic activity evaluated in the literature (21); correspondingly, walking guidelines have been proposed for individuals with knee osteoarthritis based on cardiovascular and pain outcomes (46,265). The Ottawa panel aerobic walking guidelines are consistent with general aerobic exercise guidelines, and state that individuals with knee osteoarthritis should walk 3 days per week at an intensity of 50-70% of maximal heart rate for 45-minutes per day (265). Additionally, physical activity guidelines recommend that individuals should participate in strengthening activities at least 2-3 days per week at an intensity of approximately 40-60% of their onerepetition maximum for 10 repetitions per movement (or lower intensity with higher repetitions for new exercisers) (24,45,47,67). All physical activity guidelines emphasize additional health benefits with more physical activity (24,45–47,67,70).

Although aerobic physical activity guidelines exist (24,45,47,48,67), physical activity prescription for individuals with knee osteoarthritis may not reflect these targets. A recent systematic review (266) reported that only 8% of aerobic exercise prescriptions for knee osteoarthritis populations achieved all recommendations (frequency, intensity, time, and type) provided by the American College of Sports Medicine (267). This review demonstrated that prescribed aerobic exercise elicited small to moderate improvements in cardiovascular health (e.g., VO_2, heart rate) and no decreases in markers of systemic inflammation (e.g., interleukin-6) (266). Systemic inflammation has been associated with both increased knee pain (268–270) and structural changes (271,272) in individuals with knee osteoarthritis, and can therefore influence joint health. Overall, these findings indicate that aerobic exercise is being inadequately prescribed to individuals with knee osteoarthritis (266), which may ultimately diminish the cardiovascular, systemic, and joint health benefits achieved. Thus, evidence-based physical activity prescription is required for individuals with knee osteoarthritis to optimize overall health (e.g., cardiovascular health, inflammation) in concert with joint health (e.g., pain, joint structure) outcomes.

A notable drawback of physical activity guidelines for individuals with knee osteoarthritis is that they are largely not disease specific, which may help explain inadequate physical activity prescription for this population. Evidence suggests public health physical activity guidelines are safe and effective for individuals with knee osteoarthritis (20,24); however, the lack of evidence-based disease-specific physical activity guidelines has been identified as a major barrier to physical activity prescription by healthcare providers (257,258). Clinical practice guidelines have indicated that there is insufficient evidence to recommend specific physical activity types and dosages for knee osteoarthritis populations (21,63–66), which can be at least partially attributed to missing or inadequately described dosage information in most studies examining the effects of activity interventions on knee osteoarthritis outcomes (266,273). There is also a paucity of research examining the effect of different physical activity and walking dosage parameters on knee osteoarthritis outcomes (79,274,275). Additionally, although clinical practice and physical activity guidelines consider cardiovascular and patient-reported knee osteoarthritis outcomes (19–21,24,45,199,276), they do not consider structural or mechanical outcomes including structural disease progression or joint loading, among others. Quantitative joint health features may be of particular importance within walking interventions because walking increases joint loading frequency, and structural and mechanical risk factors can contribute to knee osteoarthritis disease progression (11,12,14). Therefore, it is necessary to investigate the effects of physical activity and walking interventions on interrelated knee osteoarthritis outcomes to provide a comprehensive understanding of knee joint health.

2.3.2 Walking as a Physical Activity for Knee Osteoarthritis

Physical activity and clinical practice guidelines consistently recommend structured, land-based physical activity, including walking, to reduce knee osteoarthritis pain and improve physical function and quality of life. Walking is widely performed by individuals with knee osteoarthritis (49,50), and is one of the most commonly recommended activities across clinical guidelines (20,21,25,46,47,63,199). It is well-documented that walking exercise provides cardiovascular and overall health benefits for individuals with knee osteoarthritis (71–74,277); however, individuals with knee osteoarthritis may be less physically active than healthy counterparts (52,278), and consistently do not achieve physical activity targets (49,51–60). Additionally, few aerobic exercise interventions prescribe walking according to physical activity guidelines (266). Evidence suggests that patients and physicians report fears that walking may worsen pain or further damage the joint (116,258,279,280), limiting physical activity participation and prescription. Considering physical inactivity is a substantial risk factor for knee osteoarthritis incidence and progression (3), strategies to increase physical activity levels in this population are required. Therefore, it is essential to gain an in-depth understanding of the effects of walking interventions on patient-reported, joint loading, and structural outcomes to increase physical activity levels, improve overall health, and ultimately determine if walking is indeed a suitable activity for individuals with knee osteoarthritis.

Walking is one strategy to increase physical activity levels and is a strongly recommended physical activity type across clinical practice guidelines (18,21,25,45–48). However, walking guidelines are vague for individuals with knee osteoarthritis, and there is currently minimal evidence available to support specific walking prescription parameters (21). Recently, the ACR provided key research recommendations to address this gap in the evidence and support exercise prescription for knee osteoarthritis (21). The recommendations noted that research should examine different exercise types and dosages (i.e., duration, intensity, and frequency) with consideration of disease location and severity, effects on joint health, as well as pre- and post-exercise monitoring of cardiovascular and musculoskeletal fitness (21). Thus, direct quantitative measurements pre- and post-walking of overall health and joint-specific (clinical, biomechanical, and structural) outcomes are required to inform and optimize individualized exercise prescriptions for individuals with knee osteoarthritis.

2.3.2.1 Effect of Walking on Clinical Outcomes

Several randomized controlled trials have been conducted to examine the effects of walking interventions on knee osteoarthritis clinical outcomes. Although pain may contribute to low physical activity levels among knee osteoarthritis populations (167), walking interventions have consistently been shown to reduce pain compared to control conditions (76,77,277,281–284). Additionally, evidence suggests that walking interventions concurrently improve other patient-reported outcomes including reduced depressive symptoms (284,285), increased physical function (77,277,282–286), and increased quality of life (281,282). Walking exercise has also been shown to improve clinical metrics indicative of improved cardiovascular and overall health, including increased physical activity levels (285,286), increased aerobic capacity (77,277,285), increased muscle strength (77,286), reduced functional disability (77,284,287), and reduced medication use (283). The length of prescribed walking interventions ranged from 4-to-12 weeks, indicating that a regular walking program up to 3-months consistently improves patient-reported and clinical knee osteoarthritis outcomes.

Knee pain has also been examined following an acute bout of walking. Immediate changes in pain are often reported using the Numeric Pain Rating Scale (NPRS) (288), an 11-point scale ranging from 0 (no pain) to 10 (worst pain imaginable) (289). Evidence suggests that knee pain does not increase (290) or increases to a small degree (ranging from 0.3-to-2.0-point increase in NPRS pain) (79,112) following a continuous 30-minute walking bout. However, pain response following continuous walking may not be consistent for all individuals with knee osteoarthritis. For example, following 20-to-30 minutes of continuous walking, 42-50% of individuals with knee osteoarthritis increased pain (1.5-to-2.1-point increase), whereas 50-58% reported no change or a decrease in pain (0-to-0.05-point decrease) (81,111,291). These results illustrate that pain response to a single bout of walking may be individualized and could be dependent on predisposing patient-level factors, including gait mechanics (81). The investigation of knee pain remains an important consideration when evaluating the effect of walking on knee osteoarthritis outcomes.

2.3.2.2 Effect of Walking on Biomechanical Outcomes

Randomized controlled trials of isolated walking interventions generally focus on clinical knee osteoarthritis outcomes, and do not assess mechanical outcomes. Although walking improves clinical knee osteoarthritis outcomes and is a relatively low-load type of activity (i.e., compared to running or jumping), walking increases joint loading frequency, which may be detrimental for knee osteoarthritis disease processes (12,14,82). Several large randomized controlled trials have examined the effects of walking exercise combined with strength training on various knee osteoarthritis outcomes. Findings from these studies indicate that walking and strength training have both increased and decreased first peak knee adduction moment and decreased peak knee flexion moment (247,248). Additionally, the combined walking and strength intervention increased peak tibiofemoral compressive, shear, and resultant forces (247,248), gait speed (292), as well as knee sagittal plane range of motion and peak knee flexion angles (247,292). These findings provide an initial understanding of the effects of an intervention that includes walking exercise on biomechanical knee osteoarthritis outcomes; however, these effects cannot be isolated to walking exercise alone. Therefore, little evidence currently exists that quantifies the effect of walking-specific interventions on knee joint biomechanics.

The effects of walking on joint loading outcomes have been evaluated following an acute bout of walking. Following 30-minutes of walking, individuals with knee osteoarthritis have been show to exhibit a larger knee flexion-extension moment difference and higher knee adduction moment first peak and impulse (112), as well as decreased gait scores indicative of gait patterns previously associated with clinical knee osteoarthritis progression (i.e., higher knee adduction moment magnitude and lower joint unloading) (111). Further, evidence suggests that knee joint contact and muscle forces also increased after 30-minutes of continuous walking in individuals with knee osteoarthritis (79,80,96). Together, these results suggest that a continuous walking bout of up to 30-minutes may elicit improved and more dynamic walking patterns, in combination with increased joint loading. However, it remains unclear whether biomechanical changes following a single bout of walking can be extrapolated to explain biomechanical changes following repeated walking interventions; thus, the cumulative effects of prolonged walking on knee joint mechanics warrants further research.

Gait biomechanics within a single gait cycle have been extensively examined in knee osteoarthritis populations. Individuals with, compared to without, knee osteoarthritis experience greater knee joint loads during walking (83), which can be attributed to disease-specific walking patterns, including slower gait speed (293,294) and altered kinematic, kinetic, and neuromuscular parameters (84,239,293,295). Higher joint loads also arise from knee joint malignment and higher BMI, which interact to increase knee joint loading magnitude (190). Specific gait patterns, including altered frontal and sagittal plane moments, have been shown to differentiate between individuals with different severities of knee osteoarthritis (84,234) and contribute to eventual progression to total knee arthroplasty (90). Although these high-risk gait patterns have been identified during a single loading cycle, it is unclear how gait mechanics during prolonged walking may influence structural response or markers of disease progression. Studying biomechanical alterations following continuous walking could potentially identify gait metrics associated with worsening structural outcomes and improve our understanding of links between mechanical and structural joint health outcomes.

2.3.2.3 Effect of Walking on Structural Outcomes

The structural effects of physical activity are typically measured longitudinally using radiographs or MRI; however, few studies have examined the specific effects of walking interventions on structural knee osteoarthritis outcomes. Following an 18-month walking and strength intervention program, individuals with knee osteoarthritis experienced decreases in femoral cartilage thickness and volume (296), as well as decreases in radiographic minimal joint space width (296,297). These joint-level structural changes suggest longitudinal structural knee osteoarthritis progression, although these studies noted that the observed rates of change did not exceed natural progression rates (296,298); as such, it is unlikely that walking accelerates knee osteoarthritis progression.

Certain structural outcomes can be measured acutely following a bout of loading, including cartilage deformation using MRI. Cartilage deformation has been directly linked to extracellular matrix composition, and therefore represents mechanical properties of the articular cartilage (102). Individuals with knee osteoarthritis, compared to healthy controls, experienced similar magnitudes of cartilage deformation following compressive loading

(103), fast walking (109), and squatting (214) conditions. Following 45-minutes of compressive loading, percent changes in cartilage thickness ranged from -4.8% to +2.8% for KLG 0 knees, from -6.3% to +1.5% for KLG 2 knees, and from -8.6% to +1.0% for KLG 3 knees, dependent on the tibiofemoral sub-region (299). Considering walking and squatting are lower-load activities compared to compressive loading, and experience intermittent unloading, the corresponding magnitudes of cartilage deformation following these activities were lower, ranging from -2.2% to -3.4% for individuals with knee osteoarthritis (109,214). Since cartilage deformation relies on fluid dynamics and mechanical properties of the cartilage, both of which can be impaired in knee osteoarthritis (300–302), additional research is required to determine the effect of prolonged physical activity on cartilage deformation to understand pathological cartilage response to loading.

Cartilage response to an acute bout of loading has also been quantified using ultrasound techniques. Ultrasound is optimal for monitoring acute changes in cartilage morphology, particularly in laboratory environments, because it can assess changes immediately following a single bout of loading. Ultrasound-measured cartilage thickness in healthy individuals has been shown to decrease following walking, running, and drop-landing, with magnitudes ranging from -10.1% to +3.4%, dependent on activity type, walking speed and duration, and sex (107,108,119–121). These changes have been deemed reliable and sensitive to change following 30-minutes of high and low loading conditions in healthy individuals (107,108). However, it is unclear whether all individuals undergo cartilage deformation following loading. For instance, individuals who did, and did not, undergo cartilage deformation have been identified following walking in individuals at-risk for developing knee osteoarthritis (303). A lack of cartilage deformation may arise from knee joint alignment or cartilage mechanical properties and may therefore have implications on the development or progression of knee osteoarthritis. Considering loading influences healthy and pathological tissues differently (12,87), further research is necessary to determine how osteoarthritic joints respond to continuous walking using ultrasound.

2.3.2.4 Effect of Walking on Interrelated Knee Osteoarthritis Outcomes

Despite the overlap of mechanical and structural factors for knee osteoarthritis disease mechanisms, these factors are rarely reported as concurrent outcomes within the literature. Recent work has examined associations between mechanical and structural knee osteoarthritis outcomes both acutely and longitudinally. Acutely, in individuals with knee osteoarthritis, greater tibiofemoral joint reaction forces were associated with more lateral femoral cartilage thickness deformation following 25-minutes of walking (110), and knee valgus angle was related to lateral femoral cartilage deformation following 30-minutes of walking (109). In a healthy population, more daily steps and lower joint reaction force impulse were associated with less tibial cartilage deformation following a 15-minute run (304). Longitudinally, higher lateral ground reaction force impulse and lower vertical ground reaction force unloading were associated with medial tibiofemoral cartilage worsening over 2-years for individuals with knee osteoarthritis (305). These results provide a preliminary understanding of how mechanical and structural factors may be related, including in response to a continuous bout of walking. These recent studies examine associations between knee joint alignment, joint reaction forces, and structural outcomes, but do not consider discrete biomechanical metrics that may drive mechanical changes.

Relationships between discrete biomechanical metrics and structural outcomes have been examined cross-sectionally in knee osteoarthritis and healthy populations. For example, higher knee adduction moment peak and impulse have been associated with thinner medial femoral and tibial cartilage in knee osteoarthritis populations (306). Additionally, higher peak knee flexion moment, vertical ground reaction force, knee flexion angle peak and excursion, and knee flexion impulse, have been associated with thicker medial femoral cartilage in healthy and anterior cruciate ligament reconstructed knees (307,308), whereas larger knee adduction angle and moment have been associated with thinner medial femoral cartilage thickness in anterior cruciate ligament reconstructed knees (308). Further, BMI has been shown to influence the relationship between joint loading (peak flexion and adduction moments) and femoral cartilage characteristics (ultrasound echo intensity and medial-to-lateral thickness ratio) in healthy younger adults, which may have implications for knee osteoarthritis development (309). These studies highlight potential relationships between discrete biomechanical metrics and structural knee osteoarthritis outcomes and warrant further research to determine their relationship following prolonged walking in knee osteoarthritis populations.

Associations between knee pain and mechanical and structural knee osteoarthritis outcomes are rarely examined, but preliminary research suggests these relationships may exist. Compared to individuals with knee osteoarthritis who did not experience a pain flare (i.e., increase in knee pain), those who experienced a pain flare exhibited a slower walking cadence and higher peak knee flexion moment, second peak knee adduction moment, and total reaction moment at baseline, and larger changes in first and second peak knee adduction moments and internal rotation moment following 20-minutes of continuous walking (81). Additionally, higher pain during walking has been associated with higher risk of cartilage worsening over 2-years (305). These findings illustrate relationships between knee pain and biomechanical and structural factors in knee osteoarthritis populations, where knee pain may initiate or follow joint-level changes. Using an interdisciplinary approach to evaluate the influence of walking on interrelated knee osteoarthritis outcomes will be important for understanding the mechanisms of walking as an intervention and informing how it is prescribed for individuals with knee osteoarthritis.

2.3.3 Physical Activity and Knee Osteoarthritis Summary

A knowledge gap remains with respect to the effects of walking on biomechanical and structural knee osteoarthritis outcomes. Current evidence suggests that 30-minutes of continuous walking increases knee joint contact and muscle forces, and serum biomarkers related to cartilage metabolism (79,80,96), suggesting deleterious effects on joint health for individuals with knee osteoarthritis. Walking is known to improve cardiovascular and systemic health outcomes (277,310), although inadequate aerobic exercise prescription may attenuate these benefits (266). Evidence to inform disease-specific walking prescription parameters for individuals with knee osteoarthritis based on direct quantitative measures are currently lacking (21). More knowledge of the acute effects of walking interventions, particularly biomechanical, structural, and clinical changes, would improve our understanding of the appropriateness of walking as a treatment modality for knee osteoarthritis. Additionally, this information may identify earlier disease-specific changes in response to physical activity (e.g., modifiable walking mechanics) that may contribute to longitudinal disease progression. Therefore, more research regarding the immediate effects of walking on interrelated mechanical, structural, and pain components is required to elucidate the effects of walking on knee joint and overall health and can be used to optimize walking prescription parameters for individuals with knee osteoarthritis.

2.4 Literature Summary and Identified Gaps

In summary, physical activity, particularly walking, is widely recommended for individuals with knee osteoarthritis. Clinical practice guidelines state that all individuals with knee osteoarthritis should receive advice to exercise, although it is unclear whether this is achieved in practice. Further, research on the immediate and acute effects of walking interventions on quantitative knee osteoarthritis outcomes is scant. The mechanical, structural, and patient-reported effects of continuous walking may have important implications for knee osteoarthritis progression and should be considered simultaneously. More knowledge on the direct effects of continuous walking on disease-specific outcomes will add to our understanding of whether walking is suitable for individuals with knee osteoarthritis. This information is needed to increase physical activity levels and inform disease-specific physical activity guidelines for knee osteoarthritis populations.

Chapter 3 Quality of Non-Surgical and Non-Pharmacological Knee Osteoarthritis Care in the Maritimes

3.1 Introduction

Osteoarthritis is a common chronic and disabling joint condition that affects one in every three Canadian adults aged 55 years or older (1), with highest prevalence in the Maritime provinces (Nova Scotia, New Brunswick, and Prince Edward Island) (311). Osteoarthritis is most often found in the knee joint (1), and substantially contributes to joint pain, mobility impairments, and decreased quality of life (159). No cure for knee osteoarthritis exists, and traditional clinical management strategies focus on symptom relief using medication on a pathway to end-stage joint replacement surgery (26). However, only 28-38% of individuals waiting for a knee joint replacement in the Maritime provinces received the surgery within national benchmark timeframes in 2022 (312), indicating that surgical demand greatly exceeds healthcare system capacity. Thus, a critical shift in knee osteoarthritis management is required to improve patient care and outcomes (313,314).

Evidence-based clinical practice guidelines consistently recommend non-surgical and non-pharmacological treatments to manage knee osteoarthritis. Core management strategies include education and self-management, physical activity, therapeutic exercise, and weight management (18–25). Evidence suggests that exercise improves pain and physical function (171,315,316), and these benefits are consistent across supervised and unsupervised exercise (317,318). Additionally, weight loss, when medically indicated, reduces joint loads, inflammation, and improves clinical outcomes (247,319). Osteoarthritis treatments are traditionally coordinated by general practitioners (320,321), although patients may attempt treatment independently before consulting a physician (322,323). Further, recent recommendations suggest multidisciplinary healthcare teams should be involved to provide core management (324,325), as this model may further improve patient outcomes (326).

Despite international consensus on core management, whether individuals with knee osteoarthritis receive evidence-based care in practice is unclear. Osteoarthritis quality indicator sets have been developed to assess healthcare quality, represent the minimally acceptable standard of care, and focus on care processes provided to patients. For example, the Arthritis Foundation Quality Indicator Project developed 14 quality indicators related to osteoarthritis assessment, treatment, and follow-up (254). A sub-set of these quality indicators align with treatments related to exercise, weight loss, and assistive devices, and can therefore be used to examine the quality of core treatments. Further, healthcare quality can be assessed from the clinician or patient perspective; however, evidence suggests that medical records can be discordant with patient perceptions of care received (255). Therefore, patient self-reported quality indicator metrics are the preferred method to monitor and evaluate osteoarthritis healthcare quality because they reflect the quality of care as perceived by the patient (38).

There is limited evidence quantifying the quality or types of care individuals with knee osteoarthritis receive, and studies provide a wide range of results when examining osteoarthritis care consistent with clinical practice guidelines in Canada (30,34,36) and globally (29,31–33,35,37–39). For example, previous estimates suggest low to high achievement of exercise-related quality indicators, where 25% to 84% of individuals with osteoarthritis received advice to exercise (29–39), and low to moderate achievement of weight management-related quality indicators, where 24% to 69% received advice to lose weight (30–39). Further, quality of walking-related assessment is poor, where 0% to 40% of individuals with osteoarthritis received an assessment for a walking aid, and 0% to 19% received an assessment for other assistive devices (31–33,35–39). The quality and types of care received were dependent on demographic and social factors including age (30,34,36), sex (34,36), and education level (34,36), as well as country (39), or province within Canada (30,34,36). It is currently unknown whether clinical care aligns with current practice guidelines in the Maritime provinces of Canada, or whether patient-level factors influence the quality of knee osteoarthritis care received.

Additionally, much of the previous quality indicator work has been completed with a focus on late-stage knee osteoarthritis management, defined as severe symptoms (e.g., pain) or awaiting knee joint replacement surgery (30,33,34,37,40). While later-stage interventions prior to joint replacement may help optimize post-surgical outcomes (327) or delay surgery (328), they have less potential to slow or potentially halt knee osteoarthritis progression. Alternatively, implementing non-surgical and non-pharmacological care at earlier stages of knee osteoarthritis may contribute to slowing or preventing symptoms or structural disease progression and minimizing the burden of knee osteoarthritis (41–44). Thus, individuals with earlier stage knee osteoarthritis (i.e., mild-to-moderate, as opposed to severe, symptoms and functional impairments) represent an important target for knee osteoarthritis management to optimize patient outcomes and healthcare pathways.

The purpose of this study was to evaluate the quality and types of care individuals with mild-to-moderate knee osteoarthritis receive in the Maritimes (Nova Scotia, New Brunswick, Prince Edward Island). The objectives of this research were to determine: (**O1**) the quality of non-surgical and non-pharmacological care strategies prescribed; (**O2**) the association between the quality and types of care received with patient demographic (age, sex) and social (education, employment) factors; and (**O3**) the association between the quality and types of care received with patient-reported outcomes.

3.2 Methods

This cross-sectional survey-based study was approved by the Atlantic Partnership for Tomorrow's Health (PATH) research team and the Nova Scotia Health Research Ethics Board (file # 1025913, Appendix A).

3.2.1 Participant Recruitment

Individuals from the three Maritime provinces with self-reported osteoarthritis were recruited from the Atlantic PATH cohort. The Atlantic PATH is a regional cohort of the Canadian Partnership for Tomorrow Project (CanPath) study, which consists of over 330,000 participants within seven regional cohorts across ten provinces, and represents Canada's largest population health study (329). The CanPath study began in June 2008 and collects information on socioeconomic and lifestyle factors, biological samples, physical measures, molecular data, and environmental measures of individuals aged 30-74 at baseline (329,330). The Atlantic PATH baseline data collection was conducted between 2009 and 2015, and the first follow-up study began in 2016 (331).

Individuals from the Atlantic PATH cohort were recruited for this study if they (a) self-reported osteoarthritis at baseline (i.e., responded "yes" to the question "has a doctor ever told you that you had osteoarthritis?"), (b) currently resided in one of the Canadian Maritime provinces (Nova Scotia, New Brunswick, or Prince Edward Island), and (c) provided an email address as a method of contact. Individuals self-reporting osteoarthritis from the Atlantic PATH cohort have been shown to represent a healthier and less clinically severe group compared to the wider Canadian population with osteoarthritis (114).

3.2.2 Data Collection

Participants were invited to complete an electronic healthcare quality survey. The email invitation included information about the study and a link to provide informed consent and complete the survey electronically. This 62-question survey replicated the British Columbia Osteoarthritis (BC OA) Survey (36), which was based on recommendations provided by the Arthritis Foundation Quality Indicator Project (254). The questionnaire collected information on (a) general health and arthritis, including health services used to manage arthritis, (b) comorbidities including diabetes, high blood pressure, heart problems, liver problems, kidney and/or bladder problems, lung problems, intestinal or stomach ulcers, bowel disorder, fibromyalgia, osteoporosis, cancer, and depression, and (c) osteoarthritis outcomes (pain, stiffness, and physical function) using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (203). Supplementary standardized questionnaires collected information on patient-reported knee osteoarthritis outcomes, including pain, physical function, and quality of life. Osteoarthritis specific instruments included the Knee injury and Osteoarthritis Outcome Score (function during sport and recreational activities sub-scale; KOOS-Sport) (204), Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire (332), the 5-level Euro-QOL 5-dimension (EQ-5D-5L) questionnaire (333), and the Oxford Knee Score (334). These questionnaires were selected to comprehensively provide a global assessment of patient-reported outcomes. The KOOS-Sport sub-scale was selected because it is distinct from the WOMAC (in contrast to other sub-scales) and the selected population represents a healthier and less clinically severe knee osteoarthritis group (114); therefore, sport and recreational function may be a distinguishing feature of this sample and may inform core treatment, particularly advice to exercise. All survey responses were collected through the secure Research Electronic Data Capture (REDCap™) online portal hosted within Nova Scotia Health.

3.2.3 Data Processing

Four healthcare quality indicators were derived from BC OA survey responses: (1) advice to exercise, (2) advice to lose weight, (3) assessment for ambulatory function (e.g., mobility), and (4) assessment for non-ambulatory function (e.g., dressing). Each quality indicator included two components, the "IF" statement that determined a participant's eligibility to receive the specified care, and the "THEN" statement that determined the care process that should be performed. A pass-rate for each quality indicator was calculated by dividing the number of individuals receiving care (i.e., achieved the "THEN" statement) by the number of individuals eligible to receive the care (i.e., achieved the "IF" statement), signifying the proportion of eligible individuals who received recommended care. Eligibility for and achievement of the quality indicators were interpreted from the BC OA survey questions to align with the Arthritis Foundation Quality Indicator Project quality indicators (254).

Two sensitivity analyses were completed to ensure robust conclusions. Firstly, given recent evidence supporting the benefits of both supervised and unsupervised exercise (317,318), as well as recommendations for various healthcare practitioners to provide knee osteoarthritis care (324,325), the quality indicator criteria were updated for advice to exercise and advice to lose weight as the primary sensitivity analysis. These updated criteria reflect dichotomous (yes/no) patient-reported use of exercise and diet as arthritis treatments, consistent with recent quality indicator surveys (34,256,335). Secondly, the eligibility criteria for advice to lose weight used a body mass index (BMI) threshold of 27 kg/m^2 to define being overweight, which aligns with the Arthritis Foundation Quality Indicator Project, along with the BC OA and other previous quality indicator survey criteria (30,36,254); however, an updated BMI threshold of 25 kg/m^2 was tested as a secondary sensitivity analysis to align with more recent quality indicator surveys (34) and the now generally accepted definition of being overweight (162). The BC OA criteria for achieving each of the eligibility statements for each quality indicator, along with the sensitivity analysis criteria, are portrayed in Table 3.1.

3.2.4 Statistical Analysis

To achieve **O1**, participant demographics were summarized using the mean and standard deviation for continuous variables (e.g., age), median and interquartile range (IQR) for ordinal variables (e.g., number of comorbidities), and counts and percentages for categorial variables (e.g., sex). Survey data were summarized using frequencies to represent the pass rate for each quality indicator. The overall pass rate across all four quality indicators was calculated using Equation 3.1.

Equation 3.1.

$$Overall\ Pass\ Rate = \frac{Total\ number\ of\ individuals\ receiving\ care}{Total\ number\ of\ eligible\ individuals}\ x\ 100\%$$

Table 3.1. British Columbia Osteoarthritis Survey Criteria for Quality Indicators, Adapted from Li et al., 2011 (36).

Arthritis Foundation Quality Indicator	Eligibility for the "IF" statement	Eligibility for the "THEN" statement	Rationale	Limitation
Advice to Exercise				
IF an ambulatory patient has had a diagnosis of symptomatic knee osteoarthritis for > 3 months AND has no contraindication to exercise and is physically and mentally able to exercise THEN a directed or supervised muscle-strengthening or aerobic exercise program should have been prescribed at least once and reviewed at least once per year.	Answered "Yes" to: "Do you have osteoarthritis in one or both of your knees?" AND Answered "No" to: "Because of any condition or health problem, do you need the help of another person in personal care such as washing, dressing, or eating?"	Had one or more visits to a physiotherapist in the past year OR had attended a land-based or pool exercise program OR had used fitness facilities [OR had received exercise as a treatment for their arthritis in the past year.]*	Those with knee osteoarthritis would have participated in directed or supervised exercise at least once if they had seen a physiotherapist and/or attended a land-based/pool exercise program.	The criteria would not identify individuals with severe dementia or other conditions that would preclude them from participating in exercise programs. Those included in the analysis might or might not have had their exercise reviewed in the past year. Individuals who used fitness facilities [or received exercise as treatment]* may or may not have participated in a supervised exercise program.

Arthritis Foundation Quality Indicator	Eligibility for the "IF" statement	Eligibility for the "THEN" statement	Rationale	Limitation
Advice to Lose Weight				
IF a patient has symptomatic knee osteoarthritis AND is overweight (BMI > 27 kg/m^2) THEN the patient should be advised to lose weight at least annually AND the benefit of weight loss on the symptoms of osteoarthritis should be explained to the patient.	Answered "Yes" to: "Do you have osteoarthritis in one or both of your knees?" AND Had a BMI > 27 kg/m^2 [OR had a BMI of > 25 kg/m^2]†	Had used a weight-loss program or visited a dietician [OR had received diet as a treatment for their arthritis in the past year.]*	Those who used a weight-loss program, [diet,]* or saw a dietician would have received weight-loss counseling.	The "IF" criteria would not identify those who had been advised to lose weight and had successfully lost weight in the past year. These criteria would not necessarily include those who had been advised to lose weight by other health professionals. Among those who received weight-loss counseling, the visit might have been more than a year ago.

Arthritis Foundation Quality Indicator	Eligibility for the "IF" statement	Eligibility for the "THEN" statement	Rationale	Limitation
Assessment for Ambulatory Function				
IF a patient has had symptomatic knee osteoarthritis AND reports difficulty walking to accomplish activities of daily living for more than 3 months THEN the patient's walking ability should be assessed for need for ambulatory assistive devices.	Answered "Yes" to: "Do you have osteoarthritis in one or both of your knees?" AND Answered "severe" or "extreme" to (in the past 4 weeks): "How much pain did you have in your hip or knee walking on a flat surface?"	Had one or more visits to a physiotherapist or occupational therapist in the past year.	The criteria were modified to include people with severe or extreme pain within the past 4 weeks. There is evidence supporting the use of ambulatory assistive devices as early as possible to improve mobility. Those who saw a physiotherapist or occupational therapist would have been assessed for walking ability.	The criteria would not identify people who had been assessed for ambulatory assistive devices by other health professionals. The criteria would not identify those who had "severe" or "extreme" pain longer than 4 weeks ago but visited a physiotherapist or occupational therapist in the past year and improved.

Arthritis Foundation Quality Indicator	Eligibility for the "IF" statement	Eligibility for the "THEN" statement	Rationale	Limitation
Assessment for Non-Ambulatory Function				
IF a patient has a diagnosis of knee osteoarthritis AND reports difficulties with non-ambulatory activities of daily living THEN the patient's functional ability with problem tasks should be assessed for need of non-ambulatory assistive devices to aid with problem tasks.	Answered "Yes" to: "Do you have osteoarthritis in one or both of your knees?" AND Answered "severe" or "extreme" to: "What degree of difficulty do you have with rising from sitting, and/or putting on socks/stockings, and/or taking off socks/stockings, and/or getting in/out of bath, and/or getting on/off toilet?"	Had one or more visits to an occupational therapist in the past year.	The criteria were modified to include people with severe or extreme difficulties with non-ambulatory activities at the time of the assessment. Our assumptions were that individuals reporting severe/extreme disabilities would have experienced problems with the activities months prior to the survey, and that during this time they should have been assessed by an occupational therapist for assistive devices.	The "IF" criteria would not identify people who had severe or extreme difficulties with non-ambulatory activities, but had improved when they completed the questionnaire. The criteria would not identify those who had been assessed for assistive devices by other health professionals.

Note: BMI = body mass index. * Represents the updated quality indicator criteria used in the primary sensitivity analysis. † Represents the updated quality indicator criteria used in the secondary sensitivity analysis.

To achieve **O2**, binary logistic regression models were used to determine associations between each quality indicator and five independent demographic and social variables: (1) age, (2) sex (female, male [reference group]), (3) education level (university degree, trade certificate, high school diploma [reference group], less than high school), (4) employment (employed, retired due to medical reasons, unemployed/retired [reference group]), and (5) number of comorbidities (maximum 12). The reference group for each categorical variable was selected as the group at highest risk for receiving lower quality of care based on previous quality indicator surveys (30,34,36), and were adjusted as necessary based on the reported demographics of respondents. This method indicates the effect of patient demographic and social factors on the odds of eligible individuals receiving the recommended care for each quality indicator.

To achieve **O3**, binary logistic regression models were used to determine associations between each quality indicator and patient-reported outcome (i.e., WOMAC, KOOS-Sport, ICOAP, EQ-5D-5L, Oxford Knee Score). Summary scores were calculated for each patient-reported outcome. The WOMAC summary score was calculated as the sum of all items ranging from 0 (no difficulty) to 96 (extreme difficulty) (203). The KOOS-Sport score was calculated as the transformed average of the 5-item KOOS sport and recreation function sub-scale ranging from 0 (extreme problems) to 100 (no problems) (204). The ICOAP summary score was calculated as the percentage score of all items ranging from 0 (no pain) to 100 (maximal pain) (332). The EQ-5D-5L summary score was calculated as the sum of the five health state items ranging from 5 (no symptoms) to 25 (worst symptoms) (333). The Oxford Knee Score summary score was calculated as the sum of all items ranging from 0 (worst outcomes) to 48 (best outcomes) (334). This method indicates the effect of patient-reported outcome scores on the odds of eligible individuals receiving the recommended care for each quality indicator.

Finally, a sub-analysis was completed to replicate the regression methods of the BC OA survey (36). Full statistical methods and results for this sub-analysis are presented in Appendix B.

Outcomes were calculated as unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) for all regression models. The number of covariates for each regression model was limited to 5 to ensure there were at least 10 observations per binary outcome (336). A Box-Tidwell test was used to examine linear relationships between each continuous independent variable and its logit transformed value (337). Multicollinearity of all covariates was assessed to ensure the Variance Inflation Factor was <5 (338). Cook's distance of all continuous covariates was calculated and extreme outliers were removed (339). All regression models were run first using the pass rates calculated using the BC OA criteria, then with pass rates calculated using the updated quality indicator criteria as primary and secondary sensitivity analyses (self-reported use of exercise and diet as arthritis treatments, then adjusted BMI threshold, respectively). An OR greater than 1 indicates a higher likelihood of receiving recommended care within the specified group compared to the reference group (for categorical variables) or per one unit of change (for continuous variables). Statistical testing was performed using SPSS (IBM SPSS Statistics for Windows, Version 28.0.1.1 Armonk, NY), with an alpha value of 0.05 to represent statistical significance.

3.3 Results

The Atlantic PATH research personnel conducted three electronic survey mailings to 2990 eligible individuals. A total of 421 individuals began the survey, indicating a response rate of 14.1%. The survey was completed by 359 participants, and 241 participants indicated they had osteoarthritis in one or both knees. From the 241 individuals with knee osteoarthritis, participants reported having osteoarthritis at the knee only (20%, n=50), both knee and hip (7%, n=17), knee and other (e.g., shoulder, back) joint (37%, n=90), or knee, hip, and other joint (36%, n=84). A total of 118 participants indicated they had osteoarthritis at a joint other than the knee, including hip only (n=11), hip and other joint (n=41), other joint only (n=61), or no osteoarthritis (n=5), and were therefore excluded from the analyses.

Knee osteoarthritis participants (n=241) were 77% female and had a mean age of 67.2 ± 6.9 years. Participants had a mean BMI of 30.7 ± 7.5 kg/m^2, and 63.9% (n=154) had a BMI >27 kg/m^2. Participants had a median of 2 comorbidities (IQR 1.0, 3.0; range 0-8), and the most common comorbidities included high blood pressure (42.7%, n=103), depression (20.3%, n=49), and cancer (16.6%, n=40). Participants indicated that they would rate their general health as excellent (5%, n=12), very good (29%, n=93), good (40%, n=95), fair (15%, n=37), and poor (1%, n=3). Most participants (59%, n=140) reported that they were first told by a health professional that they had arthritis more than 11 years ago, followed by 6-10 years ago (31%, n=75), 1-5 years ago (10%, n=23), and less than 1 year ago (<1%, n=1). Most participants (95%, n=228) indicated that they have had an x-ray to confirm their arthritis. Almost all participants (96%, n=231) were eligible for at least 1 quality indicator (Table 3.2).

The overall pass rate for all quality indicators using the BC OA criteria was 42.9% and increased to 49.3% when patient-reported use of exercise and diet as arthritis treatments were included in the primary sensitivity analysis. Individual quality indicator pass-rates ranged from 4.3% to 85.7% (Table 3.3). Using the BMI threshold of 25 kg/m^2 as a secondary sensitivity analysis, pass rates for advice to lose weight were 25.9% using the BC OA criteria and 33.3% when including patient-reported use of diet. A low proportion of participants were eligible for or received care for assessment for ambulatory function and assessment for non-ambulatory function, precluding statistical analysis of these two quality indicators. Therefore, statistical testing was exclusively performed for advice to exercise and advice to lose weight.

There were no significant differences between age, sex, education level, or employment factors for individuals who did, or did not, receive advice to exercise or advice to lose weight using the BC OA criteria (Table 3.4) or within the primary sensitivity analysis including patient-reported use of exercise or diet as arthritis treatment (Table 3.5). Changing the BMI threshold did not alter these results. Additionally, there were largely no significant associations between patient-reported outcomes and advice to exercise or advice to lose weight using the BC OA criteria (Table 3.6) or within the primary sensitivity analysis (Table 3.7). However, univariate analysis using the BC OA criteria indicated that the odds of receiving advice to exercise were significantly higher for those who reported better function during sport and recreational activities using the KOOS-Sport sub-scale (OR 1.02, 95% CI [1.00, 1.03], $p = 0.018$).

Table 3.2. Sociodemographic and patient-reported outcomes of participants (n=241).

Characteristic	
Age, years: mean (SD)	67 (7)
Body mass index, kg/m^2: mean (SD)	30.7 (7.5)
Sex: n (%)	
Female	185 (76.8)
Male	56 (23.2)
Education: n (%)	
University degree	112 (46.5)
Trade certificate	91 (37.8)
High school diploma	36 (14.9)
Less than high school	1 (0.4)
Missing data	1 (0.4)
Employment Status: n (%)	
Employed	94 (39.0)
Retired due to medical reasons	32 (13.3)
Unemployed/retired	113 (46.9)
Missing data	2 (0.8)
Number of Comorbidities, 0-12: median (IQR); range	2 (1.0, 3.0); 0-8
Eligibility for Quality Indicators: n (%)	
0 quality indicators	10 (4.1)
1 quality indicator	83 (34.4)
2 quality indicators	120 (49.8)
3 quality indicators	25 (10.4)
4 quality indicators	3 (1.2)
WOMAC Score*, 0-96: mean (SD); range	27.4 (15.2); 2-86
KOOS-Sport Score†, 0-100: mean (SD); range	43.1 (26.2); 0-100
ICOAP Score*, 0-100: mean (SD); range	23.5 (16.4); 0-75
EQ-5D-5L Score*, 5-25: mean (SD); range	9.4 (2.6); 5-19
Oxford Knee Score†, 0-48: mean (SD); range	34.6 (7.8); 14-48

Note: SD = standard deviation. IQR = Interquartile range. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index. KOOS-Sport = Knee injury and Osteoarthritis Outcome Score, sport and recreation function sub-scale. ICOAP = Intermittent and Constant Pain questionnaire. EQ-5D-5L = 5-level Euro-QOL 5-dimension questionnaire. * Higher scores indicate worse patient-reported outcomes. † Higher scores indicate better patient-reported outcomes.

Table 3.3. Pass rates of each quality indicator for individuals with knee osteoarthritis (n=241).

		BC OA Criteria		Updated Criteria *	
Quality Indicator	People eligible for care (n, % of survey participants)	People who received care (n)	Pass rate (%)	People who received care (n)	Pass rate (%)
Advice to exercise	202 (83.8)	125	61.9	140	69.3
Advice to lose weight	154 (63.9)	43	27.9	54	35.1
Ambulatory function	7 (2.9)	6	85.7	-	-
Non-ambulatory function	47 (19.5)	2	4.3	-	-
Total	**410**	**176**	**42.9**	**202**	**49.3**

Note: * Updated criteria reflect the primary sensitivity analysis criteria, including patient-reported use of exercise and diet as arthritis treatments for advice to exercise and advice to lose weight, respectively. Criteria were not updated for assessment for ambulatory function or assessment for non-ambulatory function (i.e., left blank in the table) because there were no relevant patient-reported treatments for these quality indicators. The overall pass rate for the updated criteria was calculated using the updated pass rates for advice to exercise and advice to lose weight and the BC OA pass rates for ambulatory function and non-ambulatory function.

Table 3.4. Logistic regression models based on the British Columbia Osteoarthritis Survey criteria for advice to exercise and advice to lose weight, including demographic and social factors.

Independent Variable	n (received care) / n (needed care)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Advice to exercise (no. included in adjusted analysis = 201)			
Age, years	-	0.98 (0.94, 1.02)	0.98 (0.93, 1.03)
Sex (reference: Male)			
Female	97/154	1.22 (0.63, 2.35)	1.16 (0.56, 2.43)
Male	28/47	1	1
Education (reference: High school diploma)			
University degree	72/100	2.25 (0.97, 5.21)	2.37 (0.99, 5.66)
Trade certificate	37/71	0.93 (0.39, 2.17)	0.87 (0.36, 2.12)
High school diploma	16/30	1	1
Employment (reference: Unemployed/retired)			
Employed	51/80	1.16 (0.63, 2.14)	0.99 (0.48, 2.04)
Retired for medical reasons	15/23	1.24 (0.48, 3.20)	1.73 (0.56, 5.31)
Unemployed/retired	59/98	1	1
Number of comorbidities	-	0.91 (0.76, 1.08)	0.87 (0.71, 1.07)
Advice to lose weight (no. included in adjusted analysis = 153)			
Age, years	-	0.96 (0.91, 1.01)	0.96 (0.90, 1.02)
Sex (reference: Male)			
Female	34/114	1.40 (0.60, 3.26)	1.29 (0.53, 3.14)
Male	9/39	1	1
Education (reference: High school diploma)			
University degree	18/61	1.20 (0.43, 3.32)	1.17 (0.40, 3.44)
Trade certificate	18/64	1.12 (0.40, 3.10)	0.94 (0.32, 2.73)
High school diploma	7/27	1	1
Less than high school	0/1	-	-
Employment (reference: Unemployed/retired)			
Employed	20/64	1.49 (0.68, 3.25)	1.07 (0.43, 2.68)
Retired for medical reasons	8/25	1.54 (0.55, 4.26)	1.09 (0.34, 3.47)
Unemployed/retired	15/64	1	1
Number of comorbidities	-	1.09 (0.89, 1.34)	1.10 (0.88, 1.37)

Note: OR = Odds ratio. CI = confidence interval.

Table 3.5. Primary sensitivity analysis of logistic regression models based on the updated quality indicator criteria for advice to exercise and advice to lose weight, including demographic and social factors.

Independent Variable	n (received care) / n (needed care)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Advice to exercise (no. included in adjusted analysis = 201)			
Age, years	-	0.99 (0.95, 1.03)	0.99 (0.94, 1.04)
Sex (reference: Male)			
Female	107/154	1.04 (0.51, 2.08)	0.98 (0.45, 2.12)
Male	33/47	1	1
Education (reference: High school diploma)			
University degree	77/100	1.94 (0.81, 4.66)	2.04 (0.83, 5.04)
Trade certificate	44/71	0.91 (0.38, 2.20)	0.93 (0.37, 2.32)
High school diploma	19/30	1	1
Employment (reference: Unemployed/retired)			
Employed	57/80	1.15 (0.60, 2.19)	1.06 (0.50, 2.25)
Retired for medical reasons	16/23	1.06 (0.40, 2.83)	1.51 (0.48, 4.81)
Unemployed/retired	67/98	1	1
Number of comorbidities	-	0.90 (0.74, 1.07)	0.87 (0.70, 1.06)
Advice to lose weight (no. included in adjusted analysis = 153)			
Age, years	-	0.96 (0.91, 1.00)	0.96 (0.91, 1.01)
Sex (reference: Male)			
Female	41/114	1.11 (0.51, 2.39)	0.99 (0.44, 2.24)
Male	13/39	1	1
Education (reference: High school diploma)			
University degree	21/61	1.05 (0.40, 2.74)	1.07 (0.39, 2.94)
Trade certificate	24/64	1.20 (0.47, 3.09)	1.08 (0.40, 2.91)
High school diploma	9/27	1	1
Less than high school	0/1	-	-
Employment (reference: Unemployed/retired)			
Employed	25/64	1.52 (0.73, 3.17)	1.10 (0.47, 2.58)
Retired for medical reasons	10/25	1.58 (0.60, 4.14)	1.05 (0.36, 3.12)
Unemployed/retired	19/64	1	1
Number of comorbidities	-	1.10 (0.90, 1.34)	1.11 (0.90, 1.38)

Note: OR = Odds ratio. CI = confidence interval.

Table 3.6. Logistic regression models based on the British Columbia Osteoarthritis Survey criteria for advice to exercise and advice to lose weight, with patient-reported outcomes.

Independent Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Advice to exercise (no. included in adjusted analysis = 171)		
WOMAC	0.98 (0.96, 1.00)	0.97 (0.94, 1.01)
KOOS-Sport	**1.02 (1.00, 1.03)**	1.02 (1.00, 1.03)
ICOAP	1.01 (0.97, 1.05)	1.07 (0.99, 1.15)
EQ-5D-5L	0.96 (0.84, 1.09)	1.04 (0.87, 1.25)
Oxford Knee Score	1.02 (0.98, 1.06)	1.01 (0.93, 1.10)
Advice to lose weight (no. included in adjusted analysis = 119)		
WOMAC	1.00 (0.98, 1.03)	0.98 (0.94, 1.03)
KOOS-Sport	1.00 (0.98, 1.01)	1.01 (0.99, 1.02)
ICOAP	1.04 (0.99, 1.09)	1.04 (0.96, 1.13)
EQ-5D-5L	0.99 (0.86, 1.14)	0.91 (0.72, 1.14)
Oxford Knee Score	0.97 (0.93, 1.02)	0.95 (0.86, 1.05)

Note: Bolded values indicate statistical significance at $p<0.05$. OR = Odds ratio. CI = confidence interval. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index. KOOS-Sport = Knee injury and Osteoarthritis Outcome Score, sport and recreation function sub-scale. ICOAP = Intermittent and Constant Pain questionnaire. EQ-5D-5L = 5-level Euro-QOL 5-dimension questionnaire.

Table 3.7. Primary sensitivity analysis of logistic regression models based on the updated quality indicator criteria for advice to exercise and advice to lose weight, with patient-reported outcomes.

Independent Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Advice to exercise (no. included in adjusted analysis = 171)		
WOMAC	0.99 (0.97, 1.01)	1.00 (0.96, 1.04)
KOOS-Sport	1.01 (0.99, 1.03)	1.01 (1.00, 1.03)
ICOAP	1.01, 0.97, 1.06)	1.06 (0.98, 1.14)
EQ-5D-5L	0.95 (0.83, 1.09)	0.96 (0.80, 1.16)
Oxford Knee Score	1.02 (0.97, 1.06)	1.02 (0.94, 1.11)
Advice to lose weight (no. included in adjusted analysis = 119)		
WOMAC	1.00 (0.98, 1.02)	0.99 (0.95, 1.03)
KOOS-Sport	1.00 (0.98, 1.01)	1.00 (0.99, 1.02)
ICOAP	1.05 (1.00, 1.10)	1.07 (0.99, 1.15)
EQ-5D-5L	0.99 (0.87, 1.13)	0.90 (0.73, 1.11)
Oxford Knee Score	0.98 (0.93, 1.02)	0.97 (0.89, 1.06)

Note: OR = Odds ratio. CI = confidence interval. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index. KOOS-Sport = Knee injury and Osteoarthritis Outcome Score, sport and recreation function sub-scale. ICOAP = Intermittent and Constant Pain questionnaire. EQ-5D-5L = 5-level Euro-QOL 5-dimension questionnaire.

3.4 Discussion

This study quantifies the quality of care for individuals with mild-to-moderate knee osteoarthritis in the Maritime provinces and explores associations between the quality and types of care received with patient demographic, social, and patient-reported factors. Findings suggest that the quality of osteoarthritis care is low across four non-surgical and non-pharmacological quality indicators, with overall pass rates of 42.9% when using the original BC OA criteria, and 49.3% when incorporating patient-reported use of exercise and diet as arthritis treatments (Table 3.3). Less than half of the individuals with knee osteoarthritis in the Maritimes received recommended core treatment (18–25), and these pass rates were not driven by participant demographic, social, or patient-reported factors.

Notwithstanding strong recommendations regarding core knee osteoarthritis treatment (18–25), quality of osteoarthritis care remains low. The low-to-moderate overall pass rates reported in this study (43 to 49%) are consistent with previous studies that report an average overall pass rate of 45% across the literature (29–39). The current findings are comparable to previous quality indicator surveys focused on similarly aged community-dwelling individuals, where overall pass rates ranged from 47 to 51% (30–32,35,37,39). Observed pass rates are higher than overall pass rates reported over a decade ago (36,38), ranging from 22% to 31%, which may imply a general improvement over time; however, evidence suggests that the quality of osteoarthritis care has not clearly or meaningfully improved over time (113,340). Interestingly, the current overall pass rates are notably lower than those reported with more severe knee osteoarthritis populations, including individuals awaiting total knee arthroplasty (34) and physically frail samples (29), where overall pass rates ranged from 57% to 62%. These findings indicate that overall pass rates may be lower for individuals with less severe knee osteoarthritis. Low adherence to non-surgical and non-pharmacological quality indicators may reflect low healthcare provider knowledge or confidence in prescribing core treatments (62,258,341), and indicates osteoarthritis healthcare requires targeted improvement to ensure individuals with mild-to-moderate knee osteoarthritis receive optimal care.

Despite physical activity and therapeutic exercise being recognized as core treatments for knee osteoarthritis (18–25), a proportion of patients reported that they did not receive advice to exercise. The moderate pass rates for advice to exercise in this study (62% to 69%) align with existing literature on advice to exercise, where an average pass rate of 64% was achieved across previous studies (29–39). Observed pass rates for advice to exercise are generally higher than those reported in earlier quality indicator surveys (29,30,36,38), but lower than more recent surveys (31–35,37,39). Although the current findings for advice to exercise are encouraging as approximately two thirds of participants received recommended care, these results emphasize that more individuals with knee osteoarthritis in the Maritimes should receive advice to exercise, which has been achieved in other countries (31,32,35,37,39) and with more severe knee osteoarthritis populations (34). Moderate pass-rates for advice to exercise may be attributed to perceptions that exercise will exacerbate pain or uncertainty of the effects of exercise on the joint (61,62,115,116,280,342,343). However, evidence states that exercise improves pain and physical function and performance (315,344,345). Therefore, a distinct knowledge-to-practice gap exists for providing advice to exercise for osteoarthritis care. Additional research on, and translation of, the joint-specific effects of exercise may be warranted to help address this gap and increase the quality of osteoarthritis care using exercise.

Increased weight is a well-established risk factor for knee osteoarthritis incidence and progression (165,346); however, provision of advice to lose weight remains low. The low pass rates for advice to lose weight in this study (26% to 35%) are lower than previous reports where an average pass rate of 45% has been achieved across the literature (29–39). Indeed, pass-rates for advice to lose weight are lower than for Canadians awaiting total knee arthroplasty (34), and community-dwelling knee osteoarthritis populations in other countries (31–33,35,37,39). Further, advice to lose weight has shown only modest improvement from the original BC OA survey (36). Evidence suggests that physicians report limited knowledge on weight management, mistrust of dieticians, and difficulties discussing weight loss with patients (62,258), likely contributing to low pass rates for weight management. Patients have expressed complex challenges associated with weight loss (347–349), and have stated that their healthcare providers may not supply adequate resources to support weight loss (322); thus, advice to lose weight requires improvements to enhance the quality of osteoarthritis care for overweight and obese individuals.

Observed pass rates for assessment for ambulatory and non-ambulatory function varied. The high pass rate for assessment for ambulatory function in this study (86%) is considerably higher than previous studies that reported an average pass rate of 27% for walking aid assessments across the literature (31–33,35–39), likely resulting from our relatively healthy cohort who largely reported no walking difficulties. Indeed, findings from the patient-reported questionnaires (e.g., WOMAC, ICOAP) suggest that this sample group had mild-to-moderate pain, symptoms, and functional limitations. Additionally, the low pass rate for assessment for non-ambulatory function in this study (4%) is lower than the average pass rate of 15% achieved across the literature for assessment for appliances and other aids (31–33,35–39). Despite some participants reporting problems with non-ambulatory activities, it is plausible that the health status of the current sample contributed to lower pass-rates if their healthcare providers did not consider medical intervention necessary for their current health state. Assessments of ambulatory and non-ambulatory function are vital to determine a patient's ability to move around and perform daily activities, where walking aids or other assistive devices can be prescribed to reduce activity-related pain, improve balance, or increase functional independence (350,351). These findings emphasise that earlier and improved ambulatory and non-ambulatory assessment is required for less severe knee osteoarthritis cohorts to maintain function and provide more potential to slow disease progression (41–44).

The results from this study suggest that healthcare quality was not driven by patient demographic, social, or patient-reported factors. We found no significant associations between quality of osteoarthritis care and participant age, sex, education, or employment factors. This is in contrast to previous literature that determined older age, male sex, and lower education levels were associated with lower odds of receiving recommended osteoarthritis care (30,34,36). Further, unadjusted regression models indicated that individuals reporting a higher KOOS-Sport score (signifying fewer functional limitations during sport and recreational activities) may be more likely to receive advice to exercise, although this finding did not persist in adjusted analyses. Conversely, previous quality indicator surveys have reported that worse patient-reported outcomes (e.g., pain and function) are associated with higher odds of receiving recommended non-surgical and non-pharmacological care (34,36). The current results should be confirmed with a larger and more diverse sample to determine whether there are potential inequities in osteoarthritis care in the Maritimes.

A sensitivity analysis was conducted to expand on previous quality indicator criteria and include patient-reported use of arthritis treatments. The sensitivity analysis increased the observed pass-rates for advice to exercise and advice to lose weight but did not alter associations with demographic, social, or patient-reported factors. The BC OA criteria specify supervised exercise when examining advice to exercise. However, evidence suggests that both supervised and unsupervised exercise programs can elicit benefits for individuals with knee osteoarthritis (352–354), which has been reflected in recent osteoarthritis management guidelines (317,318). Further, the BC OA criteria indicate specific healthcare practitioners to provide advice to exercise (i.e., physiotherapist) and advice to lose weight (i.e., dietician). However, more general practitioners are managing osteoarthritis (113) and fewer individuals have access to specialists (355,356), highlighting the need to include multidisciplinary healthcare team members or self-management approaches when assessing the quality of osteoarthritis care (324). Future studies should implement continuously updated quality indicator criteria to gain a more comprehensive understanding of healthcare quality and to reflect advances in management guidelines.

Importantly, these survey findings should be interpreted with an understanding of the quality indicator criteria that may over or under report pass rates. For instance, receiving advice to exercise included a criterion of visiting a physiotherapist within the past year, alluding to participation in supervised exercise. However, other quality indicator surveys have analysed exercise and physiotherapy separately (34). Therefore, our eligibility criteria may overreport pass rates for advice to exercise because it encompasses both exercise and physiotherapy. Similarly, criteria descriptors identify receiving care as having seen a specialist related to each indicator (e.g., physiotherapist, dietician, occupational therapist). Therefore, these criteria may be interpreted as having received a referral to specialists, while other quality indicator surveys separate advice (i.e., receiving information) from referral (i.e., access to specialists) care processes (38,256). Adding patient-reported use of exercise or diet as a sensitivity analysis may have captured more participants who underwent exercise or weight loss, yet our criteria may still underestimate the number of participants who received information related to these quality indicators but did not pursue seeing a specialist or begin an exercise or weight-loss program. Finally, our conservative eligibility criteria included participants who said “yes”, and excluded those who said “maybe”, to having knee osteoarthritis. Consequently, it is possible that we excluded participants who had not yet received a formal diagnosis, but who were experiencing symptoms and could potentially fulfill a clinical diagnosis of knee osteoarthritis (23), resulting in a lower proportion of individuals who were eligible to receive care.

This study may be limited by the relatively small sample size and low response rate compared to previous Canadian quality indicator surveys (30,34,36). The sample group included in this study provided limited information of two quality indicators, precluding detailed statistical analysis. Specifically, few participants were eligible for or received care for assessment for ambulatory function and assessment for non-ambulatory function, driven by our mild-to-moderate knee osteoarthritis cohort who largely did not report difficulties with walking or non-ambulatory activities of daily living. Further, this study did not collect information from healthcare providers; therefore, results and interpretation are limited to the patient perspective of care received. However, patient-reported quality indicator tools are the preferred approach for quality indicator evaluations due to the discordance between patient and provider perspectives (255), and the knowledge gleaned from patient perceptions on care quality (38). Finally, the survey was completed online, which may disproportionately exclude individuals who are older, less educated, or report a lower health status (357,358).

3.5 Conclusion

In conclusion, results from the current study suggest that the quality of osteoarthritis care in the Maritimes is sub-optimal, and over half of individuals with mild-to-moderate knee osteoarthritis did not receive recommended core treatments. Healthcare quality was not driven by patient demographic, social, or patient-reported factors. A critical shift in management strategies is needed to improve care for individuals with mild-to-moderate knee osteoarthritis, and earlier healthcare intervention is needed for this patient group. Quality indicators should be routinely evaluated to determine whether clinical care aligns with current best practice guidelines and identify areas for intervention in the care pathway.

Chapter 4 The Effect of Walking Interventions on Biomechanical and Structural Knee Osteoarthritis Outcomes: A Systematic Review and Meta-Analysis

4.1 Introduction

Knee osteoarthritis is a progressive joint condition that negatively affects mobility, physical function, and quality of life (359). Non-surgical and non-pharmacological treatment strategies are consistently recommended to manage knee osteoarthritis outcomes (18–25). Aerobic, land-based physical activity, including walking, is strongly recommended across clinical practice guidelines (18–25), and walking is the most commonly performed physical activity type among individuals with knee osteoarthritis (49,50). However, many individuals with knee osteoarthritis do not receive advice to exercise (29,30,34,36,37), and most are physically inactive (58,360). Despite well-documented cardiovascular health benefits of walking (310,361,362), evidence suggests that physicians and patients may fear that walking worsens symptomatic or structural outcomes due to increased joint loading, limiting physical activity prescription and participation (116,258,279,280). It is unclear whether evidence substantiates these claims, or what evidence exists related to the effects of walking on knee joint health, specifically joint loading, and structural outcomes. Thus, a better understanding of the effects of walking interventions on quantitative knee osteoarthritis outcomes is required.

Greater magnitude, frequency, or duration of mechanical loading contribute to an increased risk of knee osteoarthritis incidence and progression (14,117,363). Joint loading is often quantified using discrete biomechanical metrics, including knee joint moments and impulse, and compressive forces. Individuals with knee osteoarthritis typically walk with higher peak knee adduction moments, lower peak knee flexion moments, and slower gait speeds compared to asymptomatic counterparts (83,84). Evidence suggests increased frequency and patterns of knee joint loading during gait are associated with both increased pain (118,241) and structural progression (95,306). Although biomechanical changes during a single gait cycle have been thoroughly investigated (364), the effects of prolonged walking on discrete biomechanical metrics remains poorly understood. Further, it is unclear whether the biomechanical effects of walking correspond to structural joint changes, especially when accumulating thousands of steps per day (248). Information on quantitative biomechanical and structural knee osteoarthritis outcomes is required to inform walking prescription for optimizing knee health while maintaining cardiovascular health benefits.

Walking guidelines suggest individuals with knee osteoarthritis should walk 3-to-5 days per week at a moderate intensity (60% of maximal heart rate) for 30-to-60 minutes per day (24,45,47,48,67). To date, walking parameters consistent with exercise prescription (i.e., duration, frequency, intensity, and progression) for knee osteoarthritis have been extracted from general physical activity guidelines for older adults (45–48,67–69). While these guidelines are based on the symptomatic and general health benefits of walking (46,365), they do not consider mechanical or structural outcomes that may contribute to clinical or structural disease progression (90–93,366). Evidence suggests that knee contact and muscle forces, as well as serum biomarkers related to cartilage metabolism, increase after 30-minutes of continuous walking in individuals with knee osteoarthritis (79,80,96), indicating potentially negative consequences on joint health. Additionally, the lack of evidence-based disease-specific physical activity guidelines has been identified as a major barrier to physical activity prescription for knee osteoarthritis (257,367), potentially contributing to lower physical activity levels among this population (60,368). Therefore, it is necessary to understand how walking parameters influence quantitative knee osteoarthritis outcomes to determine if walking is safe for knee osteoarthritis and inform disease-specific walking guidelines.

The purpose of this study was to review, synthesize, and evaluate the strength of the evidence on the effects of walking interventions on biomechanical and structural knee osteoarthritis outcomes. The specific objectives of this research were to: (**O1**) determine the biomechanical and structural effects of walking interventions on quantitative knee health; (**O2**) summarize the walking parameters prescribed for individuals with knee osteoarthritis; and (**O3**) explore associations between quantitative knee osteoarthritis outcomes and walking parameters.

4.2 Methods

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist guidelines (369).

4.2.1 Eligibility Criteria

Inclusion Criteria. This review included studies investigating the effect of a continuous, weight-bearing walking intervention on biomechanical and/or structural knee osteoarthritis outcomes. Individuals with uni- or bilateral tibiofemoral knee osteoarthritis diagnosed clinically (e.g., American College of Rheumatology criteria (197)), radiographically (e.g., Kellgren and Lawrence Grade [KLG] (194)), or by use of other modalities (e.g., magnetic resonance imaging) were included, with no restriction on disease severity, presence of patellofemoral osteoarthritis, or age of participants. Studies reporting within-group (pre- and post-walking) comparisons following isolated walking or multi-modal exercise (e.g., walking and strength training) interventions across any walking exposure (single bout or repeated) or setting (supervised or unsupervised) were included. Prospective randomized and quasi-randomized controlled trials, prospective cohort studies, and cross-sectional studies with repeated measures were eligible for inclusion. Studies from all years (inception to search date) published within full-text, peer-reviewed articles written in English were included.

All biomechanical and structural outcomes were included and summarized. Primary biomechanical outcomes included first peak knee adduction moment, knee adduction moment impulse, peak knee flexion moment, and gait speed. Secondary biomechanical outcomes included spatiotemporal variables, the remaining knee joint kinematics and kinetics, and estimates of knee joint contact loading (e.g., knee compressive force) variables. Structural outcomes included quantitative (e.g., femoral cartilage thickness) and semi-quantitative (e.g., Magnetic Resonance Imaging [MRI] Osteoarthritis Knee Score [MOAKS]) imaging metrics obtained using radiographs or MRI.

Exclusion Criteria. Studies investigating participants following total knee arthroplasty, non-human participants (e.g., rodent models), or cadavers were excluded. Interventions were excluded if they included a walking component that was non-continuous (e.g., agility training) or not fully weight-bearing (e.g., aquatic walking), or if walking was recommended but optional. Studies were excluded if they did not report a biomechanical or structural outcome, or if the reported outcomes were not specific to the knee. Observational or cross-sectional studies with a single time point, as well as non-English articles, published abstracts, study protocols, and review articles, were excluded.

4.2.2 Literature Search

Five electronic databases (CIHAHL, EMBASE, PubMED, Scopus, and SportDiscus) were searched from inception until March 2022. Searches used key words and/or subject headings including: (osteoarthritis OR arthrosis OR musculoskeletal disease) AND (knee OR knee joint) AND (exercise OR physical activity OR walking OR aerobic exercise). The search was modified for each database, and the full search strategy is listed in Appendix C. A research librarian was consulted to ensure comprehensiveness of the databases and search terms. The reference lists of included studies and previous systematic reviews on the effects of aerobic, land-based, or low-intensity exercise on knee osteoarthritis were also manually searched for relevant articles.

4.2.3 Study Selection

Full citation lists were exported from each database and imported into Covidence, an online systematic review software (Covidence Systematic Review Software, Veritas Health Innovation, Melbourne, Australia, available at www.covidence.org). Covidence was used to remove all duplicate records and screen all articles.

Database searches were performed by one reviewer. All study screening was completed by two independent reviewers. Title and abstract screening consisted of reviewers voting “yes,” “no” or “maybe” based on the inclusion criterion “exercise intervention for knee osteoarthritis.” “Exercise” was specified instead of “walking” during title and abstract screening to ensure all articles investigating aerobic and/or land-based exercises were fully screened for a walking component, including multi-modal exercise with any continuous walking element, or walking exercise prescribed to a control group (e.g., within gait retraining or aquatic interventions). Potentially relevant articles underwent full text review, during which two independent reviewers voted to “include” or “exclude” the article based on the eligibility criteria. If an article was excluded, the reason for exclusion was documented by each reviewer. Any disagreements were discussed, and consensus was reached.

The kappa statistic was calculated at each stage of the screening process to assess inter-rater reliability, and was interpreted using the following agreement cut-points: <0.00 (poor), 0.00-0.20 (slight), 0.21-0.40 (fair), 0.41-0.60 (moderate), 0.61-0.80 (substantial), and 0.81-1.00 (almost perfect) (370).

4.2.4 Data Extraction

For each included article, the participant characteristics, study design, walking intervention parameters and setting, and associated outcome measures were extracted by one reviewer and confirmed by a second independent reviewer.

The mean and standard deviation values, as well as level of significance (i.e., p-values), for all biomechanical and structural knee osteoarthritis outcomes were recorded before and after the walking intervention. The earliest measurement time point was selected for analysis of longitudinal studies to summarize the most immediate intervention effects before further follow-up time points (e.g., retention), and to represent the most acute effects of walking interventions on knee health. The earliest measurement time point reflects the initial quantitative knee joint health effects after starting a walking exercise program. If the standard deviation values were not reported within the manuscript, they were calculated from other measures of variance (standard error or 95% confidence intervals). If the data were exclusively presented in figures, outcomes were extracted using WebPlotDigitizer (version 4.5; available at www.automeris.io/WebPlotDigitizer/), which has demonstrated high inter-rater reliability and validity (371). If insufficient data were reported in the manuscript, the corresponding author was contacted to obtain the necessary data.

4.2.5 Study Quality Assessment

Methodological quality of each included study was assessed using the *QualSyst* critical appraisal tool for quantitative studies (372). This tool consists of 14-items, each of which was scored (yes=2, partial=1, no=0, or not applicable). A summary quality score was calculated by dividing the sum off all items by the total possible score (Equation 4.1).

Equation 4.1.

$$Summary\ Quality\ Score = \frac{Sum\ of\ all\ QualSyst\ items}{28\ points - [number\ of\ "not\ applicable"\ categories\ x\ 2]}\ x\ 100\%$$

The *QualSyst* tool was selected because it is not restricted to a particular study design, could be applied to all included studies, has been widely implemented across the literature, and has shown high inter-rater reliability within other recent systematic reviews (373–375). Study quality was categorized using the following thresholds: <50.0% (low), 50.0-64.9% (moderate), 65.0-80.0% (high), and >80.0% (excellent) (376).

Two independent reviewers established standardized interpretation criteria for each item based on the *QualSyst* manual for scoring of quantitative studies (372), and pilot tested the tool on five studies. After the pilot test, the reviewers met to compare scores and agreed upon the final interpretation of all items. Once all included studies were evaluated, the two reviewers met again to discuss inconsistencies and decide upon a final quality score. Inter-rater reliability of pre-agreement quality scores was evaluated using intra-class correlation coefficients (ICC) and 95% CI based on a mean-rating (k=2), absolute-agreement, two-way mixed-effects model. ICC values were interpreted using the following reliability cut-points: <0.50 (poor), 0.50-0.75 (moderate), 0.75-0.90 (good), and >0.90 (excellent) (377).

4.2.6 Data Analysis and Synthesis

To achieve **O1**, quantitative synthesis was completed for primary outcomes and involved statistically pooling data within a meta-analysis. Pooled estimates and 95% CIs for standardized mean differences (SMD) were calculated using a random-effects model to account for differences across study samples and designs (378). The SMD was calculated for paired samples using within-group differences (i.e., before and after walking) for all interventions. Magnitudes of the SMD were interpreted using Cohen's d cut-points: <0.2 (very small), 0.2-0.5 (small), 0.5-0.8 (medium), and >0.8 (large) (379). Cohen's d was selected instead of Hedge's g because most studies included in meta-analyses had moderate-to-large sample sizes (i.e., n > 30), and usual methods of Hedge's g may result in more biased meta-estimates (380). A conservative "last observation carried forward" approach was used for studies that only reported measures of variance at baseline (381). For studies that reported a non-exact p-value (e.g., p<0.001), the listed p-value was assigned as the level of significance. For studies that did not report a p-value for within-group changes, a pre-post correlation value of r=0.5 was selected. A sensitivity analysis was performed using pre-post correlation values of r=0.3 and r=0.7 to assess the robustness of the imputation method (381,382). Heterogeneity was assessed using the I^2 and Q statistics, and was interpreted using the following values of inconsistency: <40% (low), 30-60% (moderate), 50-90% (substantial), 75-100% (considerable) (383,384), and the p-value. Publication bias was evaluated using the Egger's regression test and visual analysis of funnel plots (385) and was adjusted using the trim and fill method (386), if necessary.

For records that reported data from the same overarching intervention, one record was selected for quantitative and/or descriptive analysis based on completeness of the reported data. For records in which multiple groups within the study received a walking intervention, the subgroups were combined, and the study was used as the unit of analysis. Analyses were performed first only including studies investigating repeated walking exposure, and a sensitivity analysis was completed by adding single bout walking exposures into the pooled data to explore the effect of walking exposure on quantitative outcomes. Sub-group analyses of repeated walking exposures were performed for intervention exercise type (i.e., walking vs. multi-modal) to ensure conclusions were robust and to determine whether outcomes differed based on walking intervention factors.

For all secondary outcomes, analyses remained descriptive. All studies of a given outcome were summarized based on walking exposure (repeated or single bout) and exercise type (walking only or multi-modal exercise). Results were summarized as within-group changes according to statistical testing (when within-group p-values were reported) or trends in the data (i.e., absolute changes when within-group p-values were not reported).

To achieve **O2**, prescribed walking parameters were summarized for all walking interventions. Single-bout and repeated walking studies were summarized separately. Walking duration (minutes per bout) and intensity (walking speed or percentage of heart rate reserve) were summarized for single bout studies. Intervention length (weeks), and walking duration (minutes per bout), intensity (walking speed or percentage of heart rate reserve), and frequency (bouts per week), were summarized for longitudinal studies.

To achieve **O3**, walking and study parameters were input as factors within meta-regressions. Meta-regressions were run separately for single-bout and repeated walking studies, when possible. Meta-regressions were used to determine the effect of varying walking parameters and study parameters (i.e., quality score, year of publication) on reported biomechanical or structural knee osteoarthritis outcomes. Walking parameters input into meta-regressions for single bout studies included walking bout duration and intensity, and for repeated walking studies included intervention duration and walking bout duration, frequency, and intensity, when available. Meta-regression outcomes indicated the percentage of between-study variance in treatment effects explained by the walking or study parameters (387).

Meta-analyses and meta-regressions were performed using Comprehensive Meta-Analysis (Biostat Inc, Version 4, Englewood, NJ, available from: https://www.meta-analysis.com/). Additional statistical testing (e.g., kappa values, ICCs) was performed using SPSS (IBM SPSS Statistics for Windows, Version 28.0.1.1, Armonk, NY). All statistical testing was performed using an alpha value of 0.05 or was interpreted based on whether the 95% CI failed to cross the line of no significance.

4.3 Results

4.3.1 Search Results

A total of 14,165 unique records were identified through database and manual searches (**Error! Reference source not found.**). Following title and abstract screening, 1 556 records underwent full-text review. Of those, 33 studies reported quantitative biomechanical and/or structural imaging outcomes and were included in the descriptive analysis. Data from 15 studies were combined within the quantitative meta-analysis. Inter-rater reliability for title and abstract screening was almost perfect (κ = 0.81) and for full text review was substantial (κ = 0.75).

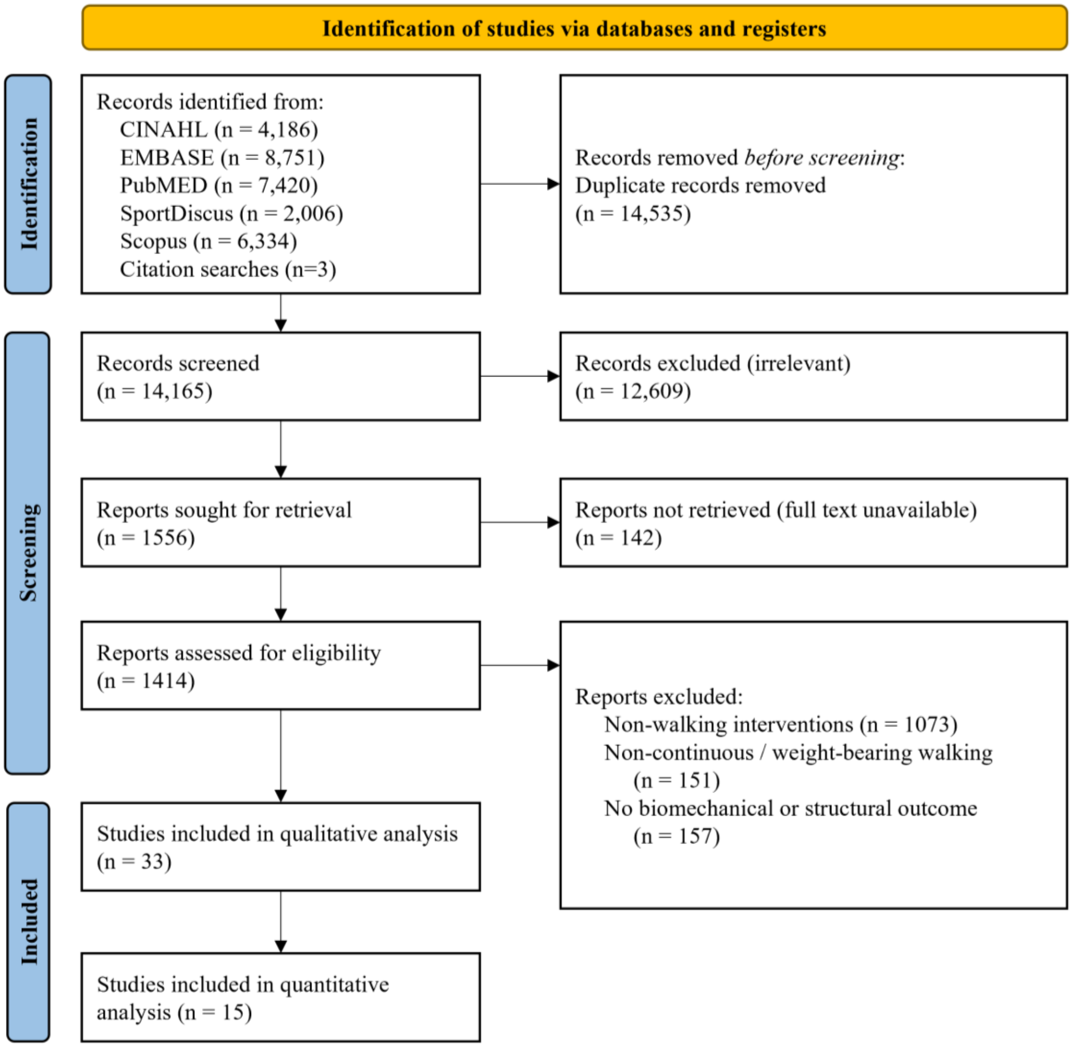


Figure 4.1. PRISMA 2020 flow diagram for new systematic reviews which include searches of databases and registers.

Reports (n=1380) were excluded after full text review. A total of 1073 articles were excluded based on the exercise intervention (n=578), report type (n=471), or population of interest (n=24). Exercise interventions were excluded if they reported effects of an intervention that did not include walking, including strength or resistance training (n=213), multi-modal exercise (n=133), unspecified exercise (n=57), tai chi (n=38), neuromuscular training (n=37), physiotherapy (n=37), aquatic exercise (n=18), yoga or Pilates (n=15), cycling (n=11), stepping exercise (n=8), stretching (n=3), circuit training (n=2), acupressure exercise (n=1), balance training (n=1), boxing (n=1), kicking (n=1), running (n=1), or squatting (n=1). Records were excluded if they were a review article (n=102), study protocol (n=99), editorial or commentary (n=88), non-English article (n=75), conference abstract (n=64), thesis (n=17), newspaper article (n=11), observational study (n=6), book chapter (n=3), cross-sectional study with a single timepoint (n=3), or retrospective study (n=3). Articles were excluded if they did not report the population of interest, including a non-knee osteoarthritis population (n=23) or non-human sample (n=1).

Additionally, 151 articles reported an exercise intervention that included walking that was non-continuous or non-weight bearing. Specifically, excluded articles contained walking within a warm-up or cool-down period only (n=34), proprioceptive or agility training (n=29), physical activity intervention (n=25), unspecified aerobic intervention (n=23), aquatic walking (n=20), recommendation only (n=13), reduced-load walking (n=6), or gait retraining (n=1). Finally, 157 articles included a continuous, weight-bearing walking component, but were excluded because they did not report a quantitative biomechanical or structural imaging outcome. One additional article investigating 30-minutes of treadmill walking in a knee osteoarthritis population was excluded because it reported kinematic outcomes not specific to the knee joint (388).

4.3.2 Quality Assessment

Quality assessment of included studies (Table 4.1) revealed that study quality was excellent (n=21, 64%), high (n=10, 30%), and moderate (n=2, 6%). No studies were rated low quality. The mean quality score was 84.0% (ranging from 57.7% to 100%), and 4 studies received a perfect (100%) quality score. Inter-rater reliability was excellent (ICC [95% CI] = 0.96 [0.92, 0.98]) for pre-consensus summary quality scores.

Table 4.1. *QualSyst* summary scores for all included studies (n=33).

Study, year	***QualSyst* Item**														**Total Score**
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
Peterson et al., 1993 (75)	1	1	2	1	1	0	NA	2	2	2	2	1	2	2	73.1%
Bautch et al., 1997 (76)	1	2	1	2	1	1	NA	2	1	0	2	1	1	2	65.4%
Ettinger et al., 1997 (77)	2	2	2	1	2	2	NA	2	2	2	2	2	1	1	88.5%
Fransen et al., 1997 (389)	1	1	1	2	NA	NA	NA	1	1	1	2	1	1	1	59.1%
Messier et al., 1997 (78)	1	2	1	2	2	1	NA	2	2	2	1	2	2	2	84.6%
Messier et al., 2000 (292)	1	2	1	2	1	2	NA	2	1	1	1	2	2	2	76.9%
Messier et al., 2004 (297)	1	2	2	2	2	2	NA	2	2	2	2	2	2	1	92.3%
Miller et al., 2004 (390)	2	2	2	2	1	2	NA	2	2	2	2	2	2	1	92.3%
Messier et al., 2005 (248)	2	2	2	2	1	1	NA	2	2	2	2	2	2	1	88.5%
Denning et al., 2010 (391)	2	2	2	2	2	NA	NA	1	1	1	2	1	2	1	79.2%
Gaudreault et al., 2011 (392)	2	1	1	2	NA	NA	NA	2	2	2	2	1	2	1	69.2%
Messier et al., 2011 (246)	2	2	2	2	1	2	NA	2	2	2	2	2	2	1	92.3%
Woollard et al., 2011 (393)	2	2	2	2	NA	NA	NA	2	1	0	1	1	2	1	72.7%
Messier et al., 2013 (319)	2	2	2	2	2	2	NA	2	2	2	2	2	2	2	100.0%
Roper et al., 2013 (394)	2	2	1	1	1	0	NA	1	1	1	2	1	1	1	57.7%
Henriksen et al., 2015 (395)	1	2	2	2	2	2	2	2	2	2	2	1	2	1	96.2%
Hunter et al., 2015 (296)	1	2	2	2	2	0	NA	2	2	2	2	2	2	2	88.5%
Farrokhi et al., 2017 (79)	2	2	2	2	0	NA	NA	2	2	2	1	1	2	2	83.3%
Henriksen et al., 2017 (396)	1	2	2	2	2	2	NA	1	1	1	2	2	2	2	84.6%
Riis et al., 2017 (397)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	100.0%
Benli Küçük et al., 2018 (398)	1	1	2	2	1	0	NA	2	2	2	1	1	2	2	73.1%
Cheung et al., 2018 (399)	2	2	2	2	2	2	NA	2	2	2	2	2	2	1	96.2%
Hunt et al., 2018 (400)	2	2	2	2	2	2	NA	2	2	2	2	2	2	1	96.2%
Messier et al., 2018 (250)	2	2	2	2	2	2	NA	2	2	2	2	2	2	2	100.0%
Boyer et al., 2019 (81)	2	2	1	2	NA	NA	NA	2	1	2	2	1	2	2	86.4%
Gustafson et al., 2019 (80)	2	1	1	2	NA	NA	NA	2	2	2	1	1	2	2	69.2%
Ho et al., 2019 (109)	2	2	1	2	NA	2	NA	2	2	2	1	0	2	2	83.3%
Messier et al., 2020 (247)	2	2	2	2	2	2	NA	2	2	2	2	2	2	2	100.0%
Bandak et al., 2021 (401)	2	2	2	2	2	2	NA	2	1	2	2	2	2	2	96.2%
Bokaeian et al., 2021 (402)	1	2	2	2	2	2	NA	2	2	2	2	1	2	1	88.5%
Chen et al., 2021 (403)	2	2	2	2	2	0	NA	1	1	2	2	1	1	2	76.9%
Wang et al., 2021 (404)	2	2	2	2	2	0	NA	2	2	2	2	1	2	1	84.6%
Gatti et al., 2022 (110)	2	2	1	2	1	0	NA	2	1	2	2	2	1	2	76.9%

Note: *QualSyst* items: 1 = Objective sufficiently described. 2 = Design evident and appropriate. 3 = Method of subject selection described and appropriate. 4 = Subject characteristics sufficiently described. 5 = Random allocation. 6 = Blinding of investigators. 7 = Blinding of subjects. 8 = Outcome measures defined and robust. 9 = Sample size appropriate. 10 = Analysis described and appropriate. 11 = Estimate of variance reported. 12 = Controlled for confounding. 13 = Results reported in sufficient detail. 14 = Results support conclusions. Total score: <50.0% (low), 50.0-64.9% (moderate; yellow), 65.0-80.0% (high; green), >80.0% (excellent; blue).

4.3.3 Study Characteristics

Study characteristics are summarized in Table 4.2. Included studies prescribed walking exercise to 1119 unique individuals, 88.4% (n=989) of which completed the bout or intervention. Participants were approximately 65% female. Seventeen studies (53%) reported radiographic knee osteoarthritis severity, and 11 studies reported specific KLG distributions. Among the 371 participants included in studies reporting specific KLG groups (n=11), participants had KLG I (n=39, 11%), KLG II (n=153, 41%), KLG III (n=101, 27%), and KLG IV (n=78, 21%). Study publication years ranged from 1993 to 2022. A total of 22 distinct walking interventions were identified within the included studies. Most interventions were randomized controlled trials (n=13, 57%), followed by single-arm studies (n=7, 32%), and quasi-randomized controlled trials (n=2, 9%). These distinct walking interventions comprised repeated (n=18) and single-bout (n=4) walking exposures. Repeated walking exposures included walking only (n=11) and multi-modal (n=7) exercise interventions. Multi-modal exercise interventions most often included strengthening, stretching, physiotherapy, and/or diet components, in addition to a walking component. All single-bout exposures were walking only. Most walking was performed in a supervised setting (73.9%, n=17), though some interventions used a combination of supervised and home-based (21.7%, n=5), or home-based only programs (4.3%, n=1).

Table 4.2. Study characteristics for all included studies (n=33).

Author, year	n, all [completed]	Participant Characteristics	Study Characteristics	Walking Parameters	Outcomes
Peterson et al., 1993 (75)	52 [47].	Age: 69.4 (range: 40-89) years. Height: 162.8 (11.3) cm. Mass: 77.5 (15.0) kg.	Design: RCT. Walking exposure: Repeated. Intervention length: 8-weeks. Exercise type: Walking only. Group: Intervention (walking). Setting: Supervised.	Duration: 5 mins. Frequency: 3x/week. Intensity: Self-selected pace. Progression: Increase duration by 2.5 mins per week until 30 mins. Increase frequency to 4x/week.	Gait speed. Spatiotemporal.
Bautch et al., 1997 (76)	17 [15]. Full outcomes obtained within sub-group (n=6).	Age: 66 (5.9) years. Sex: 2 males, 4 females. BMI: 32.59 (2.7) kg/m^2. KLG: II (n=1), III (n=1), IV (n=4).	Design: RCT. Walking exposure: Repeated. Intervention length: 12-weeks. Exercise type: Walking only. Group: Exercise group. Setting: Supervised.	Duration: 60 mins (including warm-up). Frequency: 3x/week. Intensity: Self-selected pace. Progression: Distance increased weekly.	Radiographic.
Ettinger et al., 1997 (77) *	144 [117].	Age: 69 (6.0) years. Sex: 45 males, 99 females.	Design: RCT. Walking exposure: Repeated. Intervention length: 18-months. Exercise type: Walking only. Group: Aerobic exercise. Setting: Supervised (3 months), then home-based (15-months).	Duration: 40 mins. Frequency: 3x/week. Intensity: 50-70% HRR.	Radiographic.
Fransen et al., 1997 (389)	52 [40].	Age: Males = 68.0 (3.42) years. Females = 65.8 (7.94) years. Sex: 8 males, 32 females. BMI: Males = 27.3 (2.65) kg/m^2. Females = 29.4 (4.32) kg/m^2.	Design: Single-arm trial. Walking exposure: Repeated. Intervention length: 8-weeks. Exercise type: Multi-modal. Setting: Home-based.	Duration: 20 mins. Frequency: 3x/week.	Gait speed. Spatiotemporal.

Author, year	**n, all [completed]**	**Participant Characteristics**	**Study Characteristics**	**Walking Parameters**	**Outcomes**
Messier et al., 1997 (78) *	33.	Age: 70.3 (7.5) years. Sex: 6 males, 27 females. BMI: 31.4 (5.7) kg/m^2.	Design: RCT. Walking exposure: Repeated. Intervention length: 18-months. Exercise type: Walking only. Group: Aerobic exercise. Setting: Supervised (3 months), then home-based (15 months).	Duration: 40 mins. Frequency: 3x/week. Intensity: 50-85% HRR.	Gait speed. Spatiotemporal. Knee kinematics.
Messier et al., 2000 (292)	Exercise Group: 11 [9]. Diet + Exercise Group: 13 [12].	Exercise Group: Age: 69 (16.6) years. Sex: 4 males, 7 females. BMI: 38 (19.9) kg/m^2. Diet + Exercise Group: Age: 67 (14.4) years. Sex: 3 males, 10 females. BMI: 35 (18.0) kg/m^2.	Design: RCT. Walking exposure: Repeated. Intervention length: 24-weeks. Exercise type: Multi-modal. Group: Exercise & Diet + Exercise. Setting: Supervised.	Duration: 2 x 10 mins. Frequency: 3x/week. Intensity: 50-75% HRR.	Gait speed. Spatiotemporal. Knee kinematics.
Messier et al., 2004 (297) †	Exercise Group: 80 [64]. Diet + Exercise Group: 76 [58].	Exercise Group: Age: 69 (7.2) years. Sex: 74% female. BMI: 34.2 (5.4) kg/m^2. KLG: 2.19 (0.81). Diet + Exercise Group: Age: 69 (7.0) years. Sex: 74% female. BMI: 34.0 (6.1) kg/m^2. KLG: 2.31 (0.88).	Design: RCT. Walking exposure: Repeated. Intervention length: 18-months. Exercise type: Multi-modal. Group: Exercise & Diet + Exercise. Setting: Supervised (4-months), then option of supervised and/or home-based (14-months).	Duration: 2 x 15 mins. Frequency: 3x/week. Intensity: 50-75% HRR.	Radiographic.

Author, year	**n, all [completed]**	**Participant Characteristics**	**Study Characteristics**	**Walking Parameters**	**Outcomes**
Miller et al., 2004 (390) †	Exercise Group: 79. Diet + Exercise Group: 74.	Exercise Group: Age: 69.1 (6.5) years. Sex: 75.9% female. BMI: 34.2 (4.8) kg/m^2. Diet + Exercise Group: Age: 68.7 (6.7) years. Sex: 74.3% female. BMI: 34.2 (5.6) kg/m^2.	Design: RCT. Walking exposure: Repeated. Intervention length: 18-months. Exercise type: Multi-modal. Group: Exercise & Diet + Exercise. Setting: Supervised (4-months), then option of supervised and/or home-based (14-months).	Duration: 2 x 15 mins. Frequency: 3x/week. Intensity: 50-85% HRR.	Radiographic.
Messier et al., 2005 (248) †	142 [116].	Age: 68.5 (6.2) years. Sex: 37 males, 105 females. BMI: 34.0 (5.0) kg/m^2.	Design: RCT. Walking exposure: Repeated. Intervention length: 18-months. Exercise type: Multi-modal. Group: Combined groups (Exercise, Diet, Diet + Exercise, Control). Setting: Supervised (4-months), then option of supervised and/or home-based (14-months).	Duration: 2 x 15 mins. Frequency: 3x/week. Intensity: 50-75% HRR.	KAM. KFM. Knee joint kinetics.
Denning et al., 2010 (391)	19.	Age: 59.4 (7.4) years. Sex: 3 males, 16 females. Height: 160.3 (8.22) cm. Mass: 90.8 (21.8) kg.	Design: Quasi-RCT. Walking exposure: Repeated. Intervention length: 1-week. Exercise type: Walking only. Group: Land treadmill (control). Setting: Supervised.	Duration: 20 mins. Frequency: 3x/week. Intensity: Self-selected pace. Progression: Increase speed by 0.13 m/s after each 5-minute interval; last 5-minute interval is self-selected speed.	Spatiotemporal.
Gaudreault et al., 2011 (392)	29.	Age: 63.3 (8.4) years. Sex: 7 males, 22 females. BMI: 31 (5) kg/m^2. KLG: I (n=10), II (n=5), III (n=5), IV (n=9).	Design: Single-arm trial. Walking exposure: Repeated. Intervention length: 12-weeks. Exercise type: Multi-modal. Setting: Supervised.	Duration: 10 mins. Frequency: 2x/week. Intensity: Self-selected speed.	KAM. KAM impulse. KFM. Spatiotemporal. Knee kinematics.

Author, year	**n, all [completed]**	**Participant Characteristics**	**Study Characteristics**	**Walking Parameters**	**Outcomes**
Messier et al., 2011 (246) †	142 [76].	Age: 68.5 (6.2) years. Sex: 37 males, 105 females. BMI: 34.0 (5.0) kg/m^2.	Design: RCT. Walking exposure: Repeated. Intervention length: 18-months. Exercise type: Multi-modal. Group: High & Low & No Weight-Loss. Setting: Supervised (4-months), then option of supervised and/or home-based (14-months).	Duration: 2 x 15 mins. Frequency: 3x/week. Intensity: 50-75% HRR.	KAM. KFM. Gait speed. Knee joint kinetics. Radiographic.
Woollard et al., 2011 (393)	13.	Age: 63.5 (11.4) years. Sex: 10 males, 3 females. BMI: 28.0 (4.0) kg/m^2. KLG: I (n=2), II (n=4), III (n=5), IV (n=2).	Design: Single-arm trial. Walking exposure: Repeated. Intervention length: 6-months. Exercise type: Multi-modal. Setting: Supervised (6 weeks), then home-based (4-months).	Duration: Supervised = 5 mins. Home = 30 mins. Frequency: Supervised = 2x/week. Home = 3x/week. Intensity: Self-selected pace. Progression: Supervised = increase duration to 15 minutes, then increase speed as tolerated.	Quantitative MRI.
Messier et al., 2013 (319) ‡	Exercise Group: 150 [130]. Diet + Exercise Group: 152 [138].	Exercise Group: Age: 66 (6) years. Sex: 72% female. BMI: 33.5 (3.7) kg/m^2. KLG: 2.53 (0.59). Diet + Exercise Group: Age: 65 (6) years. Sex: 72% female. BMI: 33.6 (3.7) kg/m^2. KLG: 2.59 (0.60).	Design: RCT. Walking exposure: Repeated. Intervention length: 18-months. Exercise type: Multi-modal. Group: Exercise & Diet + Exercise. Setting: Supervised (6-months), then option of supervised and/or home-based (12-months).	Duration: 2 x 15-mins. Frequency: 3x/week.	Gait speed. Knee joint kinetics.

Author, year	n, all [completed]	Participant Characteristics	Study Characteristics	Walking Parameters	Outcomes
Roper et al., 2013 (394)	14.	Age: 59.2 (7.2) years. Sex: 2 males, 12 females. BMI: 33.5 (8.4) kg/m^2.	Design: Quasi-RCT. Walking exposure: Repeated. Intervention length: 1-week. Exercise type: Walking only. Group: Land treadmill (control). Setting: Supervised.	Duration: 20 mins. Frequency: 3x/week. Intensity: Self-selected pace. Progression: Increase speed by 0.13 m/s after each 5-minute interval; last 5-minute interval is self-selected speed.	Knee kinematics.
Henriksen et al., 2015 (395) §	Intervention: 50 [45]. Placebo: 50 [44].	Intervention: Age: 61.3 (9.9) years. Sex: 56% female. BMI: 29.0 (3.9) kg/m^2. KLG: I (n=4), II (n=21), III (n=15), IV (n=10). Placebo: Age: 65.5 (8.3) years. Sex: 66% female. BMI: 28.9 (3.3) kg/m^2. KLG: II (n=18), III (n=17), IV (n=15).	Design: RCT. Walking exposure: Repeated. Intervention length: 12-weeks. Exercise type: Multi-modal. Group: Intervention & Placebo. Setting: Supervised.	Duration: 5-10 mins. Frequency: 3x/week.	Semi-quantitative MRI.
Hunter et al., 2015 (296) ‡	X-ray subsample: 325 (Exercise group = 135, Diet + Exercise group = 136). MRI subsample: 105 (98); (Exercise group = 36, Diet + Exercise group = 36).	X-ray subsample: Age: 66 (6) years. Sex: 74% female. BMI: 33.4 (3.8) kg/m^2. KLG: II (48.3%), III (51.7%). MRI subsample: Age: 65 (6) years. Sex: 73% female. BMI: 33.7 (3.8) kg/m^2. KLG: II (42.9%), III (57.1%).	Design: RCT. Walking exposure: Repeated. Intervention length: 18-months. Exercise type: Multi-modal. Group: Exercise & Diet + Exercise. Setting: Supervised (6-months), then option of supervised and/or home-based (12-months).	Duration: 2 x 15 mins. Frequency: 3x/week.	Quantitative MRI. Semi-quantitative MRI. Radiographic.

Author, year	**n, all [completed]**	**Participant Characteristics**	**Study Characteristics**	**Walking Parameters**	**Outcomes**
Farrokhi et al., 2017 (79) ‖	27.	Age: 63.7 (7.7) years. Sex: 74.1% female. BMI: 27.3 (3.7) kg/m^2. KLG: Tibiofemoral: II (n=10), III (n=8), IV (n=9).	Design: Single-arm trial. Walking exposure: Single bout. Exercise type: Walking only. Setting: Supervised.	Duration: 45 mins within continuous (1 x 45 mins) and interval (3 x 15 mins) conditions. Intensity: 1.3 m/s.	Knee joint kinetics.
Henriksen et al., 2017 (396) §	31 [24].	Age: 64.9 (9.1) years. Sex: 2 males, 22 females. BMI: 29.1 (4.1) kg/m^2.	Design: RCT. Walking exposure: Repeated. Intervention length: 12-weeks. Exercise type: Multi-modal. Group: Exercise (intervention). Setting: Supervised.	Duration: 5-10 mins. Frequency: 3x/week.	KAM. KAM impulse. KFM. Gait speed. Spatiotemporal. Knee kinematics.
Riis et al., 2017 (397) §	Intervention: 50 [45]. Placebo: 50 [46].	Intervention: Age: 60.7 (9.9) years. Sex: 57.8% female. BMI: 29.2 (3.9) kg/m^2. KLG: I (n=4). II (n=20). III (n=14). IV (n=7). Placebo: Age: 65.7 (8.2) years. Sex: 67.4% female. BMI: 29.1 (3.3) kg/m^2. KLG: II (n=16). III (n=15). IV (n=15).	Design: RCT. Walking exposure: Repeated. Intervention length: 12-weeks. Exercise type: Multi-modal. Group: Intervention & Placebo. Setting: Supervised.	Duration: 5-10 mins. Frequency: 3x/week.	Semi-quantitative MRI.
Benli Küçük et al., 2018 (398)	15.	Age: 52.5 (5.3) years. Sex: 100% female. BMI: 29.6 (3.5) kg/m^2. KLG: II (n=11), III (n=4).	Design: RCT. Walking exposure: Repeated. Intervention length: 4-weeks. Exercise type: Walking only. Group: Aerobic exercise. Setting: Supervised.	Duration: 20 mins. Frequency: 5x/week. Intensity: 4.5 km/h (1.25 m/s).	Quantitative MRI.

Author, year	n, all [completed]	Participant Characteristics	Study Characteristics	Walking Parameters	Outcomes
Cheung et al., 2018 (399)	11 [10].	Age: 63.1 (5.9) years. Sex: 5 males, 5 females. BMI: 25.2 (1.1) kg/m^2. KLG: I (n=3), II (n=7).	Design: RCT. Walking exposure: Repeated. Intervention length: 6-weeks. Exercise type: Walking only. Group: Walking exercise (control). Setting: Supervised.	Duration: 15 mins. Frequency: 1x/week. Intensity: Self-selected pace. Progression: Increase walking time to 30-mins.	KAM. KFM.
Hunt et al., 2018 (400)	39 [33].	Age: 65.4 (9.6) years. Sex: 11 males, 28 females. BMI: 27.4 (3.5) kg/m^2. KLG: II (n=18), III (n=14), IV (n=7).	Design: RCT. Walking exposure: Repeated. Intervention length: 4-months. Exercise type: Walking only. Group: Progressive walking (control). Setting: Home-based with 8 supplemental supervised sessions.	Duration: 20 mins. Progression: Increase duration to 40 mins by week 15. Increase walking in community by 40% above baseline.	KAM. KAM impulse. KFM. Gait speed.
Messier et al., 2018 (250) ‡	240.	Age: 65.8 (6.0) years. Sex: 72.1% female. BMI: 33.4 (3.8) kg/m^2.	Design: RCT. Walking exposure: Repeated. Intervention length: 18-months. Exercise type: Multi-modal. Group: <5%, ≥5%, ≥10%, ≥20% weight loss groups. Setting: Supervised (6-months), then option of supervised and/or home-based (12-months).	Duration: 2 x 15 mins. Frequency: 3x/week.	Knee joint kinetics.
Boyer et al., 2019 (81)	19. Pain Flare Group: 8. No Pain Flare Group: 11.	Pain Flare Group: Age: 62.1 (1.9) years. Sex: 5 males, 3 females. BMI: 25.89 (1.47) kg/m^2. No Pain Flare Group: Age: 62.6 (1.9) years. Sex: 1 male, 10 females. BMI: 25.69 (1.01) kg/m^2.	Design: Single-arm trial. Walking exposure: Single bout. Exercise type: Walking only. Group: Pain flare & no pain flare. Setting: Supervised.	Duration: 20 mins. Intensity: Self-selected pace.	KAM. KFM. Knee kinematics. Knee joint kinetics.

Author, year	**n, all [completed]**	**Participant Characteristics**	**Study Characteristics**	**Walking Parameters**	**Outcomes**
Gustafson et al., 2019 (80) ‖	26.	Age: 63.6 (7.8) years. Sex: 73.1% female. BMI: 27.3 (3.8) kg/m^2. KLG: Medial compartment, symptomatic limb: 0 (n=1), I (n=1), II (n=13), III (n=9), IV (n=2).	Design: Single-arm trial. Walking exposure: Single bout. Exercise type: Walking only. Setting: Supervised.	Duration: 45 mins. Intensity: 1.3 m/s.	Knee joint kinetics.
Ho et al., 2019 (109)	9.	Age: 55.6 (4.5) years. Sex: 5 males, 4 females. BMI: 32.4 (4.4) kg/m^2. KLG: 2.3 (0.5).	Design: Single-arm trial. Walking exposure: Single bout. Exercise type: Walking only. Group: Knee osteoarthritis. Setting: Supervised.	Duration: 30 mins. Intensity: 3-4 mph (1.34 – 1.79 m/s).	Quantitative MRI.
Messier et al., 2020 (247) ‡	454 [399]. Exercise Group: 111. Diet + Exercise Group: 111.	Age: 66 (6) years. Sex: 72% female. BMI: 33.6 (3.7) kg/m^2. KLG: 2.56 (0.59).	Design: RCT. Walking exposure: Repeated. Intervention length: 18-months. Exercise type: Multi-modal. Group: Exercise & Diet + Exercise. Setting: Supervised (6-months), then option of supervised and/or home-based (12-months).	Duration: 2 x 15 mins. Frequency: 3x/week.	KAM. KFM. Gait speed. Spatiotemporal. Knee kinematics. Knee joint kinetics.
Bandak et al., 2021 (401) §	31 [16].	Age: 67.2 (8.2) years. Sex: 87.5% female. BMI: 27.7 (3.4) kg/m^2.	Design: RCT. Walking exposure: Repeated. Intervention length: 12-weeks. Exercise type: Multi-modal. Group: Exercise (intervention). Setting: Supervised.	Duration: 5-10 mins. Frequency: 3x/week.	Semi-quantitative MRI.

Author, year	**n, all [completed]**	**Participant Characteristics**	**Study Characteristics**	**Walking Parameters**	**Outcomes**
Bokaeian et al., 2021 (402)	18.	Age: 56.7 (4.7) years. Sex: 4 males, 14 females. BMI: 31.5 (1.8) kg/m^2.	Design: RCT. Walking exposure: Repeated. Intervention length: 4-weeks. Exercise type: Walking only. Group: Treadmill walk. Setting: Supervised.	Duration: 20 mins. Frequency: 3x/week. Intensity: Self-selected pace.	KAM. KFM. Gait speed.
Chen et al., 2021 (403)	10.	Age: 58.30 (8.54) years. Sex: 2 males, 6 females. BMI: 23.02 (1.37) kg/m^2. KLG: II (n=7), III (n=3).	Design: RCT. Walking exposure: Repeated. Intervention length: 2-weeks. Exercise type: Walking only. Group: Overground walk (control). Setting: Supervised.	Duration: 3 x 5 mins. Frequency: 6x/week. Intensity: Self-selected pace.	Gait speed. Spatiotemporal. Knee kinematics.
Wang et al., 2021 (404)	36 [31].	Age: 61.7 (6.8) years. Sex: 14 males, 17 females. Height: 1.65 (0.08) m. Mass: 64.2 (10.6) kg. KLG: I (n=16), II (n=15).	Design: RCT. Walking exposure: Repeated. Intervention length: 6-weeks. Exercise type: Walking only. Group: Walking exercise (control). Setting: Supervised.	Duration: 15 mins. Frequency: 1x/week. Intensity: Self-selected pace. Progression: Increase duration by 3 mins each session (until 30 mins).	KAM. KAM impulse. KFM.
Gatti et al., 2022 (110)	7. Walking visit only: 4. Walking and cycling visits: 3.	Walking visit only: Age: 59.7 (5.7) years. Sex: 100% female. BMI: 29.5 (4.1) kg/m^2. Walking and cycling visits: Age: 65.3 (3.5) years. Sex: 100% female. BMI: 26.2 (7.6) kg/m^2.	Design: Single-arm trial. Walking exposure: Single bout. Exercise type: Walking only. Setting: Supervised.	Duration: 25 mins. Intensity: Fast self-selected pace or Froude (Fr) speed (Fr = 0.25; speed normalized to leg length).	Knee joint kinetics. Quantitative MRI.

Note: Not all studies reported all data points. If available, the study characteristics are presented in the table. n represents the number of participants in the relevant walking group only, with the number of participants who fully completed the intervention listed in square brackets. BMI = body mass index. HRR = heart rate reserve. KLG = Kellgren and Lawrence grade. Mph = miles per hour. RCT = randomized controlled trial. **Participant Characteristics:** Age presented as mean (standard deviation), or mean (range), in years. Sex presented as number of males and females, or % female. BMI presented as mean (standard deviation) in kg/m^2 or mean (standard deviation) of height and mass separately. KLG presented as number of participants within each severity level (0-4) or mean (standard deviation). **Study Characteristics:** Study design is selected as RCT, quasi-RCT (e.g., crossover study), or single-arm trial. Walking exposure reflects the study design and is selected as either single-bout or repeated walking. Intervention length is reported for longitudinal studies only and reflects the number of weeks (or months) of the exercise intervention. Exercise type reflects the types of exercise performed within the intervention and is selected as either walking only (single intervention) or multi-modal (mixed exercise or combined intervention). Group reflects the name of the walking sub-group within the study, if applicable, and corresponds to the group characteristics presented within the table. Setting is the setting of the exercise performed within the intervention and is selected as either supervised or home-based (or a combination thereof, specified per study). **Walking Parameters:** These measures pertain to the walking component of the study only (not other exercise components within multi-modal exercise interventions). Duration is listed as minutes per walking bout. Frequency is listed as number of walking bouts per week (and only pertains to longitudinal studies). Intensity is presented as walking speed or cardiovascular characteristics (e.g., HRR). Progression presents any changes in the walking program as the intervention progressed, and could reflect changes in duration, frequency, or intensity components. **Other:** Overarching RCTs (repeat interventions) are identified when the same intervention was reported across multiple records: * Fitness, Arthritis, and Seniors Trial (FAST). † Arthritis, Diet, and Activity Promotion Trial (ADAPT). ‡ Intensive Diet and Exercise for Arthritis (IDEA). § Functional and Individualized Therapeutic Exercise program for participants with knee OsteoArthritis (FITE-OA). ‖ University of Pittsburgh.

4.3.4 Walking Parameters

Walking parameters are summarized in Table 4.3. For repeated walking exposures (n=18), 30-minutes was the most investigated walking duration. Four studies prescribed a progression of increasing walking duration through the intervention (75,399,400,404). Walking frequency was reported in all but one study, and walking was most often prescribed 3x/week. Walking intensity was reported within 14 interventions and was most often prescribed as participant self-selected speed. Three interventions prescribed a cardiovascular target of intensity (77,292,297), and one study specified a standardized speed of 4.5 km/h (1.25 m/s) for all participants (398). For single-bout walking exposures (n=5), walking duration was most often prescribed as a 30-minute bout, and intensity was prescribed as participant self-selected speed. Two interventions prescribed walking at a specific speed (1.3 m/s and 3-4 miles/h [1.34 – 1.79 m/s], respectively) (79,109).

Table 4.3. Summary of prescribed walking parameters within distinct interventions.

Walking Parameter	Mean	Median	Range
Repeated Walking Exposures (n=18)			
Intervention Length (weeks)	20.9	10	1 – 78
Duration (minutes per bout)	26.1	25	5 – 60
Frequency (bouts per week)	3.0	3	1 – 6
Single-Bout Walking Exposures (n=5)			
Duration (minutes per bout)	30.0	30	20 – 45

Within sub-group analyses, repeated walking exposures were separated by exercise type. Within interventions that involved walking exercise only, mean intervention length was 12.6 (range: 1–78) weeks, mean walking duration was 29.5 (range: 15–60) minutes per bout, and mean walking frequency was 3.1 (range: 1–6) bouts per week. Within interventions that involved multi-modal exercise, the mean intervention length was 34 (range: 8–78) weeks, mean walking duration was 20.7 (range: 5–30) minutes per bout, and mean walking frequency was 2.9 (range: 2–3) bouts per week.

4.3.5 Outcome Measures

4.3.5.1 First Peak Knee Adduction Moment

Nine studies reported the effects of walking on the first peak external knee adduction moment (Figure 4.2A); eight studies evaluated repeated walking exposure (247,248,392,396,399,400,402,404), and one study evaluated a single walking bout (81). Meta-analysis revealed a very small, statistically significant increase in first peak knee adduction moment (SMD = 0.13, 95% CI [0.01, 0.24], p = 0.028; I^2 = 18.9%, p = 0.280). Adjusting the pre-post correlation had minimal effect on the results. No publication bias was identified using Egger's regression test (intercept = 0.26, 95% CI [-1.90, 2.41], p = 0.780) or visualization of the funnel plot (Figure 4.3A). The sensitivity analysis, adding the single bout walking exposure into the pooled analysis, reduced the treatment effect (SMD = 0.11, 95% CI [-0.01, 0.22], p = 0.083; I^2 = 26.9%, p = 0.205), suggesting a very small, non-significant increase in first peak knee adduction moment.

Four (of 8 repeated walking studies) investigated walking only interventions (399,400,402,404), and four investigated multi-modal exercise interventions (247,248,392,396). Sub-group analyses indicated no significant difference in first peak knee adduction moment following walking only (SMD = 0.20, 95% CI [-0.01, 0.40], p = 0.063; I^2 = 0%, p = 0.827) or following multi-modal exercise interventions (SMD = 0.09, 95% CI [-0.09, 0.28], p = 0.318; I^2 = 58.6%, p = 0.064).

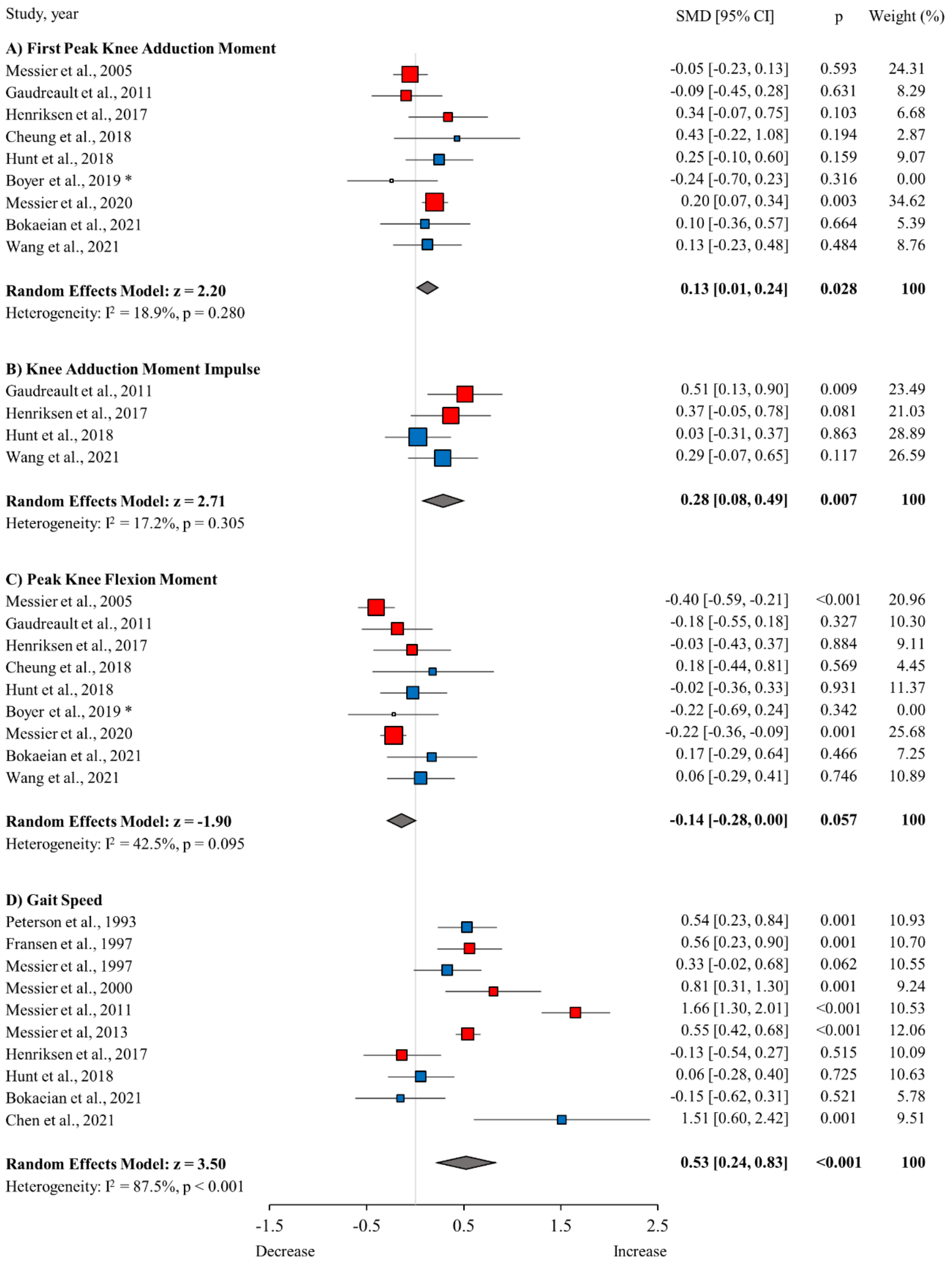


Figure 4.2. Forest plots for meta-analyses. Squares represent the standardized mean difference (SMD) with 95% confidence intervals (CI). Square colours represent intervention sub-groups: white = single bout walking; blue = repeated walking; red = repeated multi-modal exercise. Grey diamonds represent the pooled effect size using a random effects model. Asterisks (*) represent single bout studies; these studies were excluded from pooled data in the main analyses presented above (i.e., weight = 0%) but were included in sensitivity analyses (in-text).

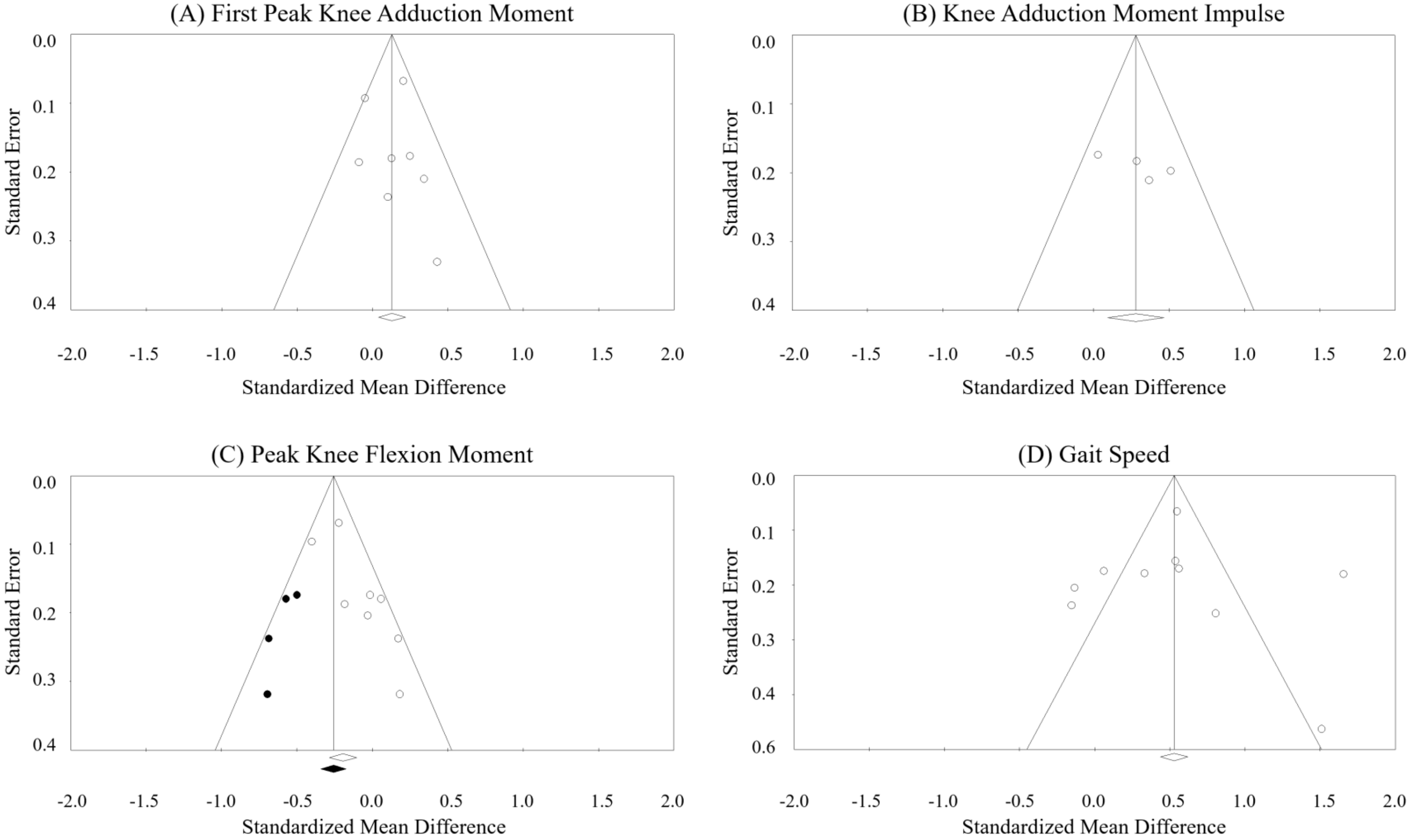


Figure 4.3. Funnel plots illustrating publication bias with standard error (y-axis) plotted by standardized mean difference (x-axis). White and black circles represent observed and adjusted studies, respectively, and white and black diamonds represent the observed and adjusted pooled effect sizes for each outcome.

Meta-regression analyses were completed to examine associations between treatment effects and walking parameters or study characteristics (Table 4.4). All meta-regressions were completed for repeated walking studies only because an insufficient number of studies (n=1) reported single bout biomechanical outcomes. All but one study included in meta-analyses prescribed walking at participant self-selected speed; therefore, walking intensity was not included in meta-regressions. There were no significant associations between first peak knee adduction moment effect sizes and walking parameters (walking intervention length, bout duration, or frequency) or study quality score. There was a significant association between the first peak knee adduction moment effect size and publication year, whereby later publication years were associated with an increase in first peak knee adduction moment effect size (Table 4.4).

Table 4.4. Meta-regressions including walking parameters and study characteristics.

	Intervention Length (weeks)	Walking Bout Duration (minutes)	Walking Frequency (bouts / week)	Study Quality Score	Publication Year
Knee Adduction Moment					
β	0.00	0.00	-0.05	0.01	0.02
[95% CI]	[0.00, 0.00]	[-0.02, 0.01]	[-0.22, 0.12]	[0.00, 0.02]	[0.00, 0.03]
p-value	0.595	0.622	0.573	0.057	**0.015**
Knee Adduction Moment Impulse					
β	-0.02	-0.03	0.13	-0.02	-0.03
[95% CI]	[-0.08, 0.03]	[-0.06, 0.01]	[-0.11, 0.36]	[-0.04, 0.00]	[-0.09, 0.03]
p-value	0.418	0.119	0.289	0.070	0.289
Knee Flexion Moment					
β	-0.01	-0.02	-0.07	0.01	0.03
[95% CI]	[-0.01, 0.00]	[-0.03, 0.00]	[-0.30, 0.17]	[-0.02, 0.03]	[0.01, 0.05]
p-value	**0.001**	0.055	0.575	0.603	**0.001**
Gait Speed					
β	0.01	0.02	0.33	0.00	0.00
[95% CI]	[-0.01, 0.02]	[-0.01, 0.05]	[-0.10, 0.75]	[-0.03, 0.03]	[-0.04, 0.03]
p-value	0.308	0.192	0.132	1.000	0.872

Note: All covariates were entered into the models separately. All regression models include longitudinal studies only. Bolded values indicate statistical significance at $p < 0.05$. CI = Confidence Interval.

4.3.5.2 Knee Adduction Moment Impulse

Four studies reported the effects of walking on knee adduction moment impulse (Figure 4.2B). All four studies examined repeated walking exposure (392,396,400,404). Meta-analysis revealed a small, statistically significant increase in knee adduction moment impulse (SMD = 0.28, 95% CI [0.08, 0.49], p = 0.007; I^2 = 17.2%, p = 0.305). Adjusting the pre-post correlation had no effect on the results. No publication bias was identified using Egger's regression test (intercept = 10.3, 95% CI [-14.6, 35.2], p = 0.217) or visualization of the funnel plot (Figure 4.3B). A sensitivity analysis was not completed since no studies reported knee adduction moment impulse following a single walking bout.

Two studies investigated interventions with walking only (400,404), and two investigated multi-modal exercise (392,396). Sub-group analyses indicated no difference in knee adduction moment impulse following walking only (SMD = 0.15, 95% CI [-0.01, 0.40], p = 0.236; I^2 = 3.5%, p = 0.309), and a small, statistically significant increase in knee adduction moment impulse following multi-modal exercise interventions (SMD = 0.45, 95% CI [0.16, 0.73], p = 0.002; I^2 = 0%, p = 0.616). Meta-regression analyses indicated no significant associations between knee adduction moment impulse effect size and walking parameters or study characteristics (Table 4.4).

4.3.5.3 Peak Knee Flexion Moment

Nine studies reported the effects of walking on the peak knee flexion moment (Figure 4.2C); eight studies evaluated repeated walking exposure (247,248,392,396,399,400,402,404), and one study evaluated a single walking bout (81). Meta-analysis revealed no significant difference in peak knee flexion moment (SMD = -0.14, 95% CI [-0.28, 0.00], p = 0.057; I^2 = 42.5%, p = 0.095). Adjusting the pre-post correlation had no effect on the results. Asymmetry was observed in the funnel plot (Figure 4.3C) and significant publication bias was identified using Egger's regression test (intercept = 1.99, 95% CI [0.24, 3.73], p = 0.03). The adjusted SMD was -0.25 (95% CI [-0.39, -0.11]) using the trim and fill method, indicating a small, statistically significant decrease in peak knee flexion moment. The sensitivity analysis, adding the single-bout walking exposure into the pooled analysis, indicated a very small, statistically significant decrease in peak knee flexion moment (SMD = -0.15, 95% CI [-0.28, -0.02], p = 0.022; I^2 = 34.4%, p = 0.142).

Four (of 8 repeated walking studies) investigated interventions with walking only (399,400,402,404), and four investigated multi-modal exercise (247,248,392,396). Sub-group analyses indicated no difference in peak knee flexion moment following walking only (SMD = 0.07, 95% CI [-0.14, 0.27], p = 0.520; I^2 = 0%, p = 0.907), and a small, statistically significant decrease in peak knee flexion moment following multi-modal exercise (SMD = -0.26, 95% CI [-0.38, -0.13], p < 0.001; I^2 = 22.0%, p = 0.279).

Meta-regressions revealed that peak knee flexion moment effect sizes were significantly associated with walking intervention duration and publication year. Longer interventions were associated with decreases, and later publication years were associated with increases, in peak knee flexion moment effect sizes (Table 4.4). Walking bout duration and study quality score were not significantly associated with peak knee flexion moment treatment effects.

4.3.5.4 Gait Speed

Ten studies reported the effects of walking on gait speed (Figure 4.2D). All studies examined repeated walking exposures (75,78,246,292,319,389,396,400,402,403). Meta-analysis revealed a moderate, statistically significant increase in gait speed (SMD = 0.53, 95% CI [0.24, 0.83], $p < 0.001$; $I^2 = 87.5\%$, $p < 0.001$). Adjusting the pre-post correlation had no effect on the results. No publication bias was identified using Egger's regression test (intercept = 0.05, 95% CI [-4.46, 4.56], p = 0.981) or visualization of the funnel plot (Figure 4.3D). A sensitivity analysis was not performed because no studies reported the effect of a single bout of walking on gait speed.

Five studies investigated interventions with walking only (75,78,400,402,403), and five investigated multi-modal exercise interventions (246,292,319,389,396). Sub-group analyses indicated a non-significant increase in gait speed following walking only (SMD = 0.34, 95% CI [-0.01, 0.70], p = 0.058; $I^2 = 72.8\%$, p = 0.005), and a moderate, statistically significant increase in gait speed following multi-modal exercise interventions (SMD = 0.69, 95% CI [0.21, 1.17], p = 0.005; $I^2 = 91.7\%$, $p < 0.001$). Meta-analyses indicated no significant associations between gait speed effect sizes and walking parameters or study characteristics (Table 4.4).

4.3.5.5 Spatiotemporal Variables

Nine studies examined the effects of walking on spatiotemporal variables. All nine studies investigated repeated walking exposure; four studies examined walking only (75,78,391,403), and five studies examined multi-modal exercise (247,292,389,392,396).

Nine studies reported the effects of walking on stride or step length. Most results indicated that stride length increased following walking interventions. Two studies reported significant increases in stride length following repeated walking exercise (75,403), and trends from two additional studies aligned with these findings (78,391). Similarly, three studies reported significant increases in stride or step length following multi-modal exercise interventions (292,389,392), and the trend of another study aligned with these results (247); however, one study reported a decrease in step length (396). Percent changes in stride length ranged from -2.8% to +11% across interventions.

Nine studies examined changes in step cadence, and results were inconsistent across studies. Two studies reported non-significant increases in step cadence following repeated walking exercise interventions (75,403), and trends from two other studies showed conflicting results (78,391). Further, step cadence both increased (247,292,389) and decreased (392,396) following multi-modal exercise interventions. Mean changes in step cadence ranged from -3.6 to +5.5 steps/min across interventions, and changes were similar between walking and multi-modal exercise.

Two studies reported changes in stance time, and results suggested that stance time decreased following walking interventions. The trend from one study indicated that stance time decreased following repeated walking exercise (78), and one study reported that stance time significantly decreased following a multi-modal exercise intervention (292). Stance time decreased by an average of 0.04 ± 0.01 seconds across interventions.

4.3.5.6 Knee Joint Kinematics

Eight studies reported the effects of walking on knee joint kinematics. Four studies investigated the effects of walking exercise across repeated (78,394,403) and single bout (81) exposures, and four studies investigated multi-modal exercise interventions (247,292,392,396).

Studies reporting sagittal plane knee kinematics following repeated walking exercise reported trends indicating sagittal plane range of motion increased (78), maximal knee flexion angle increased (403), and changes in angular velocity were conflicting (78,394). Following a single bout of walking, trends showed the knee flexion angles at heel-strike, toe-off, and peak during loading response changed by ≤ 1° within sub-groups who did and did not experience a pain flare (change in numeric pain rating scale of ≥ 1 during a 20-minute walk) (81). Following repeated multi-modal exercise, studies reported no significant differences in sagittal plane knee range of motion (292,392) or peak knee flexion or extension angles (247,392,396). Messier et al., (292) reported significant increases in mean angular velocity for sub-groups who received multi-modal exercise with and without a concurrent diet intervention.

Changes in frontal plane kinematics were reported in two studies (247,392). No significant differences were reported for peak adduction or abduction angles, or frontal plane range of motion, following a multi-modal exercise intervention (392). Additionally, trends indicated that there was a decrease or no change in varus thrust for sub-groups receiving multi-modal exercise with or with a diet intervention, respectively (247).

Transverse plane kinematics were reported in three studies (81,392,394). A trend of decreased angular velocity during the swing phase of gait was reported following a repeated walking exercise intervention (394). Following a single bout of walking, trends indicated that during stance, the sub-group experiencing a pain flare underwent more internal rotation and the sub-group not experiencing a pain flare underwent more external rotation, though the magnitude of these changes were ≤ 0.5° (81). Additionally, no significant differences were reported for peak internal or external rotation angles, or transverse plane range of motion, following a multi-modal exercise intervention (392).

4.3.5.7 Knee Joint Forces

Five interventions examined the effects of walking on knee joint kinetics; two interventions investigated the effects of a single bout of walking (79,81), and three investigated multi-modal exercise interventions (247,248,396).

Changes in total knee joint kinetics (estimated joint contact forces and total reaction moments) were measured following a single bout of walking (79,81) and repeated multi-modal exercise (396). Trends in total knee contact forces, defined as the sum of muscle and joint reaction forces, showed increases in first and second peak knee contact forces for both interval and continuous walking conditions (79). There was a significant increase in first, but not second, peak knee contact force following 30- and 45-minutes of walking (79). Trends in knee total reaction moments, defined as the root-mean-square of three-dimensional knee joint moments, following a 20-minute walking bout suggested that total reaction moment decreased for individuals who experienced a pain flare, and increased for those who did not experience a pain flare (81). Further, trends indicated increases in first and second peak resultant moments following repeated multi-modal exercise (396).

Studies indicated that compressive knee joint forces increased following walking. Trends from two studies highlighted that peak tibiofemoral compressive force increased following multi-modal exercise interventions (247,248). Trends from the Intensive Diet and Exercise for Arthritis (IDEA) trial indicated that peak tibiofemoral compressive forces increased by 72 N and 337 N for sub-groups receiving multi-modal exercise with and without a concurrent dietary intervention, respectively (247). The same study reported that peak patellofemoral compressive forces increased by 53 N and 125 N for sub-groups receiving multi-modal exercise with and without dietary intervention, respectively (247).

Trends from two studies indicated that peak anteroposterior tibiofemoral shear forces and resultant knee joint forces also increased following repeated multi-modal exercise interventions (247,248). The IDEA study reported trends of increases in peak tibiofemoral shear forces of 35 N and 50 N, and increases in resultant knee joint forces of 75 N and 339 N, for sub-groups receiving multi-modal exercise with and without dietary intervention, respectively (247).

4.3.5.8 Quantitative Magnetic Resonance Imaging

Five studies examined the effects of walking on quantitative MRI outcomes. Three studies investigated walking exercise within repeated (398) and single bout (109,110) exposures, and two studies investigated multi-modal exercise interventions (296,393).

Three studies reported the effects of walking on cartilage thickness (109,110,296), and trends in this evidence suggested that cartilage thickness decreased following walking. Trends indicated that medial and lateral femoral cartilage thickness decreased by 2.2% and 3.0%, respectively, following a single 30-minute bout of walking (109). Further, a 25-minute bout of walking (analyzed concurrently with a cycling bout) decreased cartilage thickness on the lateral tibial plateau (110). Additionally, trends from the IDEA trial revealed that for multi-modal exercise sub-groups with and without dietary intervention, cartilage thickness over the medial femoral condyle decreased by 5.95% and 2.66% and cartilage thickness over the area of the central weight-bearing medial femur decreased by 8.66% and 3.91%, respectively (296). Further, for multi-modal exercise sub-groups with and without dietary intervention, cartilage thickness over the area of the medial tibia decreased by 2.65% and 0.58% and cartilage thickness over the area of the central medial tibia decreased by 4.10% and 1.59%, respectively (296). Trends from the IDEA trial indicated that medial femoral and tibial cartilage thickness decreased following repeated exposure to multi-modal exercise (296).

Three studies reported changes in cartilage volume (296,393,398). Trends within one study indicated that femoral cartilage volume increased (by 0.20 mm^3 or 0.01%) and patellar cartilage volume did not change following repeated walking exercise (398). Trends among two additional studies were inconsistent with respect to changes in femoral and tibial cartilage volumes following multi-modal exercise interventions (296,393). For multi-modal exercise sub-groups with and without dietary intervention, Hunter et al. (296) indicated that cartilage volume within the medial femoral condyle decreased by 5.8% and 2.6%, and cartilage volume over the area of the media tibia decreased by 2.1% and 0.4%, respectively. Woollard et al. (393) reported that the median changes in cartilage volume for the medial and lateral femoral condyles were -3.8% and 0%, respectively, and for the medial and lateral tibial plateaus were +0.8% and +0.1%, respectively. Finally, one study reported the effects of a single bout of walking on T2 relaxation time, and reported that 25-minutes of walking decreased T2 at the lateral trochlea (110).

4.3.5.9 Semi-Quantitative Magnetic Resonance Imaging

Three studies reported the effects of walking on semi-quantitative MRI outcomes (296,397,401), all following multi-modal exercise programs. Two studies reported the effects of walking on Boston-Leeds Osteoarthritis Knee Score (BLOKS) values (296,397). One study reported BLOKS scores, including maximal bone marrow lesion (BML) size, BML count, maximum synovitis score, and effusion score (296). Trends indicated that the multi-modal exercise sub-group without dietary intervention tended to have higher maximum BML scores and BML count (296). A second study reported a BLOKS effusion score, and the trend indicated no change following multi-modal exercise (397). Two studies reported changes in MOAKS values (397,401). Trends in the MOAKS synovitis score (range: 0-6) increased (change scores: 0.03-0.26), and MOAKS BML score (range: 0-45) increased (change score: 0.21), following multi-modal exercise (397,401).

4.3.5.10 Radiographic Measures

Six studies examined the effects of walking on radiographic changes. All studies reporting radiographic outcomes included repeated walking exposure; two studies investigated walking exercise (76,78) and four investigated multi-modal exercise interventions (246,296,297,390). Trends within two studies indicated that minimum joint space width decreased following multi-modal exercise (296,297). Changes in minimum medial joint space decreased for multi-modal exercise sub-groups with (change: -0.27 to -0.30 mm) and without (change: -0.18 to -0.19 mm) dietary intervention. (296,297). Further, Messier et al., (297) reported mean changes in minimum lateral joint space width of -0.22 mm and -0.06 mm for multi-modal exercise sub-groups with and without dietary intervention, respectively. Changes in Kellgren and Lawrence grades were reported in two studies (76,246). The first study reported no radiographic changes following a 12-week walking exercise intervention (76), and the second study reported trends of increasing radiographic severity following an 18-month multi-modal exercise intervention (246). Changes in knee x-ray scores were assessed in two studies using a classification system adapted from Altman et al., (405). One study reported no change in x-ray score following an 18-month walking exercise intervention (77), and another study reported trends of increased overall mean x-ray scores following an 18-month multi-modal exercise intervention (390); compartmental or feature-specific scores were not reported.

4.4 Discussion

This systematic review with meta-analysis and meta-regression demonstrates that walking exercise, alone or in combination with other forms of exercise therapy, elicits minimal-to-no change in discrete biomechanical metrics of joint loading, and moderately improves the functional biomechanical metric of gait speed. When considered separately, quantitative analysis indicates that walking provides no significant effect on biomechanical outcomes, whereas multi-modal exercise programs that include a walking component provide a small increase in knee adduction moment impulse, small decrease in peak knee flexion moment, and moderate increase in gait speed. These findings from the literature to date suggest that walking interventions have the potential to provide functional benefits to individuals with knee osteoarthritis but direct effects on knee joint loading may be minimal.

Repeated walking exercise interventions provide very small-to-small effects (SMD = 0.13 to 0.28) on the first peak knee adduction moment and knee adduction moment impulse, suggesting that only a small increase in medial compartment loading may be achieved with walking exercise. Although the small effects observed suggest that walking interventions may potentially contribute to altered biomechanics and loading patterns at the knee joint, the clinical relevance of these small changes remains unclear. Nevertheless, it has been proposed that even small changes in joint loading may have clinically meaningful effects, particularly when extrapolated over thousands of steps per day (248). Increased first peak knee adduction moment and knee adduction moment impulse have been associated with increased pain (118,241) and knee osteoarthritis structural disease progression (92). However, the current results align with previous systematic reviews that reported trends toward an increased first peak knee adduction moment following exercise therapy, with concurrent improvements in pain, physical function, and muscle strength (406,407). The symptomatic and functional benefits of walking exercise have been established (345) and may suggest a net positive effect on knee osteoarthritis despite increased joint loading. To explore these relationships further, future research should incorporate discrete biomechanical metrics with symptomatic and structural outcomes to understand the holistic effects of walking on knee osteoarthritis.

These analyses indicate that repeated walking, with or without other forms of exercise, elicits small-to-no reductions (SMD = -0.26 to 0.07) in peak knee flexion moment, and that decreases in peak knee flexion moment are associated with longer walking interventions. Numerous studies propose that the peak knee flexion moment reflects the net muscular contribution to total knee joint loading (408,409), and in concert with the knee adduction moment, contributes to medial knee contact forces (236,237,410). Whether the peak knee flexion moment is associated with osteoarthritis structural disease progression is unclear due to conflicting biomechanical findings (91,95). However, lower peak knee flexion moments are indicative of osteoarthritic gait (84) and may be a movement strategy employed to reduce joint loading in response to pain (248,411,412). Therefore, although a decrease in peak knee flexion moment may contribute to decreased knee joint loading, it may be an adaptive response to the pain experience. The meta-regression results demonstrate that shorter walking interventions may mitigate these potentially negative effects of walking exercise on peak knee flexion moments.

Current findings of a moderate increase (SMD = 0.34 to 0.69) in gait speed are consistent with previous evidence that suggests walking exercise may be protective against declines in gait speed (413,414). Reported increases in gait speed may also help explain the noted increases in first peak knee adduction moment (415,416). Conversely, increases in knee adduction moment impulse are typically associated with slower gait speeds due to longer stance durations (416); however, since knee adduction moment impulse is influenced by both the magnitude and duration of loading, the observed small increases in knee adduction moment impulse were likely driven by increases in loading magnitude. Gait speed is a key functional metric for individuals with knee osteoarthritis, and slower gait speeds have been associated with mortality risk (417). Knee osteoarthritis is a risk factor for gait speed declines (418), and gait speed decreases with age (419) and pain levels (235). The interplay between the loading and functional effects of walking exercise remains an important consideration when examining continuous walking as these factors collectively contribute to the cumulative loading effects of walking (304,306,420,421).

Current descriptive findings suggest that walking interventions improve or do not change spatiotemporal gait characteristics. For instance, walking interventions increased step and stride length and decreased stance time, although cadence changes were inconsistent. Evidence suggests individuals with severe knee osteoarthritis exhibit decreased gait speed, stride and step length, and cadence, and increased stance time compared to healthy or less severe osteoarthritis patients (422,423); therefore, noted spatiotemporal changes collectively suggest improved gait function. Spatiotemporal changes may also help explain the reported increases in peak knee joint moments (424). Although shorter stride lengths have been proposed as a gait retraining mechanism for individuals with knee osteoarthritis, this strategy has been shown to decrease knee adduction moment impulse, but not peak knee adduction or flexion moments (425,426). Spatiotemporal gait parameters are readily measured in clinical settings using technologies including wearable devices, and thus represent accessible clinical metrics that may provide insight into joint loading parameters and the functional effects of walking interventions.

Additionally, descriptive findings indicate walking exercise produces minimal-to-no change in other biomechanical or structural knee joint outcomes. Walking interventions increased sagittal plane range of motion and peak knee flexion angles, indicating a more dynamic walking strategy, with no changes in frontal or transverse plane kinematics. Although trends in the evidence suggest walking provides small increases in knee joint forces and decreases in quantitative radiographic (e.g., joint space width) and MRI (e.g., cartilage thickness) measures, suggesting structural progression, reported magnitudes of structural changes were similar to previously reported natural structural progression thresholds (298,427). Together, these findings indicate that despite increased joint loading, there is little current evidence to suggest that walking accelerates knee osteoarthritis structural disease progression beyond natural changes. Our results are consistent with previous reviews that concluded exercise is not harmful to knee joint structure (428,429). These results may encourage physicians and individuals with knee osteoarthritis to increase physical activity prescription and participation, respectively, without detrimental effects to knee joint health.

Little evidence exists on the immediate effects of a single bout of walking on quantitative knee joint health outcomes. Single bout walking exposures decreased treatment effect sizes for first peak knee adduction moment and peak knee flexion moment when included in the pooled analyses, indicating potentially different treatment effects between repeated and single bout exposures. However, this trend is difficult to substantiate since only one single bout walking exposure was included (81), highlighting a critical need for more biomechanical investigations following single walking bouts. Further, there is limited evidence to clarify whether the effects of a single bout of walking are compounded over time with repeated walking exposure, or whether repeated exposure has a linear or exponential influence on outcomes. Acute joint loading has been associated with pain flares and inflammation following a single continuous bout of walking (79,81,96). Pain is a primary barrier to physical activity (280); therefore, understanding the mediating or moderating effects of pain and inflammation during repeated walking exposure is warranted to clarify the potential cumulative effects on knee joint health. Additionally, the use of MRI affords the opportunity to investigate immediate structural changes in response to walking, which has been reported in two studies to date (109,110). While evidence suggests that the immediate structural effects of exercise on healthy cartilage tissue may be transient (373), the effects on pathological tissue remains unclear. Additional research on the immediate and longitudinal structural effects of walking would help confirm the appropriateness of walking as a therapeutic exercise intervention for knee osteoarthritis.

Findings from multi-modal exercise interventions in this review should be interpreted with caution as the effects on knee osteoarthritis outcomes are not isolated to walking alone. Rather, most multi-modal interventions included a walking component in addition to strength training or physiotherapy components. These additional factors may help explain some of the noted differences between isolated walking and multi-modal exercise interventions, whereby walking exercise resulted in no significant effects, and multi-modal exercise resulted in a small increase in knee adduction moment impulse, small decrease in peak knee flexion moment, and moderate increase in gait speed. Despite hypotheses that muscle strengthening may decrease knee joint loading (430), evidence suggests knee or hip muscle strengthening may not alter knee joint biomechanics, including knee flexion moment (431), knee adduction moment (432), or knee joint compressive force (433). However, muscle strengthening can reduce pain and improve physical function (434,435), and increased strength has been associated with increased gait speed (436). In addition to strengthening components, physiotherapy interventions may include proprioceptive training, balance exercises, and neuromuscular training, which may further improve clinical and functional outcomes, including pain and gait speed (437). However, the specific biomechanical mechanisms by which walking exercise differs from multi-modal exercise remains unclear and represents a pathway for future investigations.

The prescribed walking parameters within the included studies align with current walking guidelines for older adults and knee osteoarthritis populations (24,45,47,48,67). Different walking bout durations were not associated with the biomechanical outcomes included in meta-regressions. Notably, only one research group objectively tested the effect of different walking parameters on quantitative joint health outcomes (79,80). A continuous 30-minute bout of walking is recommended and commonly prescribed for individuals with knee osteoarthritis (45–47,67,70); however, walking recommendations for knee osteoarthritis are based on clinical and other systemic health benefits (46,365), and do not consider joint health outcomes. Meanwhile, quantitative evidence suggests that knee joint loading increases following 30-minutes of both interval and continuous walking (79,80). Importantly, there is insufficient evidence to recommend specific physical activity types or doses for individuals with knee osteoarthritis (21,171,438), yet physical activity programs are most beneficial when provided as a specific recommendation (21). This lack of evidence-based disease-specific physical activity guidelines likely inhibits physical activity prescription (257,367); therefore, more research is needed to determine the optimal walking dosage for individuals with knee osteoarthritis, incorporating clinical and quantitative joint health outcomes.

Limitations of the literature exist and should be acknowledged. Included studies varied by design, intervention type, and walking parameters. This limitation was addressed in the current study as walking interventions and exposures were separated into sub-groups, therefore providing a more detailed investigation of single bout versus repeated walking exposure, and isolated walking versus multi-modal exercise, on joint health outcomes. Although meta-regression was used to address study variability, few associations with joint health outcomes were found. Despite the variability across included studies, more than 90% of studies were of high to excellent quality. Further, only approximately half of the included studies (53%) reported knee osteoarthritis structural disease severity, limiting our understanding of the effects of walking interventions on varying severities of knee osteoarthritis. Our current understanding primarily encompasses individuals with mild-to-moderate radiographic knee osteoarthritis (i.e., KLG II-III), whereas individuals with low (i.e., KLG I) or high (i.e., KLG IV) structural severities made up small proportions of the included participants (approximately 10% and 20% respectively). Considering gait parameters differ within different severities of knee osteoarthritis (84,234), more complete descriptions of the severity levels of included participants are needed when examining the effects of walking on mechanical and structural knee osteoarthritis outcomes.

Several gaps within the literature were identified. Firstly, of the studies reporting the effects of walking exercise on knee osteoarthritis outcomes (n=190), few reported biomechanical or structural outcomes (17%, n=33), highlighting the need for additional research quantifying the effects of walking on knee osteoarthritis joint health. Secondly, no studies investigated the effect of isolated repeated walking exposure on knee joint kinetics, cartilage thickness, or semi-quantitative imaging metrics. Few studies (n=5) reported the effects of a single bout of walking; spatiotemporal metrics and cartilage volume have not been investigated following a single bout of walking. The lack of existing literature investigating the structural response to walking-based interventions prevented quantitative analysis in this review. Additionally, only two studies reported the effects of walking, either in a single bout or repeated exposure, on simultaneous biomechanical and structural outcomes; therefore, our understanding of whether biomechanical and structural effects of walking are related remains poorly understood and warrants further research.

This review provides a thorough overview of the existing literature examining the biomechanical and structural effects of walking interventions on knee joint health for individuals with knee osteoarthritis. Notable limitations of our approach also exist. Only the earliest measurement time point from each study was extracted. Despite providing an understanding of the immediate and short-term effects of walking, it remains unknown whether the observed effects persist at later follow-up timepoints or how many repeated exposures are necessary to provide clinically meaningful changes in the reported outcomes.

4.5 Conclusion

Walking exercise, alone or in combination with other forms of exercise, provides minimal-to-no changes in discrete biomechanical metrics of joint loading, and moderately improves gait speed. Walking exercise does not appear to contribute to structural disease progression based on the current evidence. Walking exercise was most often prescribed for 30-minute bouts at participant self-selected speed across single-bout and repeated exposures, and 3 bouts per week for repeated exposures, which align with current walking guidelines. Walking parameters provided few associations to quantitative joint health outcomes, although longer walking interventions were associated with decreased peak knee flexion moment effect sizes. Taken together, these results may encourage healthcare practitioners to prescribe physical activity for knee osteoarthritis, and individuals with knee osteoarthritis to engage in physical activity, without detrimental effects to knee joint health. Findings are tempered by the limited number of studies reporting walking-specific effects on quantitative joint health outcomes and the high variability across walking intervention exposures and parameters. More research is needed to thoroughly inform walking prescription parameters for knee osteoarthritis populations.

Chapter 5 The Immediate Effect of a 30-minute Continuous Walking Bout on Biomechanical and Structural Imaging Outcomes in Knee Osteoarthritis

5.1 Introduction

Knee osteoarthritis is a disabling musculoskeletal joint condition that affects approximately 350 million individuals worldwide, and prevalence is continually increasing (1). Knee osteoarthritis commonly results in pervasive knee pain and impaired joint function, ultimately reducing mobility, physical activity levels, and quality of life (16,159). The etiology of knee osteoarthritis is complex, and growing evidence supports that osteoarthritis arises from interactions between mechanical, inflammatory, and biological factors (3,14,154). Knee osteoarthritis can be described using a combination of patient-reported symptoms (e.g., pain) and joint-level structural changes (15). Characteristic structural changes in the joint may arise due to abnormal joint mechanics (12,14,15,148). For instance, individuals with, compared to without, knee osteoarthritis typically experience increased joint loading during gait (83,439,440), which may contribute to knee pain (118,241) or structural progression (14,82,117), highlighting potential relationships between mechanical, structural, and patient-reported factors.

Clinical practice guidelines consistently recommend walking as a form of physical activity for knee osteoarthritis (18,21,24). However, a main concern of walking as a treatment for knee osteoarthritis arises from the increased loads placed on the joint (61,116), particularly when accumulating thousands of steps per day (248). Physical activity guidelines recommend 30-minute bouts of walking to improve cardiovascular outcomes (24,46), but these recommendations do not consider the effects of physical activity on knee joint pain, loading, or structural outcomes (79,80). The biomechanical and structural effects of walking for knee osteoarthritis have received little attention to date. In Chapter 4, only 17% of studies investigating continuous walking reported a quantitative biomechanical or structural knee osteoarthritis outcome. Recent work has investigated the effect of a single walking bout on quantitative knee osteoarthritis outcomes (79–81,109,110,112); however, these studies vary based on walking parameters and outcome measures and it remains difficult to draw distinct conclusions to recommend walking dosage based on quantitative joint health outcomes. Thus, there is minimal evidence on the effect of prolonged walking on biomechanical and structural knee osteoarthritis outcomes.

Knee osteoarthritis is a whole-joint condition (441), but cartilage loss is a hallmark structural feature, and cartilage thickness loss measured directly (e.g., using magnetic resonance imaging; MRI) or indirectly (e.g., using radiographic joint space narrowing) is a primary imaging biomarker used to define the incidence and progression of knee osteoarthritis (213,442). In addition to cartilage thickness characterising knee joint structure, acute changes in cartilage morphology can provide further insight into cartilage health. The immediate change in cartilage morphology in response to loading has been proposed as a proxy measure of cartilage composition (101), representing the mechanical and physiological properties of the cartilage. Changes in cartilage composition occur at earlier stages of the disease process and have been associated with longitudinal structural knee osteoarthritis progression (104–106). Thus, immediate changes in cartilage morphology may represent a more sensitive imaging biomarker and indicator of cartilage health than longitudinal cartilage thickness loss (101).

Immediate changes in structural outcomes can be assessed using non-invasive imaging techniques, including MRI and ultrasound. MRI is an excellent research-based tool to assess the whole joint and can be used to examine the immediate effects of physical activity on articular cartilage (101,443). Previous MRI studies have shown that individuals with knee osteoarthritis experience a 2-3% decrease in cartilage thickness following 30-minutes of fast walking (109), and a 3-4% decrease in cartilage volume following a 30-repetition squatting exercise (214). These findings indicate that prolonged loading activities may have a small effect on knee osteoarthritis cartilage morphology, which may have implications for structural knee osteoarthritis progression (101,104–106). However, MRI can be costly and time-intensive, limiting its practicality for widespread use. Alternatively, ultrasound is cost-effective, portable, and permits more immediate visualization of joint structures compared to MRI. The concurrent validity of morphological cartilage assessment with ultrasound compared to MRI shows promise in healthy populations (444–446) but has yet to be examined in pathological populations. Ultrasound has been used to quantify femoral cartilage thickness changes immediately following walking in healthy adults (107,108,120,447), but not in individuals with knee osteoarthritis; as such, it is unclear how prolonged loading may influence pathological cartilage response. A previous ultrasound study identified healthy individuals whose cartilage responded (i.e., decreased cross-sectional area) or did not respond (i.e., no change in cross-sectional area) following walking (303), which has implications for understanding how loading may contribute to cartilage response, particularly among individuals with knee osteoarthritis (87). Immediate morphological changes may help inform the suitability of walking as a type of activity for knee osteoarthritis by indicating how cartilage structure responds to loading, and therefore represents a measure of cartilage health or tissue changes that may be indicative of longitudinal structural disease progression (122).

Limited studies have considered the additional benefits of combining biomechanical with structural imaging outcomes to understand the implications of physical activity and joint loading more thoroughly in knee osteoarthritis populations. For example, only two studies in Chapter 4 examined concurrent biomechanical and structural outcomes. In individuals with knee osteoarthritis, higher tibiofemoral compressive forces have been associated with decreases in lateral femoral cartilage thickness following 25-minutes of walking (110). Additionally, higher ground reaction force impulse, lower vertical ground reaction force unloading, and higher pain during walking have been associated with medial tibiofemoral cartilage worsening (305). These findings collectively support an association between joint loading, pain, and acute and longitudinal structural changes, although discrete walking mechanics that may contribute to increased joint loading and clinical and structural knee osteoarthritis progression have been omitted (90–93,366). However, knee joint mechanics have been cross-sectionally associated with cartilage thickness, as well as knee pain. Larger peak knee adduction moment and impulse have been associated with thinner medial femoral and tibial cartilage (306), and increased knee pain (118,241), in individuals with knee osteoarthritis. Further, larger knee flexion angles and moments have been associated with thicker medial femoral cartilage, and larger knee adduction angles and moments have been associated with thinner medial femoral cartilage, in anterior cruciate ligament reconstructed and healthy individuals (307,308). Together, these findings highlight a preliminary understanding of how mechanical, structural, and patient-reported knee osteoarthritis outcomes may be interconnected, although our understanding of their response to prolonged walking remains limited. Therefore, a more comprehensive understanding of the relationships between biomechanical, structural, and patient-reported knee osteoarthritis outcomes following 30-minutes of continuous walking is required to determine how walking influences interconnected outcomes for knee osteoarthritis.

The purpose of this study was to determine the immediate effect of a 30-minute continuous walking bout on biomechanical, structural, and patient-reported outcomes in individuals with knee osteoarthritis. The objectives of this research were to: (**O1**) describe and quantify how gait biomechanics change following 30-minutes of continuous walking; (**O2**) describe, quantify, and compare articular cartilage thickness changes following 30-minutes of walking using ultrasound and MRI; and (**O3**) explore sub-groups of responders and non-responders based on structural (cartilage thickness) and patient-reported (pain) changes following walking to examine sub-group differences based on baseline metrics or biomechanical response to walking.

5.2 Methods

5.2.1 Study Design and Overview

This was a laboratory-based experimental study. The study protocol consisted of two data collection visits: one visit to the Dynamics of Human Motion Laboratory at Dalhousie University (visit A), and one visit to the QEII Health Sciences Centre in Halifax, Nova Scotia (visit B). Each visit took approximately 3-hours to complete, and visit order was dependent on participant and MRI scanner availability. Data collection start time (i.e., morning or afternoon) was matched between visits whenever possible to limit potential effects of diurnal fluctuations on structural outcomes (448,449). Participants were asked to limit their vigorous physical activity for 36-hours prior to each scheduled data collection session and were asked to be transported to the visits in a car or via public transport to limit potential effects of activity on structural outcomes. This study protocol was approved by the Nova Scotia Health Research Ethics Board (file # 1024411, Appendix D).

5.2.2 Participant Recruitment

Community-dwelling individuals with knee osteoarthritis were recruited from a single, local, high-volume osteoarthritis assessment clinic. Individuals were eligible for this study if they had symptomatic and moderate knee osteoarthritis, as diagnosed by an experienced orthopaedic surgeon, based on radiographic and clinical assessment using the American College of Rheumatology criteria (197). Moderate knee osteoarthritis was defined using functional criteria to ensure participants had a reasonably high level of function, which included the ability to jog 5 meters, walk a city block, and reciprocally climb stairs (450). Individuals were excluded if they had undergone a total knee replacement or high tibial osteotomy surgery, or indicated a significant surgical (e.g., arthroscopy), musculoskeletal (e.g., back pain, recent fracture), cardiovascular (e.g., stroke, heart attack), inflammatory (e.g., rheumatoid arthritis, gout), or neurological (e.g., Parkinson’s disease) condition that would influence their health or safety during study participation. Potential participants also completed an MRI screening questionnaire (Appendix E) to determine their suitability to enter the MRI machine. Individuals were excluded if they answered “yes” to any of the MRI screening questions, were over 300 lbs (due to scanner bore diameter), or indicated they were claustrophobic and would be unwilling to enter the scanner. Participants were enrolled during two recruitment periods due to a COVID-19 research disruption, and all recruitment was completed between December 2019 and April 2023.

5.2.3 Data Collection

5.2.3.1 Consent and Questionnaires

Prior to data collection, participants were sent a link to provide informed consent and complete electronic questionnaires within the secure REDCap™ (Research Electronic Data Capture) online portal, hosted within Nova Scotia Health. Informed consent was obtained using an e-consent form with embedded capacity questions. Additionally, all participants were provided an overview of study procedures at the beginning of each data collection visit, as well as a chance to have any questions answered before data collection began. Questionnaires collected information regarding participant overall health, quality of life, knee joint symptoms and function, and physical activity levels. Specific questionnaires included the Knee injury and Osteoarthritis Outcome Score (KOOS) (204), Knee Outcome Survey (451), Intermittent and Constant Osteoarthritis Pain (ICOAP) scale (332), Oxford Knee Score (334), 5-level Euro-Qol 5-dimension (5L-EQ-5D) questionnaire (333), Pain Catastrophizing scale (452), International Physical Activity Questionnaire Short-Form (IPAQ-SF) (453), and the Physical Activity Scale for the Elderly (PASE) (454). The consent process and supplemental questionnaires took approximately 30-minutes to complete, and participants were asked to complete these forms in REDCap™ within 24-hours of their scheduled data collection.

5.2.3.2 Protocol Overview

During both data collection visits, participants were asked to complete 30-minutes of continuous treadmill walking at their self-selected speed. For individuals with bilateral osteoarthritis, the more symptomatic of their two knees was selected as the study limb and was matched between visits. During each visit, participants were asked to change into comfortable walking clothing, including a relatively tight-fitting t-shirt, shorts, and running shoes. Participants wore their own comfortable, everyday walking shoes during overground and treadmill walking and were asked to wear the same footwear to both visits to eliminate the effect of different footwear on gait parameters (455,456). Participants were asked to don a chest-mounted heart rate monitor (Polar H10, Polar Electro Oy, Kempele, Finland) with the sensor positioned over the xyphoid process to record heart rate and determine clinical exercise intensity throughout the walk. Participants rested for 30 minutes before each collection began to unload their articular cartilage for structural imaging analysis. Before and after the treadmill walk, overground gait analysis and ultrasound imaging were completed during visit A (Figure 5.1A) and MRI scanning was completed during visit B (Figure 5.1B). The total overall loading exposure between structural imaging timepoints was similar between visits and included the 30-minute treadmill walk (Visits A and B) in addition to the overground gait analysis (Visit A) and walking between the MRI suite and physiotherapy department (Visit B).

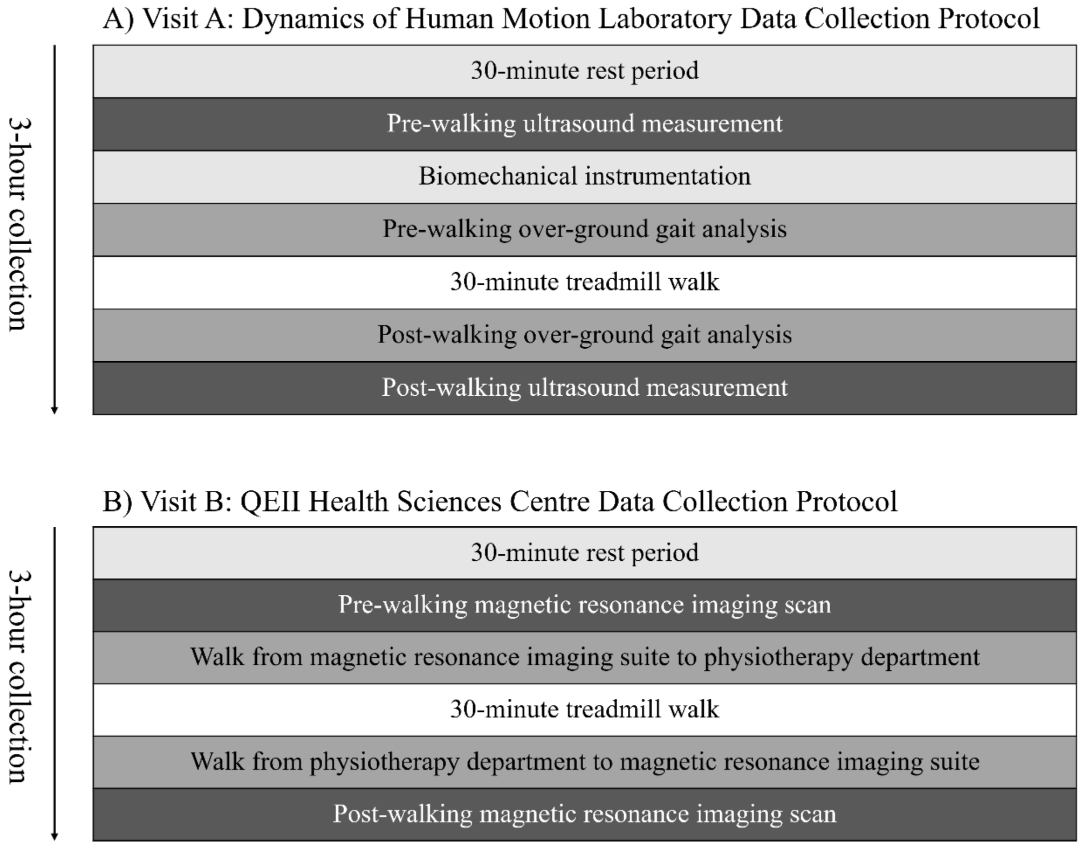


Figure 5.1. Overview of the study protocol during data collection visits A and B. The order of data collection visits was dictated by participant and MRI scanner availability.

5.2.3.3 Ultrasound Image Acquisition

Participants were asked to rest on a treatment table for at least 30-minutes with their legs in an open joint position (i.e., 20-30 degrees flexion) to unload the articular cartilage and maximize the joint space (107,120,457). A pillow was placed behind the knees for comfort. During image acquisition, participants were asked to sit in a standardized position on the treatment table with their back against the backrest, and their more symptomatic knee in maximal flexion (120,447,458–460). The maximal knee flexion angle was measured using a manual goniometer, and the achieved flexion angle was recorded before and after the treadmill walk. Maximal knee flexion (i.e., angle of approximately 140°) provides optimal visualization of the articular cartilage without surrounding tissues (459).

Measurements were obtained using a LOGIQ™ P9 ultrasound system (GE Healthcare, Chicago, IL, USA), with a 3-12 MHz probe by a single, trained investigator (frequency = 12 MHz, depth = 3.0 cm, gain = 61). The probe was placed linearly in the suprapatellar area to visualize the medial and lateral femoral condyles (460). A transparent grid was placed over the ultrasound display monitor and the intercondylar notch was centered in the grid to ensure the same position was replicated before and after the treadmill walk. Three images were recorded at each measurement timepoint (before and after the treadmill walk), and measurements were averaged across the three images. An example of the participant and ultrasound probe positioning is displayed in Figure 5.2.

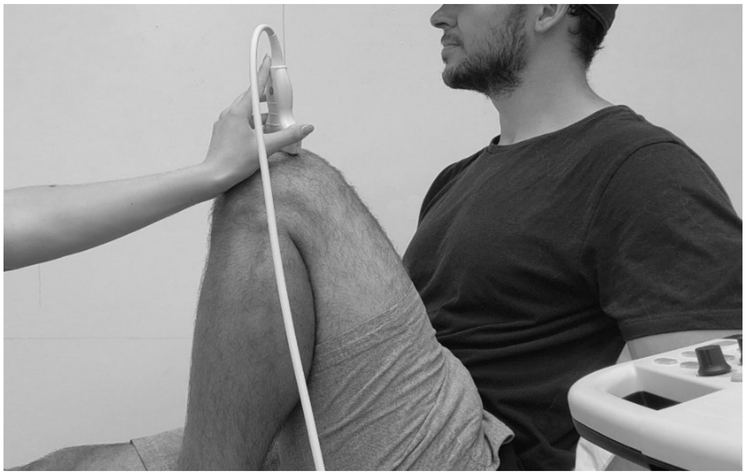


Figure 5.2. Example participant and ultrasound probe positioning.

5.2.3.4 Overground Gait Analysis

Participant height and body mass were obtained before gait analysis, and the participant was instrumented for biomechanical collection. Passive retro-reflective motion capture markers were placed on anatomical landmarks bilaterally on the lower limbs (461,462). Rigid plastic clusters each containing four passive markers were placed on the pelvis, thighs, shanks, and feet segments, and were secured using Fabrifoam® wraps and surgical tape. Individual anatomical markers were placed on the seventh cervical vertebra, and bilaterally on the shoulders, lateral epicondyles, ulnar styloid processes, lateral femoral condyles, lateral malleoli, second metatarsal heads, and calcanei, and were used to track the participant throughout the walking trials. Additional calibration markers were placed bilaterally on the iliac crests, anterior superior iliac spines, greater trochanters, medial femoral condyles, medial and lateral tibial condyles, medial malleoli, and first and fifth metatarsal heads, and were used to define segments but were removed after initial subject calibration (Figure 5.3).

The 10-camera motion capture system (Motion Analysis Corporation, Rohnert Part, CA) was calibrated prior to each data collection session. A 2-second static standing calibration file was collected to capture the positions of all 59 retro-reflective markers within the full marker set. Calibration markers were then removed, and a second 2-second static calibration file was collected to capture the positions of the remaining 41 tracking markers and permit automatic detection of the model template within the walking trials.

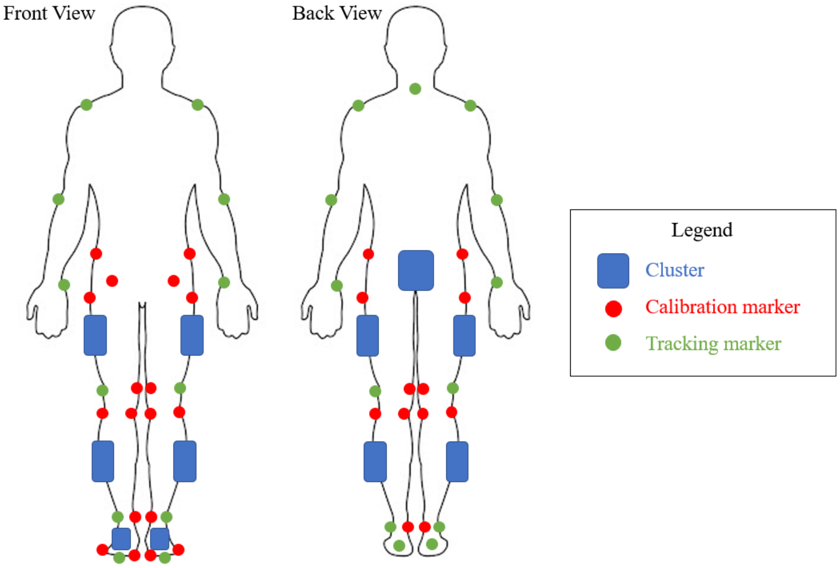


Figure 5.3. Schematic of the whole-body passive-reflective marker set. ***Note:*** Clusters (each containing four passive markers; blue) and tracking markers (green) remained affixed to the participant during the duration of the walking trials. Calibration markers (red) were placed on the participant for initial calibration and were removed for the walking trials.

Participants performed a minimum of 5 instrumented overground walking trials across a 6-m walkway at their comfortable, self-selected walking speed. This testing procedure has previously been shown to elicit high inter-day reliability of biomechanical outcomes for individuals with knee osteoarthritis (463). During these trials, three-dimensional motion capture sampled at 100 Hz and ground reaction forces sampled at 1200 Hz (2 force plates, AMTI, Walkerton, MA) were collected synchronously. Participants were not informed of the positions of the floor-embedded force plates. Participant self-selected overground walking speed was calculated and extracted from these trials using the average forward speed of the four pelvis cluster markers. Participants completed overground walking trials immediately before and after the 30-minute treadmill walk.

5.2.3.5 Magnetic Resonance Imaging Acquisition

Upon arrival at the MRI suite during visit B, participants sat in a chair to rest for 30-minutes, during which they were asked to complete a screening questionnaire specific to the imaging centre to supplement the initial MRI screening questionnaire. The MRI scans were completed using a GE 3.0-Tesla Discovery™ MR750 scanner (GE Healthcare, Chicago, IL, USA). The participant laid supine on the MRI bed with their affected knee immobilized and placed within a 16-channel flex coil with custom padding for comfort. Participants entered the scanner feet-first. The MRI scanning protocols were based on recommended imaging protocols for knee joint cartilage morphology (443,464). A three-dimensional fast imaging employing steady-state acquisition (3D FIESTA) scan was used to quantify cartilage thickness. Imaging parameters are listed in Table 5.1.

Table 5.1. MRI acquisition parameters.

Parameter	**3D FIESTA**
Acquisition time (min:s)	4:21
TR (ms)	6.2
TE (ms)	2.9
Number of Echoes	1
FOV (cm)	16.0
Slice thickness (mm)	1.0
Frequency	320
Phase	320
Flip angle (degrees)	25

Note: TR = relaxation time. TE = echo time. FOV = field of view.

5.2.3.6 Treadmill Walking Protocol

Participants performed a 30-minute continuous walk on a level treadmill during both visits. During visit A, the 30-minute treadmill walk was performed within the biomechanics laboratory using a Biodex (RTM600, Biodex Medical Systems, Inc.) treadmill, and participants remained fully instrumented for gait analysis (i.e., full body marker set). During visit B, the treadmill walk was performed within the hospital's physiotherapy suite, located less than 200 metres from the MRI suite, using a BH Fitness (LK590, BH Group, Vitoria-Gasteiz, Spain) treadmill. COVID-19 restrictions prevented the use of a hospital-provided wheelchair for research purposes, so the protocol was standardized to have all participants walk between the MRI and physiotherapy suites during visit B.

Participants attached the treadmill safety clip before beginning each continuous walk. Participants were given several minutes to acclimatize to the treadmill. Treadmill speed was set to participant self-selected walking speed (where participants indicated they could maintain the walking speed for 30-minutes) and was within ± 10% of overground walking speed calculated during pre-treadmill gait analysis. Treadmill speed was matched between study visits. Patient-reported outcomes were collected at baseline and 10-minute intervals during the walk (i.e., minutes 0, 10, 20, 30). Participants were asked to verbally rate the pain in their affected knee using the Numeric Pain Rating Scale (NPRS) (288), which ranges from 0 "no pain at all" to 10 "worst pain imaginable" (289), as well as their rating of perceived exertion using the Borg Scale, which ranges from 6 "no exertion" to 20 "maximal exertion" (465). Heart rate was continuously monitored using a mobile application (Elite HRV®, Asheville, NC) via Bluetooth. Paired with exertion scores, heart rate data were used to calculate the clinical physical activity intensity. The recommended aerobic training intensity is 40-60% of age-adjusted maximal heart rate (220 – age) with a score of 12-13 on the Borg scale (466). At the end of the 30-minute walk, the treadmill came to a slow stop, and the safety clip and heart rate monitor were removed.

5.2.4 Data Processing

5.2.4.1 Questionnaires

Summary scores were calculated for each questionnaire. The KOOS summary score (KOOS5) was calculated as the average percentage score of the 5 sub-scales (pain, symptoms, function in activities of daily living, function in sports and recreational activities, and knee-related quality of life) ranging from 0 (extreme problems) to 100 (no problems) (204). The Knee Outcome Survey summary score was calculated as the average of the 2 sub-scales (activities of daily living and sports activity) ranging from 0 (worst functioning) to 100 (best functioning) (451). The ICOAP summary score was calculated as the percentage score of all items ranging from 0 (no pain) to 100 (maximal pain) (332). The Oxford Knee Score summary score was calculated as the sum of all items ranging from

0 (worst outcomes) to 48 (best outcomes) (334). The EQ-5D-5L summary score was calculated as the sum of the five health state items ranging from 5 (no problems) to 25 (extreme problems) (333). The Pain Catastrophizing Scale summary score was calculated as the sum of all items ranging from 0 (no catastrophizing) to 52 (most catastrophizing) (452). The IPAQ-SF summary score was calculated as a continuous score representing the total number of metabolic equivalent (MET)-minutes per week, where higher scores indicate higher levels of physical activity (453). The PASE summary score was calculated as the sum of all items after multiplying each activity type by frequency, ranging from 0 (no activity) to 793 (maximal activity) (454).

5.2.4.2 Ultrasound Outcomes

All ultrasound images were processed using ImageJ software (version 1.53t, National Institutes of Health, Bethseda, MD, available from https://imagej.nih.gov/ij/). Femoral condylar cartilage thickness (mm) was extracted from the medial and lateral regions, defined as the straight-line distance between the cartilage-bone interface and synovia-cartilage interface (107,447,467). Pre- and post-walking ultrasound images were vertically aligned to standardize the horizontal distance from the intercondylar notch. Three measurements were taken within each region, and the average measurement was used to represent regional cartilage thickness (Figure 5.4). All measurements were taken by a single rater. Each image was measured twice, with at least one week between measurements, to assess intra-rater reliability. The percent change in ultrasound-measured cartilage thickness (before and after treadmill walk) was calculated in each femoral cartilage region using Equation 5.1.

Equation 5.1

$$Cartilage\ Thickness\ Percent\ Change = \left(\frac{mean\ thickness\ after\ walk - mean\ thickness\ before\ walk}{mean\ thickness\ before\ walk}\right) \times 100$$

Figure 5.4. Femoral cartilage thickness assessment for a right osteoarthritic knee using ultrasound. Cartilage thickness is indicated by the straight-line distances in each region (lateral condyle, left; medial condyle, right). The average of 3 measurements represents the regional cartilage thickness.

5.2.4.3 Biomechanical Outcomes

Knee joint angles and moments from overground walking conditions (pre- and post-treadmill walking) were processed and extracted using Cortex (version 8.0, Motion Analysis Corporation, Rohnert Part, CA), Visual 3D (v2023.04.2, C-motion Inc., Germantown, MD, USA), and custom MATLAB (R2021a, The MathWorks, Inc., Natick, MA, USA) softwares. Motion and force data were filtered using recursive fourth-order low-pass Butterworth filters with 6 Hz and 30 Hz cut-off frequencies, respectively (468,469). Knee joint angles and moments were calculated using an XYZ (sagittal, frontal, transverse) rotation sequence (470). The knee flexion angle was calculated as the shank with respect to the thigh segment (471) and was time-normalized to 100% of the gait cycle. One gait cycle was defined between ipsilateral heel-strikes, with events identified as the maximal distance between the pelvis segment and heel marker (472). Net external knee flexion and adduction moments were calculated using bottom-up rigid-linked-segment modelling procedures (473,474). Moments were filtered using a recursive fourth-order low-pass Butterworth filter with 10 Hz cut-off frequency and were time-normalized to 100% of the stance phase, and amplitude-normalized to participant body mass (475). The stance phase was defined between heel-strike and toe-off while the foot segment was in contact with the force plate, with events identified using a 20 N force platform threshold. Ensemble average waveforms were calculated for each participant from individual overground walking trials before and after the treadmill walk.

Discrete metrics were extracted from joint angle and moment waveforms for analysis using pre- and post-treadmill walking trials. Outcomes included peak knee flexion angle during stance (extracted within the first 30% of the gait cycle), peak knee flexion moment, first peak knee adduction moment (extracted within the first 50% of the stance phase), and knee adduction moment impulse. Knee adduction moment impulse was calculated as the time integral of the knee adduction moment curve during stance. Discrete metrics extracted from knee angle and moment waveforms have demonstrated moderate to excellent reliability, including peak knee flexion angle (intra-class correlation coefficient [ICC] = 0.77), peak knee flexion moment (ICC = 0.57), peak knee adduction moment (ICC = 0.86 to 0.91), and knee adduction moment impulse (ICC = 0.86) (463,476,477).

5.2.4.4 Magnetic Resonance Imaging Outcomes

All MRI scans were processed using 3D Slicer (v 4.11.20210226, available at https://www.slicer.org/), a free, open-source software package for medical imaging (478). The pre- and post-walking 3D FIESTA scans were registered to each other using the general registration (BRAINS) pipeline (479) to ensure the same slices were segmented before and after walking. Manual segmentation of articular cartilage was completed using the segment editor module (480) on every other slice to decrease processing time without sacrificing sensitivity to changes in cartilage thickness (481). Skipped slices were interpolated using "fill between slices," a morphological contour interpolation algorithm, to complete the segmentations based on the shape of the specified segments (482).

Femoral cartilage segmentations were obtained from the weight-bearing regions of the medial and lateral femoral condyles (Figure 5.5). The weight-bearing region was defined as 60% of the distance between the anterior border (parallel to the femur and through the trochlear notch) and posterior aspect of each femoral condyle (483). Cartilage thickness was extracted from segmentations using a custom pipeline and was defined as the minimum Euclidean distance between the bone-cartilage interface and articular surface. Segmentation was completed by a single rater, and a random sub-group of scans were measured twice to assess intra-rater reliability. The percent change in MRI-measured cartilage thickness (before and after treadmill walk) was calculated in each femoral cartilage region using Equation 5.1.

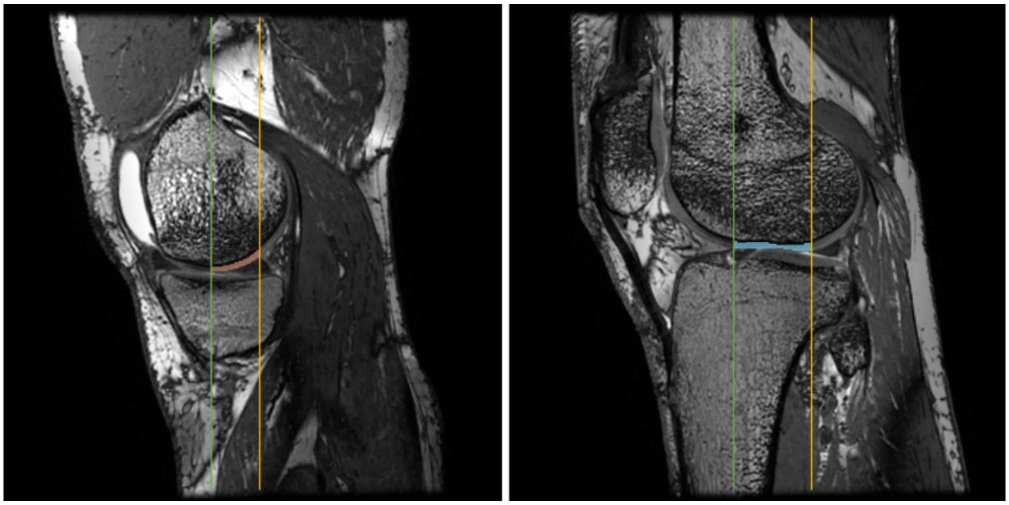


Figure 5.5. Femoral cartilage thickness assessment using magnetic resonance imaging. The shaded brown (left) and blue (right) areas represent the medial and lateral weight-bearing femoral cartilage regions, respectively. The green and yellow vertical lines represent the anterior and posterior boundaries for the 60% weight-bearing regions, respectively.

5.2.5 Statistical Analysis

All statistical analysis was completed in SPSS (IBM SPSS Statistics for Windows, Version 28.0.1.1 Armonk, NY), using an alpha value of 0.05 to represent statistical significance. Data were tested for normality using a Shapiro-Wilk test and Q-Q plots, and for equal variance using a Levene's test. Data sphericity was tested using Mauchly's test of sphericity, and a Greenhouse-Geisser correction was applied if data were non-spherical. Participant descriptive statistics were summarized using means and standard deviations for continuous variables (e.g., age), and counts and percentages for categorical variables (e.g., sex). A mixed analysis of variance was used to determine the main effects of time (i.e., minutes 0, 10, 20, and 30) and visit (A and B), and their interaction, on patient-reported outcomes (pain and ratings of perceived exertion) during the treadmill walk. Tukey's post hoc tests were applied to examine pairwise comparisons.

To achieve **O1**, within-person changes in overground gait speed, kinematic (peak knee flexion angle during stance), and kinetic (peak knee flexion moment, first peak knee adduction moment, knee adduction moment impulse) outcomes before and after the 30-minute continuous treadmill walk were quantified using mean differences and 95% confidence intervals (CI).

To achieve **O2**, within-person changes (before and after treadmill walk) in medial and lateral cartilage thickness measured using ultrasound and MRI were quantified using mean differences and 95% CI. Percentage change in cartilage thickness was calculated for each cartilage region with each imaging modality. Intra-rater reliability for ultrasound and MRI measurements was assessed using ICCs and corresponding 95% CIs based on a mean-rating (k=2), absolute agreement, two-way mixed effects model, and was interpreted using the following cut-points: <0.50 (poor), 0.50-0.75 (moderate), 0.75-0.90 (good), and >0.90 (excellent) (377). Agreement between ultrasound and MRI cartilage thickness measures at baseline and changes following walking within medial and lateral femoral cartilage regions was assessed using Bland-Altman plots (484,485). Sensitivity analyses were completed by removing participants recruited during the first recruitment wave to ensure conclusions based on MRI outcomes were robust and did not vary based on time between study visits.

To achieve **O3**, exploratory analyses were performed to examine potential biomechanical contributions for sub-groups of participants identified as responders and non-responders for structural (cartilage thickness) and patient-reported (pain) outcomes following walking. For structural outcomes, a responder was defined as a participant whose cartilage thickness decreased following walking (i.e., "responded" to loading), and a non-responder was defined as a participant whose cartilage thickness increased following walking (303). Structural responders and non-responders were determined for ultrasound and MRI measurements separately (based on absolute changes in cartilage thickness within each imaging modality). A Cohen's kappa statistic was used to determine agreement of responder and non-responder sub-group allocation using ultrasound and MRI, and was interpreted using the following agreement cut-points: <0.00 (poor), 0.00-0.20 (slight), 0.21-0.40 (fair), 0.41-0.60 (moderate), 0.61-0.80 (substantial), and 0.81-1.00 (almost perfect) (370). For pain outcomes, a responder was defined as a participant who reported an increase (≥1 point) in NPRS pain following walking, and a non-responder was defined as a participant who reported no change (i.e., <1 point increase) or a decrease in pain following walking (81,486,487). Between-group (i.e., responders vs. non-responders) differences were presented as mean differences and 95% CI for all baseline outcomes and changes in biomechanical outcomes following the 30-minute treadmill walk. Statistical significance was indicated when the CI failed to cross the line of no significance.

5.3 Results

5.3.1 Participants

A total of 40 individuals were recruited for this study. Twenty-two individuals were excluded based on reporting a contraindicating health condition (n=7), surgical contraindication (n=6), scheduling conflict (n=4), unwillingness or inability to undergo an MRI scan (n=3), or recent injury (n=2). Therefore, a total of 18 individuals were enrolled in this study. Based on participant and MRI scanner availability, 9 participants completed visit A first, and 9 participants completed visit B first (Figure 5.6). Two participants were lost to follow-up (one could not be reached to book the subsequent data collection session, and one reported that they could no longer walk 30-minutes continuously), resulting in 16 participants for analysis. Participant demographics are listed in Table 5.2.

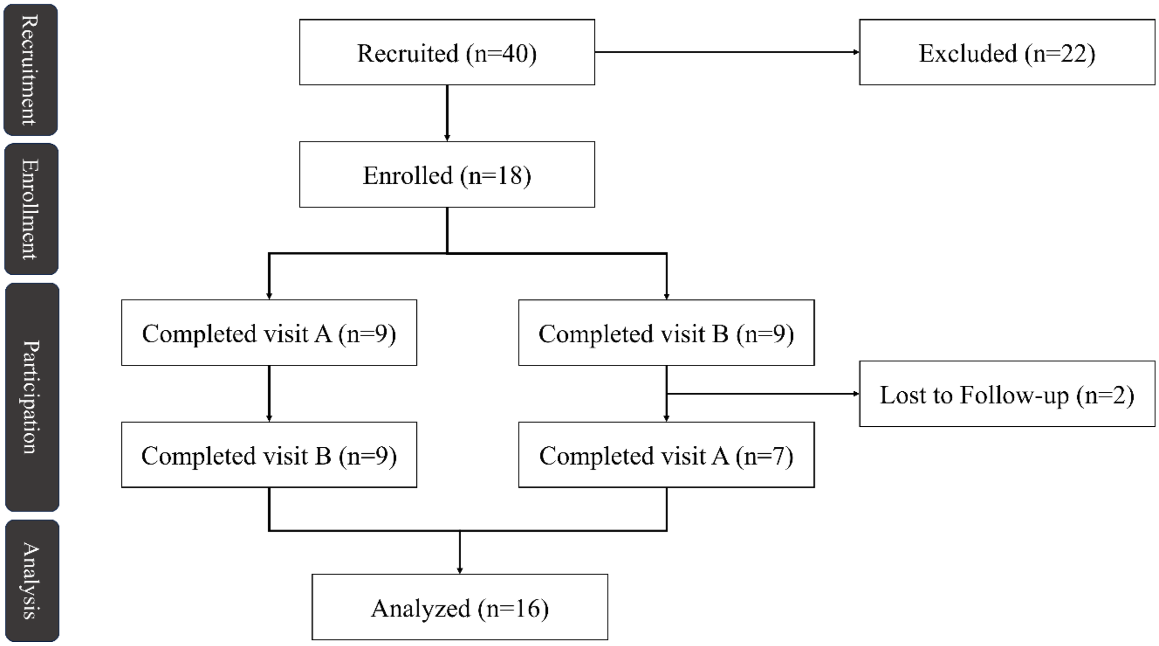


Figure 5.6. Participant flow diagram. A total of 16 participants completed both data collection visits and were analyzed in this study.

Table 5.2. Participant Demographics and Baseline Outcomes (n=16).

Participant Characteristic	
Age, years	63 (6)
Height, m	1.73 (0.08)
Mass, kg	84.12 (9.53)
Body mass index, kg/m^2	28.3 (3.7)
Sex, n (%)	
Female	7 (43.8)
Male	9 (56.2)
Bilateral, n (%)	10 (62.5)
Affected limb, n (%)	
Left	9 (56.2)
Right	7 (43.8)
KOOS5 Score†, 0-100	63.1 (15.9); range: 37.3 – 93.3
Knee Outcome Survey†, 0-100	70.0 (15.4); range: 40.9 – 94.9
ICOAP Score*, 0-100	21.0 (17.6); range: 0 – 52.3
Oxford Knee Score†, 0-48	38.6 (7.6); range: 23.0 – 48.0
EQ-5D-5L Score*, 5-25	7.3 (2.3); range: 5 – 13
Pain Catastrophizing*, 0-52	4.9 (4.8); range: 0 – 13
IPAQ-SF Score†	3300.4 (2568.0); range: 0 – 9918.0
PASE Score†, 0-793	175.2 (80.3); range: 55 – 321

Note: All values are listed as mean (standard deviation) unless otherwise indicated. KOOS5 = Knee injury and Osteoarthritis Outcome Score, average of 5 sub-scales. ICOAP = Intermittent and Constant Pain questionnaire. EQ-5D-5L = 5-level Euro-QOL 5-dimension questionnaire. IPAQ-SF = International Physical Activity Questionnaire Short-Form. PASE = Physical Activity Scale for the Elderly. * Higher scores indicate worse patient-reported outcomes. † Higher scores indicate better patient-reported outcomes.

Participants were enrolled following two recruitment waves due to a COVID-19 research disruption. Average time between visits was 279.8 ± 19.1 days (range: 263 – 307 days) for those recruited during the first wave (n=4), and 15.8 ± 17.5 days (range: 4 – 67 days) for those recruited during the second wave (n=12). Across all participants (n=16), visits were completed on average 81.8 ± 119.3 days apart. Data collection start time was matched for 9 (of 16) participants, and the average start time difference between collections for all participants was 2 hours and 20 minutes.

5.3.2 Outcomes During the 30-minute Walk

Changes in patient-reported outcomes (pain and ratings of perceived exertion) during the 30-minute treadmill walk across both study visits are listed in Table 5.3. Average treadmill walking speed was 1.27 ± 0.20 m/s and was matched between visits. The main effect of study visit was not statistically significant, indicating that the two study visits did not elicit different patient-reported outcomes. The main effect of time was statistically significant for both pain and ratings of perceived exertion. On average, pain increased by 0.6 points, and ratings of perceived exertion increased by 3.8 to 4.4 points, between baseline (0 minutes) and the end of the 30-minute walk across both study visits. Post-hoc pairwise comparisons revealed that compared to baseline, pain was significantly higher ($p = 0.021$) at 30-minutes, and exertion scores were significantly higher ($p < 0.001$) at each 10-minute interval, except between 20 and 30-minutes of walking. There was no significant interaction effect between time and study visit.

Table 5.3. Patient-reported outcomes at 10-minute intervals throughout the 30-minute walk for each study visit.

	0-minutes	**10-minutes**	**20-minutes**	**30-minutes**	**p-value (time)**	**p-value (visit)**
Pain						
Visit A	0.7 (1.4)	1.3 (1.8)	1.2 (1.8)	1.3 (1.6)	**0.006**	0.976
Visit B	0.8 (1.3)	1.0 (1.3)	1.2 (1.6)	1.4 (1.8)		
RPE						
Visit A	6.0 (0.0)	8.9 (2.1)	9.4 (2.0)	9.8 (2.3)	**<0.001**	0.154
Visit B	6.3 (0.9)	9.9 (2.5)	10.5 (2.3)	10.7 (2.0)		

Note: Values are listed as mean (standard deviation). RPE = rating of perceived exertion using a Borg scale (6 to 20-point scale). Bolded p-values indicate statistical significance at $p < 0.05$.

Full heart rate data were available for 13 (of 16) participants during each study visit. At minutes 0, 10, 20, and 30 of the treadmill walk, participants respectively walked at 46.7%, 56.6%, 57.1%, and 56.9% of their age-adjusted maximal heart rate during visit A, and 43.4%, 57.1%, 58.3%, and 59.6% during visit B, indicating they achieved the recommended aerobic training intensity during each continuous walk.

5.3.3 Pre and Post Walking Biomechanical Outcomes

The biomechanical differences pre and post the 30-minute treadmill walk are presented in Figure 5.7. The peak knee flexion angle during stance, peak knee flexion moment, and first peak knee adduction moment increased following the continuous walk (indicated by confidence intervals not crossing zero); the magnitude of these increases ranged from 2.2% to 7.0% (Table 5.4). There were no differences in knee adduction moment impulse following the 30-minute walk (Table 5.4).

5.3.4. Pre and Post Walking Ultrasound Imaging Outcomes

The average maximum knee flexion angle for ultrasound measurements before walking was 132.4 ± 11.8 degrees, and after walking was 130.8 ± 12.2 degrees. Intra-rater reliability of ultrasound cartilage thickness measurements was excellent, indicated by an ICC [95% CI] value of 0.99 [0.98, 1.00]. Percent change (mean ± standard deviation) in cartilage thickness measured using ultrasound was 1.2% (± 5.3%) and 0.0% (± 7.3%) for medial and lateral femoral cartilage regions, respectively. The mean differences and 95% confidence intervals revealed no significant changes in ultrasound-measured cartilage thickness pre- to post-walking for medial or lateral femoral regions (Table 5.4).

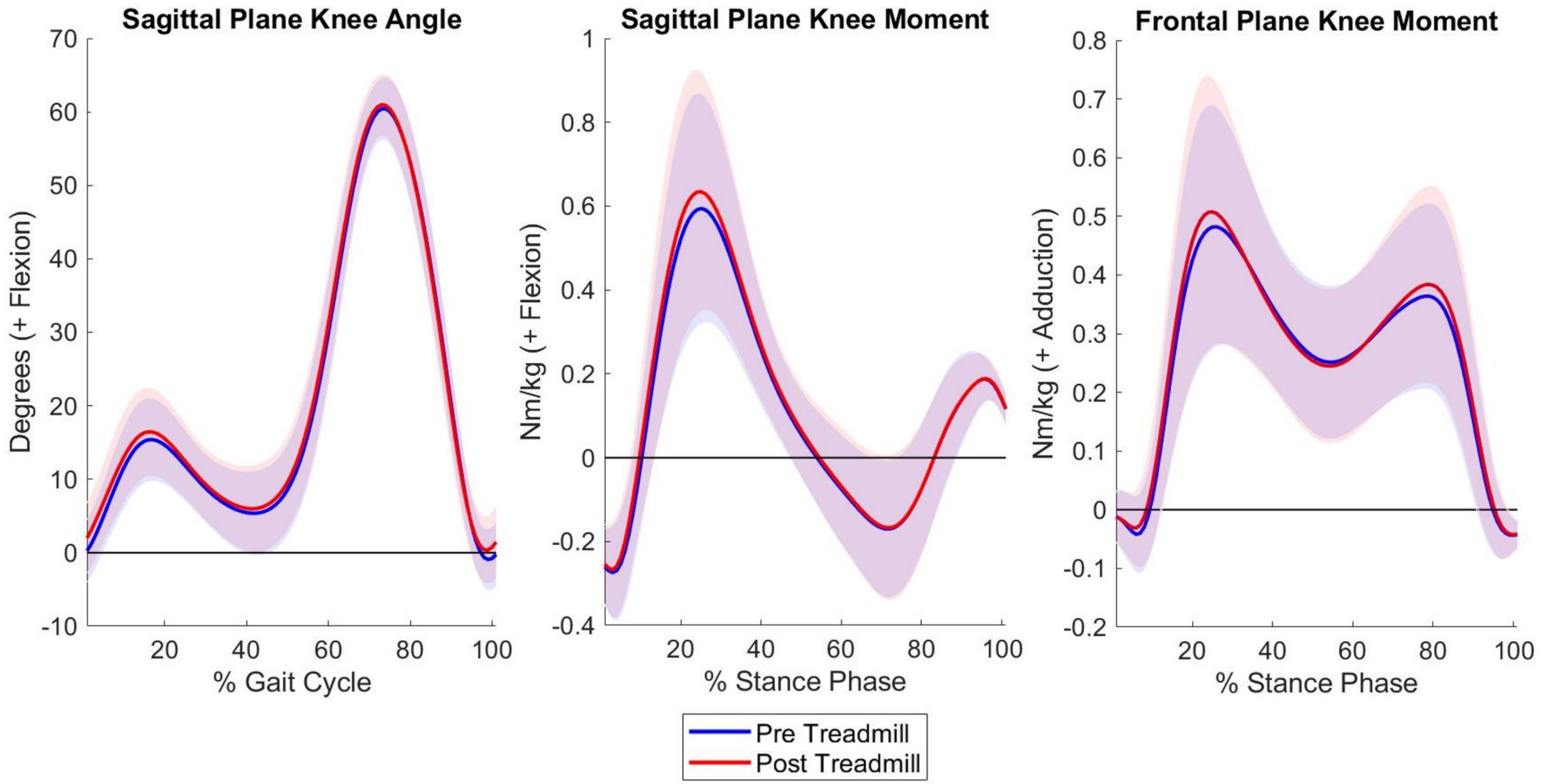


Figure 5.7. Ensemble average waveforms before (blue) and after (red) treadmill walking for sagittal plane knee angle (left), sagittal plane knee moment (middle), and frontal plane knee moment (right). Shaded areas represent the standard deviation before (blue) and after (red) walking.

Table 5.4. Within-group (n=16) differences in biomechanical and structural imaging outcomes before and after 30-minutes of walking.

	Pre-Treadmill	Post-Treadmill	Mean Difference [95% CI]
Biomechanical Outcomes			
Overground gait speed (m/s)	1.37 (0.19)	1.40 (0.19)	**0.03 [0.00, 0.05]**
Peak KFA during stance (degrees)	15.7 (5.5)	16.8 (6.0)	**1.05 [0.42, 1.68]**
Peak KFM (Nm/kg)	0.61 (0.27)	0.65 (0.29)	**0.04 [0.01, 0.08]**
First peak KAM (Nm/kg)	0.51 (0.19)	0.54 (0.22)	**0.03 [0.01, 0.05]**
KAM impulse (Nm*s/kg)	0.18 (0.08)	0.19 (0.08)	0.00 [-0.01, 0.01]
Ultrasound Outcomes			
Medial femoral thickness (mm)	2.09 (0.51)	2.13 (0.60)	0.03 [-0.03, 0.10]
Lateral femoral thickness (mm)	1.93 (0.46)	1.94 (0.54)	0.01 [-0.08, 0.10]
Magnetic Resonance Imaging Outcomes			
Medial femoral thickness (mm)	1.40 (0.59)	1.44 (0.63)	0.04 [-0.03, 0.10]
Lateral femoral thickness (mm)	1.41 (0.38)	1.44 (0.40)	0.03 [-0.06, 0.12]

Note: CI = confidence interval. KFA = knee flexion angle. KFM = knee flexion moment. KAM = knee adduction moment. Mean differences are presented as change values (after walking minus before walking), where a positive value indicates an increase post-walking, and a negative value indicates a decrease post-walking. Bolded values indicate within-group differences for which the 95% CI does not cross the zero-line.

5.3.5 Pre and Post Walking Magnetic Resonance Imaging Outcomes

Intra-rater reliability of MRI cartilage thickness measurements was excellent, as determined by an ICC [95% CI] value of 0.97 [0.94, 0.99]. Percent change (mean ± standard deviation) in cartilage thickness measured using MRI was 1.7% (± 8.0%) and 2.3% (± 12.5%) for medial and lateral femoral cartilage regions, respectively. The mean differences and 95% confidence intervals indicated no significant changes in MRI-measured cartilage thickness pre- to post-walking for either femoral sub-region (Table 5.4).

5.3.6 Agreement Between Ultrasound and Magnetic Resonance Imaging

Bland-Altman plots assessed agreement between ultrasound and MRI measures at baseline (Figure 5.8) and changes following 30-minutes of walking (Figure 5.9). At baseline, mean differences between imaging modalities displayed a bias whereby MRI measures were consistently smaller than ultrasound measures by 0.69 mm in the medial femoral region and 0.52 mm in the lateral femoral region (Figure 5.8). The sensitivity analysis decreased the bias for medial cartilage thickness (mean difference [95% CI] = -0.56 [-2.02, 0.90] mm), and increased the bias for lateral cartilage thickness (mean difference [95% CI] = -0.63 [-1.34, 0.08] mm), although the trends remained unchanged.

Changes in cartilage thickness following 30-minutes of walking demonstrate agreement between ultrasound and MRI measures (Figure 5.9). Mean differences in medial and lateral femoral cartilage thickness changes were 0.00 mm and 0.02 mm, respectively, between ultrasound and MRI. The sensitivity analysis had no effect on changes in medial cartilage thickness (mean difference [95% CI] = 0.00 [-0.30, 0.29] mm) and slightly decreased the bias and widened the limits of agreement for changes in lateral cartilage thickness (mean difference [95% CI] = 0.01 [-0.34, 0.35] mm).

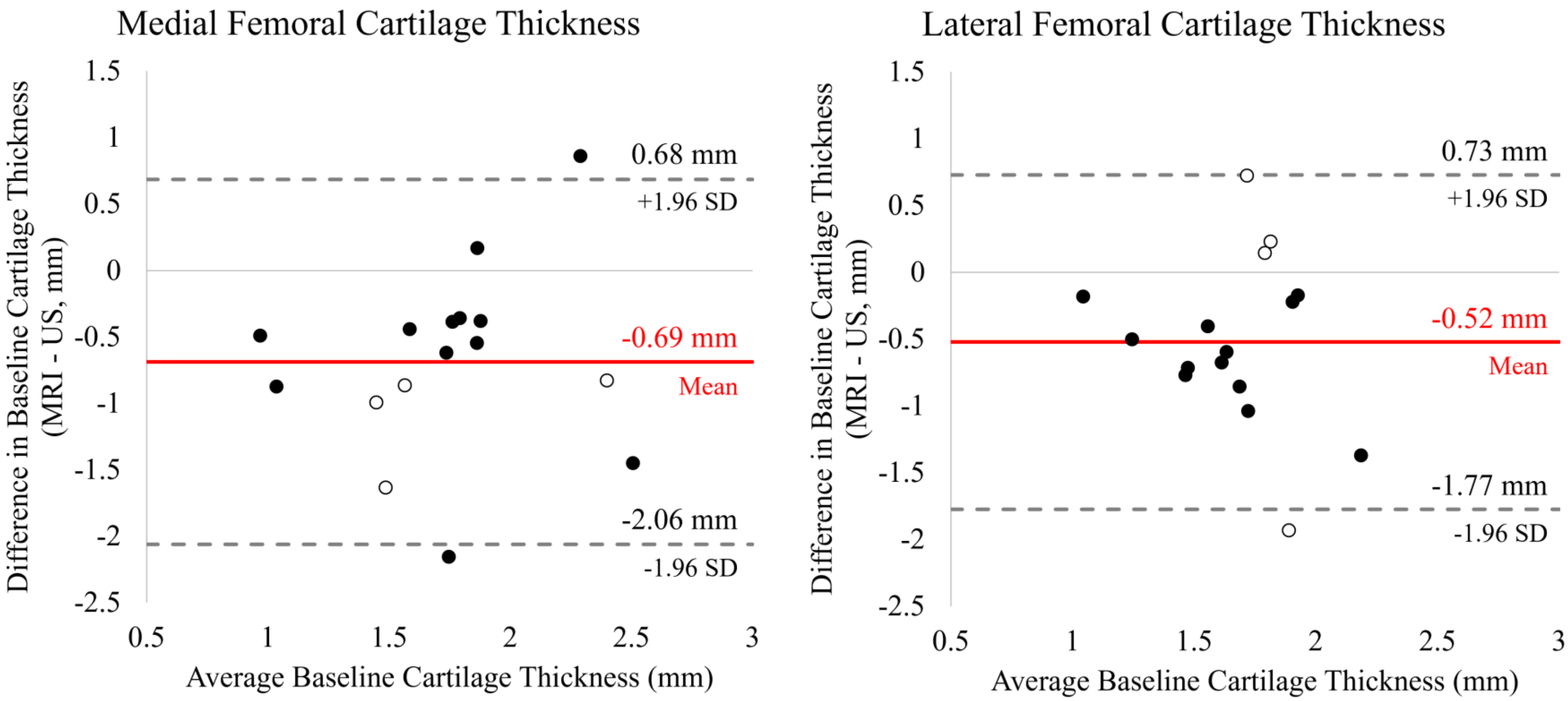


Figure 5.8. Bland-Altman plots comparing baseline cartilage thickness measured using magnetic resonance imaging (MRI) and ultrasound (US) for medial (left) and lateral (right) femoral cartilage regions. The x-axis shows the average baseline cartilage thickness across the two imaging modalities, and the y-axis shows the difference between the two imaging modalities (MRI minus US). The solid red line indicates the mean difference between modalities, and the dashed grey lines indicate the upper and lower limits of agreement (± 1.96 standard deviation, SD). White circles represent participants from the first recruitment wave (removed for the sensitivity analysis), and black circles represent participants from the second recruitment wave.

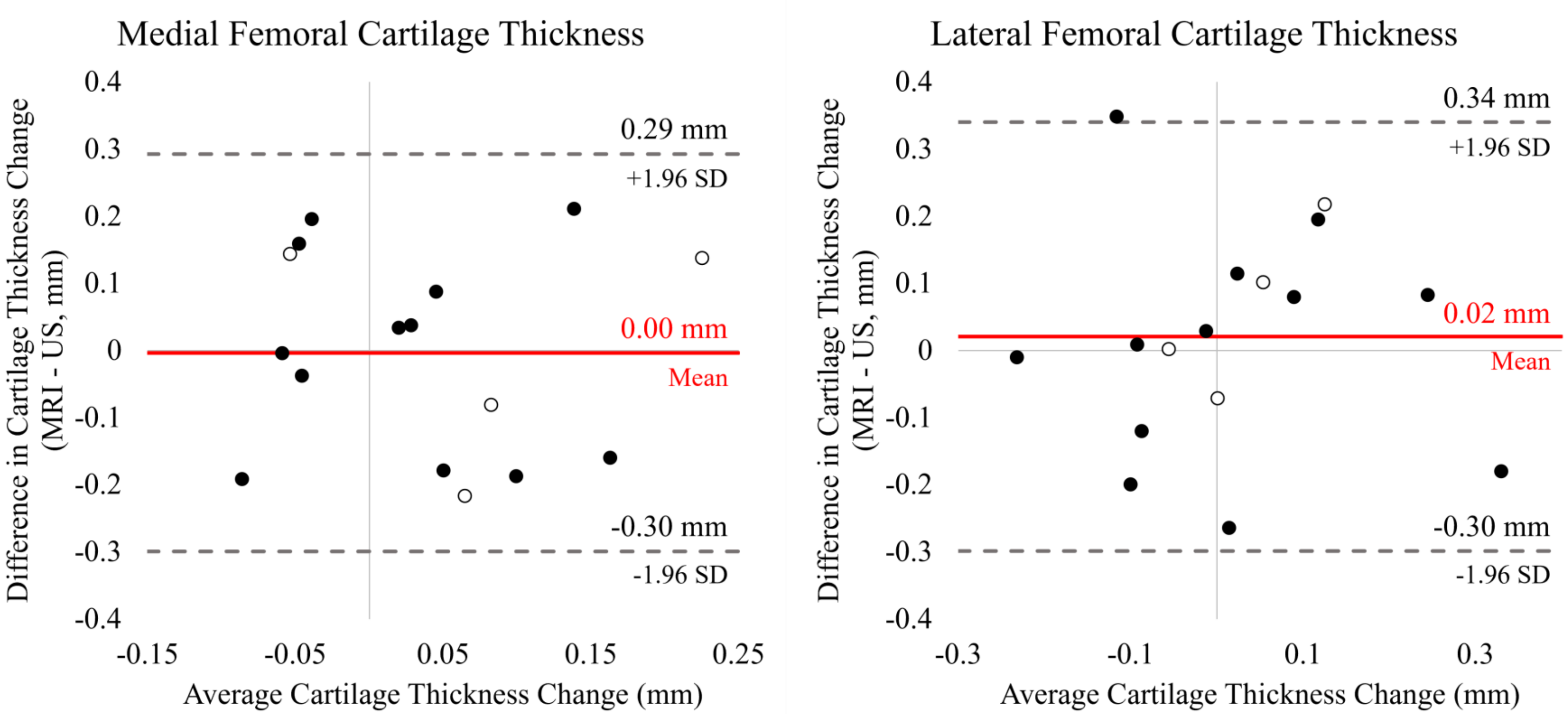


Figure 5.9. Bland-Altman plots comparing change in cartilage thickness measured using magnetic resonance imaging (MRI) and ultrasound (US) for medial (left) and lateral (right) femoral cartilage regions. The x-axis shows the average change in cartilage thickness across the two imaging modalities, and the y-axis shows the difference between the two imaging modalities (MRI minus US). The solid red line indicates the mean difference between modalities, and the dashed grey lines indicate the upper and lower limits of agreement (± 1.96 standard deviation, SD). White circles represent participants from the first recruitment wave (removed for the sensitivity analysis), and black circles represent participants from the second recruitment wave.

5.3.7 Exploring Responders and Non-Responders

Participants were dichotomized into sub-groups of responders and non-responders based on structural (cartilage thickness) and patient-reported (pain) outcomes (Table 5.5.). Pain sub-groups were determined based on the mean response following 30-minutes of walking across both data collection visits. Agreement of structural sub-group allocation was slight (κ = 0.127, p = 0.611) for medial and fair (κ = 0.238, p = 0.341) for lateral femoral regions between ultrasound and MRI-measured changes in cartilage thickness.

Table 5.5. Mean changes in structural and pain outcomes for exploratory sub-groups (responders and non-responders) following 30-minutes of continuous walking.

	Responders		Non-Responders	
	n	Pre-Post	n	Pre-Post
Ultrasound				
Medial cartilage thickness (mm)	5	-0.09 (0.05)	11	0.10 (0.09)
Lateral cartilage thickness (mm)	7	-0.11 (0.11)	9	0.10 (0.14)
Magnetic Resonance Imaging				
Medial cartilage thickness (mm)	5	-0.08 (0.06)	11	0.09 (0.09)
Lateral cartilage thickness (mm)	7	-0.13 (0.07)	9	0.15 (0.10)
Pain	6	1.67 (0.52)	10	-0.05 (0.28)

Note: Change values are presented as mean (standard deviation).

There were few baseline differences between responders and non-responders, regardless of ultrasound (Figure 5.10), MRI (Figure 5.11), or pain (Figure 5.12) sub-groupings. MRI-measured lateral cartilage responders, compared to non-responders, reported lower (worse) Oxford Knee Score summary scores (mean difference [95% CI] = -7.60 [-14.92, -0.28]) at baseline. Pain responders, compared to non-responders, exhibited higher knee adduction moment impulse (mean difference [95% CI] = 0.09 [0.01, 0.16]) and lower (worse) Knee Outcome Survey summary scores (mean difference [95% CI = -16.58 [-31.42, -1.73]) at baseline. Responders, compared to non-responders, tended to report higher baseline pain across all sub-groupings (except for ultrasound-measured medial cartilage sub-groups); however, between-group differences were not identified based on the confidence intervals. There were no other between-group (responder versus non-responder) differences at baseline for structural or patient-reported sub-groups.

Mean between-group differences for changes in biomechanical outcomes are presented in Table 5.6. Ultrasound-measured medial cartilage responders, compared to non-responders, experienced larger increases in peak knee flexion angle during stance and peak knee flexion moment (Figure 5.13). There were no other between-group differences for ultrasound-measured, MRI-measured, or pain sub-groups based on changes in biomechanical outcomes (Table 5.6). The sensitivity analysis did not alter these findings.

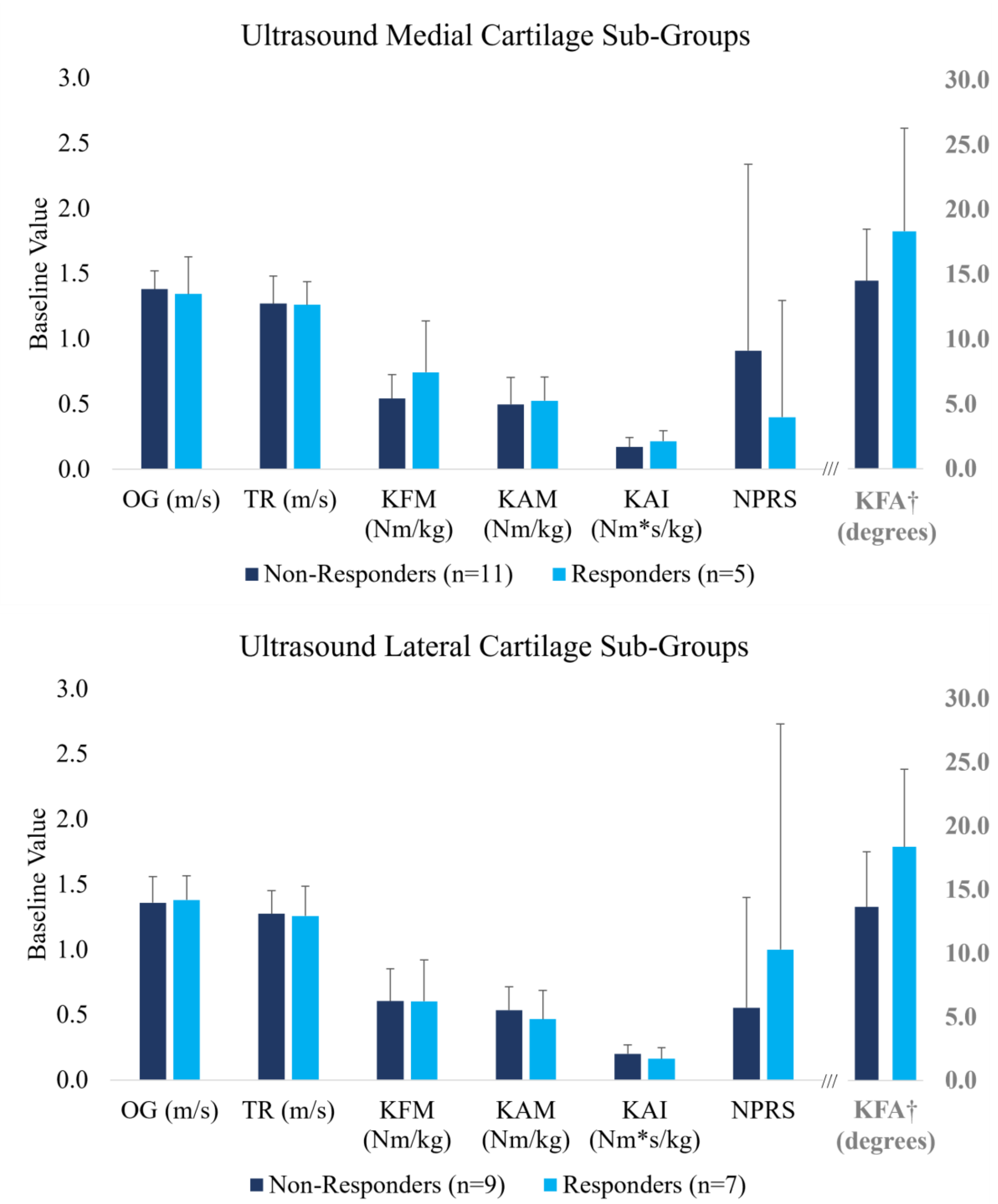
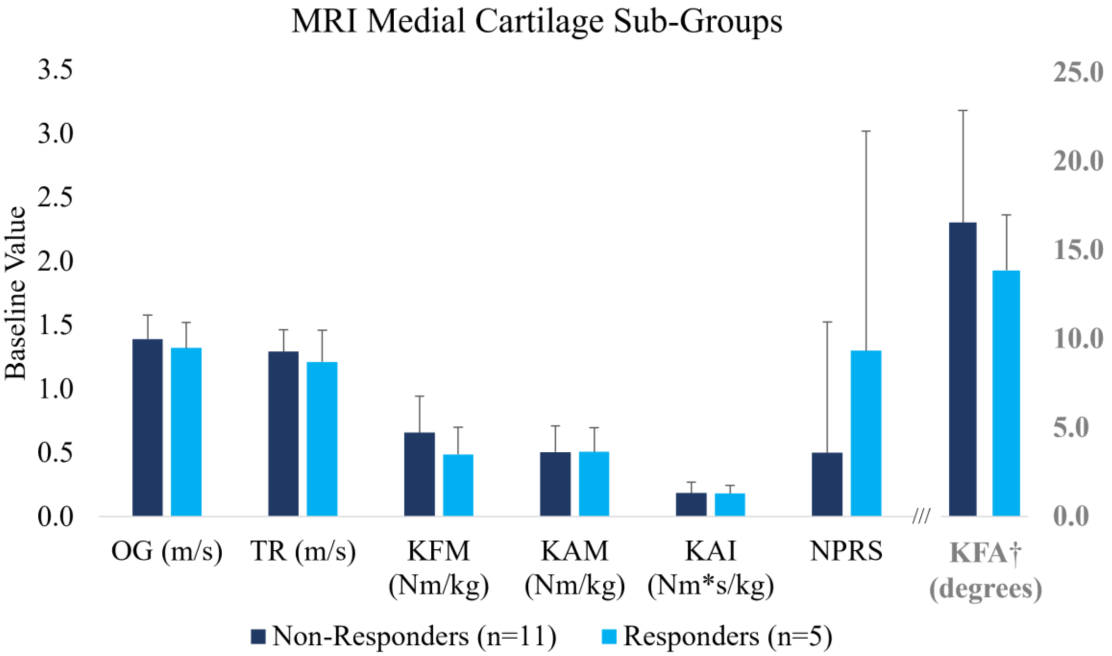


Figure 5.10. Mean (+ standard deviation) baseline outcomes for non-responders and responders based on ultrasound-measured cartilage thickness sub-groups, including medial (top) and lateral (bottom) regions. Asterisks (*) represent between-group differences in baseline outcomes based on confidence intervals. † Represents data presented on the secondary y-axis (right hand side). OG = overground walking speed. TR = treadmill walking speed. KFM = peak knee flexion moment. KAM = first peak knee adduction moment. KAI = knee adduction moment impulse. NPRS = numeric pain rating scale. KFA = peak knee flexion angle during stance (presented on secondary y-axis).



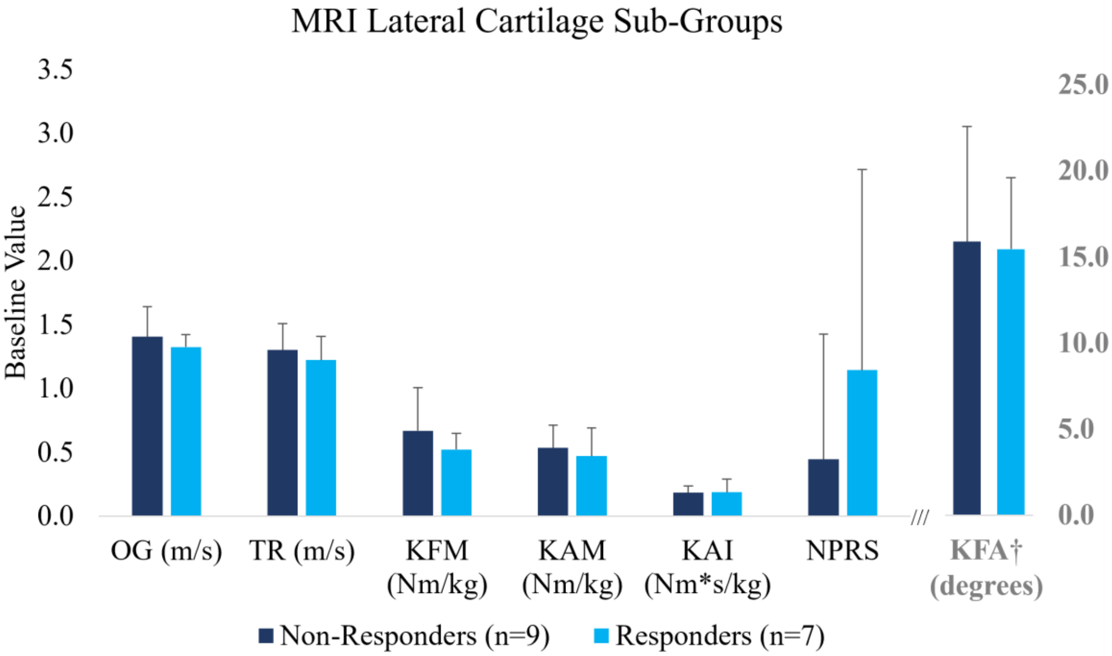


Figure 5.11. Mean (+ standard deviation) baseline outcomes for non-responders and responders based on magnetic resonance imaging (MRI)-measured cartilage thickness sub-groups, including medial (top) and lateral (bottom) regions. Asterisks (*) represent between-group differences in baseline outcomes based on confidence intervals. † Represents data presented on the secondary y-axis (right hand side). OG = overground walking speed. TR = treadmill walking speed. KFM = peak knee flexion moment. KAM = first peak knee adduction moment. KAI = knee adduction moment impulse. NPRS = numeric pain rating scale. KFA = peak knee flexion angle during stance (presented on secondary y-axis).

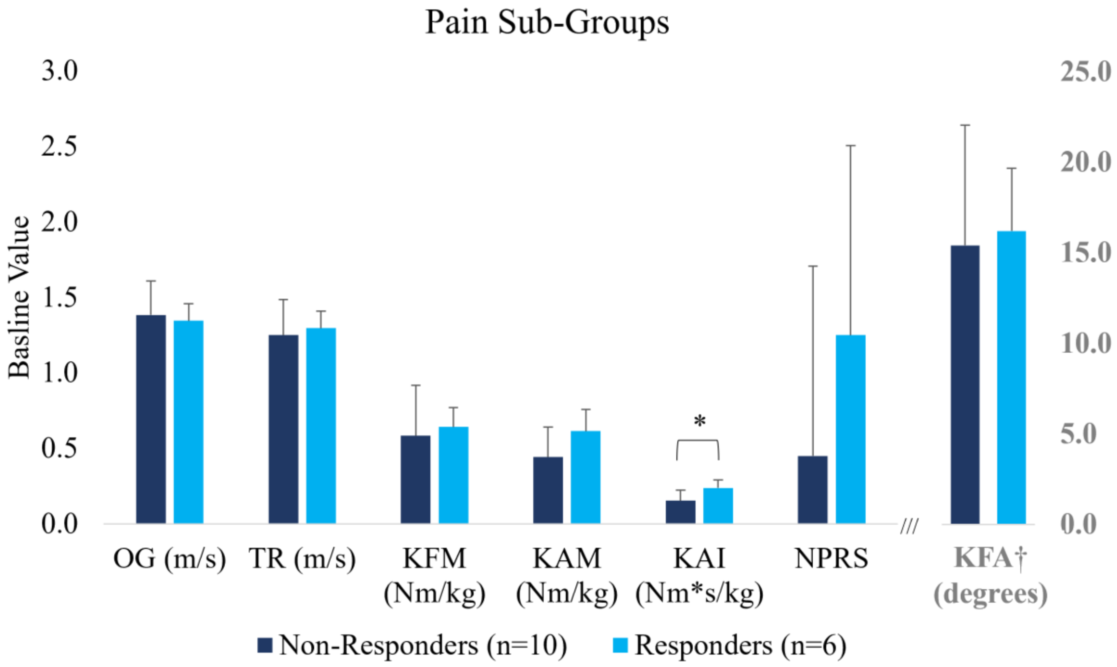


Figure 5.12. Mean (+ standard deviation) baseline outcomes for non-responders and responders based on patient-reported pain. Asterisks (*) represent between-group differences in baseline outcomes based on confidence intervals. † Represents data presented on the secondary y-axis (right hand side). OG = overground walking speed. TR = treadmill walking speed. KFM = peak knee flexion moment. KAM = first peak knee adduction moment. KAI = knee adduction moment impulse. NPRS = numeric pain rating scale. KFA = peak knee flexion angle during stance (presented on secondary y-axis).

Table 5.6. Between-group differences (responders vs. non-responders; defined for structural and pain outcomes) in changes in biomechanical outcomes following 30-minutes of walking.

Change following the 30-minute walk	**Ultrasound Sub-Groups**		**MRI Sub-Groups**		**Pain Sub-Groups**
	Medial	Lateral	Medial	Lateral	
	Mean Difference [95% CI]				
Overground gait speed (m/s)	0.00 [-0.05, 0.06]	0.01 [-0.04, 0.06]	-0.03 [-0.09, 0.02]	0.01 [-0.04, 0.06]	-0.02 [-0.07, 0.03]
Peak KFA during stance (degrees)	**-1.35** **[-2.53, -0.16]**	0.69 [-0.57, 1.94]	0.44 [-0.95, 1.82]	0.82 [-0.41, 2.05]	0.66 [-0.64, 1.95]
Peak KFM (Nm/kg)	**-0.07** **[-0.13, -0.01]**	0.00 [-0.07, 0.07]	-0.05 [-0.12, 0.02]	0.06 [-0.01, 0.12]	0.02 [-0.05, 0.09]
First peak KAM (Nm/kg)	-0.04 [-0.07, 0.00]	0.00 [-0.04, 0.04]	-0.03 [-0.07, 0.01]	0.03 [-0.01, 0.06]	0.01 [-0.03, 0.05]
KAM impulse (Nm*s/kg)	0.00 [-0.01, 0.02]	0.00 [-0.01, 0.01]	0.01 [0.00, 0.02]	0.00 [-0.01, 0.01]	0.00 [-0.02, 0.01]

Note: MRI = magnetic resonance imaging. CI = confidence interval. KFA = knee flexion angle. KFM = knee flexion moment. KAM = knee adduction moment. Bolded values indicate statistical significance where the CI does not cross zero. Mean differences are presented non-responders minus responders, where a positive value indicates a larger increase in the non-responder group, and a negative value indicates a larger increase in the responder group.

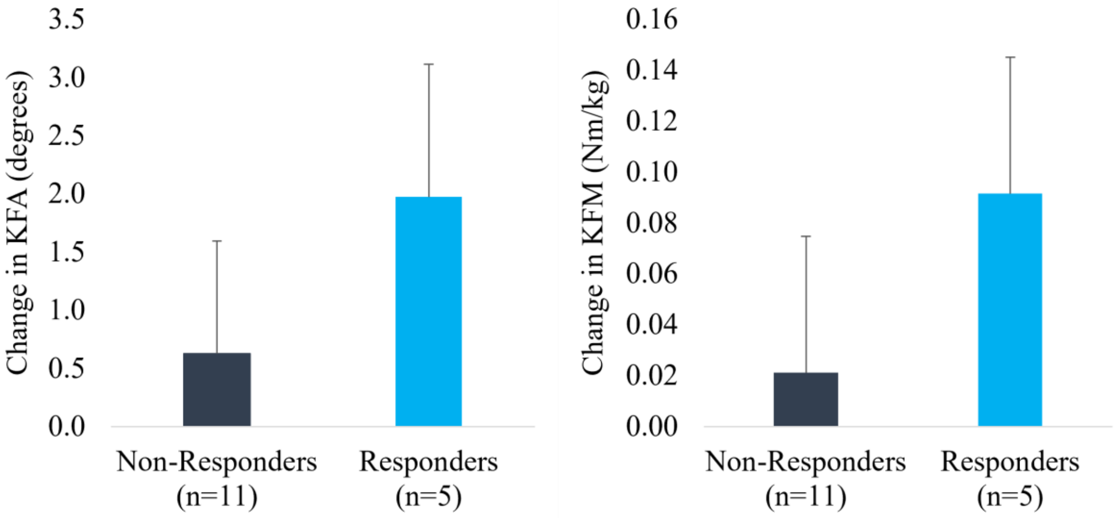


Figure 5.13. Significant between-group differences (mean + standard deviation) in peak knee flexion angle (KFA) during stance (left) and peak knee flexion moment (KFM; right) for ultrasound-measured medial cartilage sub-groups following 30-minutes of continuous walking.

5.4 Discussion

This study describes the immediate effect of a 30-minute continuous walking bout on biomechanical, structural, and patient-reported knee osteoarthritis outcomes. Our findings signify that 30-minutes of continuous walking elicits significant increases in discrete biomechanical metrics, indicative of a faster gait speed and higher peak loading, and no changes in cartilage thickness measured using ultrasound or MRI. Additionally, exploratory results demonstrate relationships between ultrasound-measured medial cartilage thickness responder groups, compared to non-responders, based on sagittal plane biomechanics. This study adds to our current knowledge on the effect of an acute bout of walking on quantitative and interrelated knee osteoarthritis outcomes, and presents novel information regarding potential relationships between biomechanical, structural, and patient-reported outcomes following a continuous walking bout.

This study sample can be characterized as a mild-to-moderate knee osteoarthritis group, demonstrated by the baseline questionnaire responses that indicate low-to-moderate pain and symptoms, and moderate-to-high quality of life and physical activity levels. Additionally, participants reported low baseline pain, and most participants reported no pain before treadmill walking. Heart rate data indicated that participants walking at their self-selected speed achieved the recommended moderate aerobic exercise intensity during the continuous walking bout (466); yet, ratings of perceived exertion suggested that patient-reported exertion was below recommendations (i.e., light versus somewhat hard). Underreporting of exertion scores compared to heart rate monitors has been previously reported (488), and participants may be more likely to underreport physical exertion due to response bias (489). The discrepancy between patient-reported and objective measurements of exercise intensity in this study supports the need for quantitative measurements of cardiovascular outcomes in exercise research as recommended by the ACR (21). The 30-minutes of walking prescribed in this study represents the most widely recommended and implemented exercise duration for knee osteoarthritis populations (24,47,48,365,490); therefore, the intensity and duration of the continuous walking bout employed in this study are representative of widely prescribed exercise parameters for mild-to-moderate knee osteoarthritis. Future research can expand on this work by investigating different exercise prescription parameters in different severity levels of knee osteoarthritis to understand how walking prescription can be optimized for general knee osteoarthritis populations (21).

The significant increase in knee pain following 30-minutes of continuous walking (approximately 0.6 points using the NPRS) is consistent with previous evidence reporting no change (290) or small increases (i.e., 0.3 points) (112) in pain following 30-minutes of walking. Importantly, the increase in pain reported in this study does not exceed the previously established clinically meaningful difference of 2 points (486,487,491). Additionally, pain sub-groups emerged, where approximately 37% of the current participants reported an increase in pain (average increase of 1.67 points), and 63% reported no change or a decrease in pain following 30-minutes of continuous walking. Pain response sub-groups support previous research stating approximately 40-50% of individuals with knee osteoarthritis experience an increase in pain (of 1.5 to 2.1 points using the NPRS) following 20-30 minutes of continuous walking (81,111,291). Knee pain can substantially contribute to high levels of physical inactivity among individuals with knee osteoarthritis (167). However, this evidence suggests that not all individuals meaningfully increase pain following walking, and individuals with mild-to-moderate osteoarthritis could be encouraged to participate in bouts of up to 30 minutes of walking without exacerbating knee pain.

Participants experienced increased peak sagittal and frontal plane knee joint loading following 30-minutes of continuous walking. These increases in peak knee flexion and adduction moments (by approximately 6.0% to 7.0%) are consistent with previous work that reported increases in peak knee flexion and adduction moments (by approximately 1.5% to 7.3%) (112), and align with reported increases in knee joint contact forces (79,80), following 30-minutes of walking. Increases in frontal plane loading suggest a potentially deleterious effect of walking on the knee joint since knee adduction moment features (including first peak and impulse) have been associated with structural knee osteoarthritis progression (90–93). Further, increased sagittal plane loading reflects the net muscular contribution to joint contact forces (408,409) and contributes to medial compartment loading (236,237,410), although evidence investigating the effect of higher peak knee flexion moment on structural disease progression has produced conflicting findings (91,93,95). Nevertheless, noted increases in peak knee joint moments did not result in clinically relevant increases in pain or changes in cartilage thickness measures. Current findings should be confirmed over repeated walking exposure to determine whether increased walking frequency may result in worse symptoms or structural progression because of increased peak knee joint loading.

Noted increases in peak knee joint loading may be explained by concurrent increases in gait speed, where overground gait speed increased by approximately 2% following the 30-minute walking bout. Evidence suggests that decreases in gait speed are associated with increased pain (235) and fatigue (492), indicating that the current bout of walking did not result in functional decline for this cohort of individuals with mild-to-moderate knee osteoarthritis. Increases in gait speed contribute to higher magnitudes of knee flexion moments (240,294) and knee adduction moments (240,416,493); as such, reducing walking speed may be one strategy to reduce peak knee joint loading in response to pain (81,412). However, increases in gait speed are also associated with decreases in knee adduction moment impulse (416) and less longitudinal cartilage change (91), collectively suggesting lower cumulative loading. No changes in knee adduction moment impulse or cartilage thickness were found in this study. Therefore, this moderate intensity bout of walking may provide functional benefit by increasing gait speed, and despite increased peak knee joint loading, does not increase markers of cumulative loading (i.e., knee adduction moment impulse or cartilage thickness). Integrating objective physical activity monitoring would augment these findings by quantifying the frequency of knee joint loading (i.e., steps per day) in addition to loading magnitude and duration to understand cumulative knee joint loading exposure more thoroughly within daily activities.

No changes in cartilage thickness were observed following the 30-minute continuous walking bout. Absolute changes in ultrasound-measured cartilage thickness (0.03 mm for medial, and 0.01 mm for lateral) did not exceed previously established ultrasound-measured minimal detectable change (MDC) thresholds in healthy individuals (0.09 mm for medial femur and 0.10 mm for lateral femur) (108). Similarly, absolute changes in MRI-measured cartilage thickness (0.04 mm for medial, and 0.03 mm for lateral) did not exceed previously established MRI-measured MDC thresholds in osteoarthritis cohort studies (0.09 mm for medial femur and 0.12 mm for lateral femur)

(494,495). These results align with a previous study that reported no change in medial or lateral femoral cartilage thickness following 30-minutes of walking for individuals with knee osteoarthritis (109). Current and previous (109) magnitudes of changes in cartilage thickness following walking are smaller than those reported following 45-minutes of compressive loading (299). Therefore, walking may be a suitable activity for knee osteoarthritis because it elicits small increases in knee joint loads, resulting in minimal-to-no cartilage deformation. Exploring quantitative measures of cartilage composition, including T1-rho or T2 relaxation times, may supplement these findings by directly examining cartilage quality and fluid movement that may drive morphological changes.

Bland-Altman plots suggest that ultrasound may be an appropriate technique to measure changes in cartilage thickness compared to MRI, although cartilage thickness measures displayed a bias between imaging modalities at baseline. Cartilage thickness changes in this study showed little-to-no bias (0.00 mm for medial, 0.02 mm for lateral femoral cartilage), indicating excellent agreement between imaging modalities. However, ultrasound measures were approximately 0.5 to 0.7 mm larger than MRI measures at baseline. Differences between ultrasound and MRI measures may arise from the imaging parameters employed in this study. For instance, ultrasound measures were two-dimensional images taken in the transverse plane with the knee in full flexion (i.e., 140°), whereas MRI measures were derived from three-dimensional images in the sagittal plane with the knee in 20-30° flexion. These imaging parameters alter both the imaging plane and how the femur and tibia articulate and may consequently affect how cartilage thickness is displayed and measured. Additionally, ultrasound visualizes the anterior portion of the femoral condyles (108), while the weight-bearing portions of the femoral condyles were segmented using MRI (483). The weight-bearing aspects of the femoral condyles undergo the highest rate of cartilage thinning (496), and may help explain why MRI provided thinner cartilage measures compared to ultrasound. Measurement of different femoral sub-regions may promote improved absolute agreement between imaging modalities (445). Despite the offset between baseline ultrasound and MRI measures, current findings support the use of ultrasound to measure within-person changes in cartilage thickness that are comparable to MRI. Modified ultrasound imaging approaches, including patient positioning (e.g., 20-30° versus 140° flexion), imaging planes (e.g., medial or lateral joint line versus supra-patellar), or machine parameters (e.g., 3D versus 2D images) should be explored to determine whether different methodologies better replicate MRI findings.

Comparing responders versus non-responders, ultrasound-measured medial cartilage thickness responders displayed larger increases in peak knee flexion angles and moments. This relationship suggests that participants who exhibited more changes in their sagittal gait pattern following walking underwent more decreases in ultrasound-measured medial cartilage thickness, and aligns with evidence that states the knee flexion moment contributes to medial knee joint loading (236,237). Increased first peak knee flexion moment coupled with more cartilage thickness decreases collectively suggest increased compressive forces and overall knee joint loading (110,304,497), which may have important implications for clinical and structural knee osteoarthritis progression (90,91). Interestingly, overground and treadmill walking speeds were not different between structural responder and non-responder groups, which is in contrast to previous findings that associated slower walking speeds with larger decreases in ultrasound-measured cartilage thickness following 30-minutes of walking in healthy younger adults (447).

Differences between the current and previous findings may be explained by cartilage health whereby healthy and pathological tissues may respond to loading differently (87), or by the increased BMI of the current sample group since BMI has been shown to moderate the relationship between gait parameters and cartilage response (309,447). These results represent a preliminary understanding of how structural responders and non-responders may biomechanically differ and suggest an interplay between biomechanical and structural outcomes, requiring further investigation. Also, whether acute biomechanical changes precede or follow structural joint changes should be explored.

Pain responders and non-responders did not differ based on changes in biomechanical outcomes, although pain responders had a higher knee adduction moment impulse at baseline. This relationship aligns with previous research that has demonstrated independent associations between higher knee adduction moment impulse and increased knee pain in moderate knee osteoarthritis populations (118,241,498). Higher knee adduction moment impulse, but not peak, suggests other gait characteristics that influence the shape and consequently increase the area under the knee adduction moment curve (e.g., less mid-stance unloading) may contribute to increased knee pain following walking (111). These findings also have implications for understanding the relationship between pain and structural changes because higher knee adduction moment impulse has been cross-sectionally associated with thinner medial cartilage (306). Although cartilage thickness and pain response were not significantly related in this study, most cartilage thickness responder groups tended to report higher pain at baseline (i.e., approximately 1.2 points for responders and 0.5 points for non-responders). Therefore, pain may be an important indicator of both biomechanical and structural features, and interrelationships between knee pain, joint loading, and structural changes should be confirmed with larger samples.

This study is the first to our knowledge to examine potential relationships between biomechanical, structural, and patient-reported knee osteoarthritis outcomes immediately following a continuous bout of walking. However, there are limitations that should be acknowledged. Firstly, there are potential limitations in the definitions of structural imaging responders and non-responders as defined in this study. Non-responders were defined as individuals whose cartilage thickness increased following walking, but this may suggest an alternative physiological or patient-specific response (rather than non-response) that warrants further investigation. Additionally, absolute increases and decreases in cartilage thickness were used to dichotomize participants into responder groups; however, this resulted in poor agreement between imaging modalities. Although the current sample group did not permit dichotomization based on MDC thresholds because few participants surpassed these change metrics, future research should consider defining responders and non-responders based on established MDC thresholds (108,303,494). Secondly, participants completed the 30-minute continuous walking bout on a treadmill during both data collection visits, which has been shown to alter participant energy expenditure compared to overground walking (499). Nevertheless, participants in this study achieved the recommended aerobic training intensity as prescribed in physical activity guidelines (466). Finally, this study is under sampled due to restrictions imposed by the COVID-19 pandemic, driving our descriptive approach.

5.5 Conclusion

A single, 30-minute continuous bout of walking at participant self-selected speed was prescribed to individuals with mild-to-moderate knee osteoarthritis. Participants reported a significant, but not clinically meaningful, increase in knee pain, and achieved the recommended moderate intensity aerobic physical activity threshold based on age-adjusted heart rate. The walking bout elicited increases in overground gait speed, indicative of functional improvement, and increases in peak knee flexion and adduction moments, indicative of increased knee joint loading. No changes were observed in ultrasound or MRI-measured cartilage thickness in the medial or lateral femoral condyles following walking. Ultrasound and MRI demonstrated agreement for measuring within-person changes in cartilage thickness, but not baseline metrics. Sub-group analyses suggested potential relationships between biomechanical, structural, and patient-reported outcomes, worthy of future investigation. Current findings can be used to inform larger studies and future work should consider concurrent knee osteoarthritis outcomes to optimize exercise prescription for knee osteoarthritis populations incorporating biomechanical, structural, and patient-reported outcomes.

Chapter 6 Discussion and Conclusions

6.1 Summary of Findings

The overall aim of this thesis was to better understand whether and how physical activity, particularly walking, is prescribed to manage knee osteoarthritis, and to add to our understanding of the effects of walking on quantitative joint health outcomes for individuals with knee osteoarthritis. This was achieved within three study chapters: Chapter 3, a healthcare quality survey for individuals with mild-to-moderate knee osteoarthritis; Chapter 4, a systematic review and meta-analysis of the effects of walking interventions on quantitative biomechanical and structural knee osteoarthritis outcomes; and Chapter 5, a laboratory-based study on the immediate biomechanical, structural, and patient-reported effects of a 30-minute continuous walking bout for knee osteoarthritis.

6.1.1 Summary of Chapter 3

Chapter 3 addressed the first objective of this thesis, which was to evaluate the quality and types of care individuals with mild-to-moderate knee osteoarthritis receive in the Maritime provinces of Canada. Chapter 3 contributed to the overall purpose of this thesis by examining whether physical activity is prescribed for individuals with knee osteoarthritis, along with other types of core treatment. This multi-provincial dataset provides insight into the non-surgical and non-pharmacological care pathways implemented for mild-to-moderate knee osteoarthritis, and highlights gaps in knee osteoarthritis management, particularly related to exercise prescription and weight management in this mild-to-moderate knee osteoarthritis group.

The results from Chapter 3 indicate that the overall quality of care for individuals in the Maritime provinces of Canada is sub-optimal, where under half of the survey respondents (approximately 43-49%) received recommended core treatment across four healthcare quality indicators. Examining specific quality indicators, approximately 62-69% of eligible participants received advice to exercise, and 26-35% received advice to lose weight. There were no significant associations between the quality and types of care and any patient demographic (age or sex), social (education level or employment), or patient-reported outcomes (WOMAC, KOOS-Sport, ICOAP, EQ-5D-5L, Oxford Knee Score) in the adjusted logistic regression models. However, these findings may be limited by the relatively small sample size and low survey response rate.

6.1.2 Summary of Chapter 4

Chapter 4 addressed the second objective of this thesis, which was to review, synthesize, and evaluate the strength of the evidence quantifying the effects of walking interventions on quantitative biomechanical and structural knee osteoarthritis outcomes. Chapter 4 contributed to the overall purpose of this thesis by examining how walking is currently prescribed for individuals with knee osteoarthritis and summarizes existing literature on the effects of walking interventions on quantitative biomechanical and structural knee osteoarthritis outcomes. This chapter was motivated by the moderate pass-rates for advice to exercise observed in Chapter 3. A summary of existing evidence was needed to address the quantitative joint health effects of walking for individuals with knee osteoarthritis. This evidence can determine whether it offers clinical benefit for healthcare providers to prescribe walking for knee osteoarthritis populations, with a goal of increasing exercise-related healthcare quality and informing walking prescription parameters.

The findings from Chapter 4 suggest that prescribed walking exercise, alone or within a multi-modal exercise program, elicits moderate improvements in gait speed, small-to-no changes in biomechanical metrics, and minimal-to-no changes in structural outcomes. Despite small increases in joint loading metrics, structural changes suggest that walking interventions do not worsen knee osteoarthritis structural progression beyond natural changes. Prescribed walking parameters varied, and 30-minutes of walking at participant self-selected speed were the most prescribed duration and intensity, respectively, across the literature. Walking parameters had little-to-no associations with biomechanical outcomes, although longer intervention lengths were associated with lower peak knee flexion moments. Most of the included studies were excellent quality. Gaps in the literature were identified, particularly related to the immediate effects of a single walking bout, and simultaneous evaluation of biomechanical and structural imaging outcomes. Chapter 4 suggests that walking interventions elicit minimal quantitative joint health effects for individuals with knee osteoarthritis.

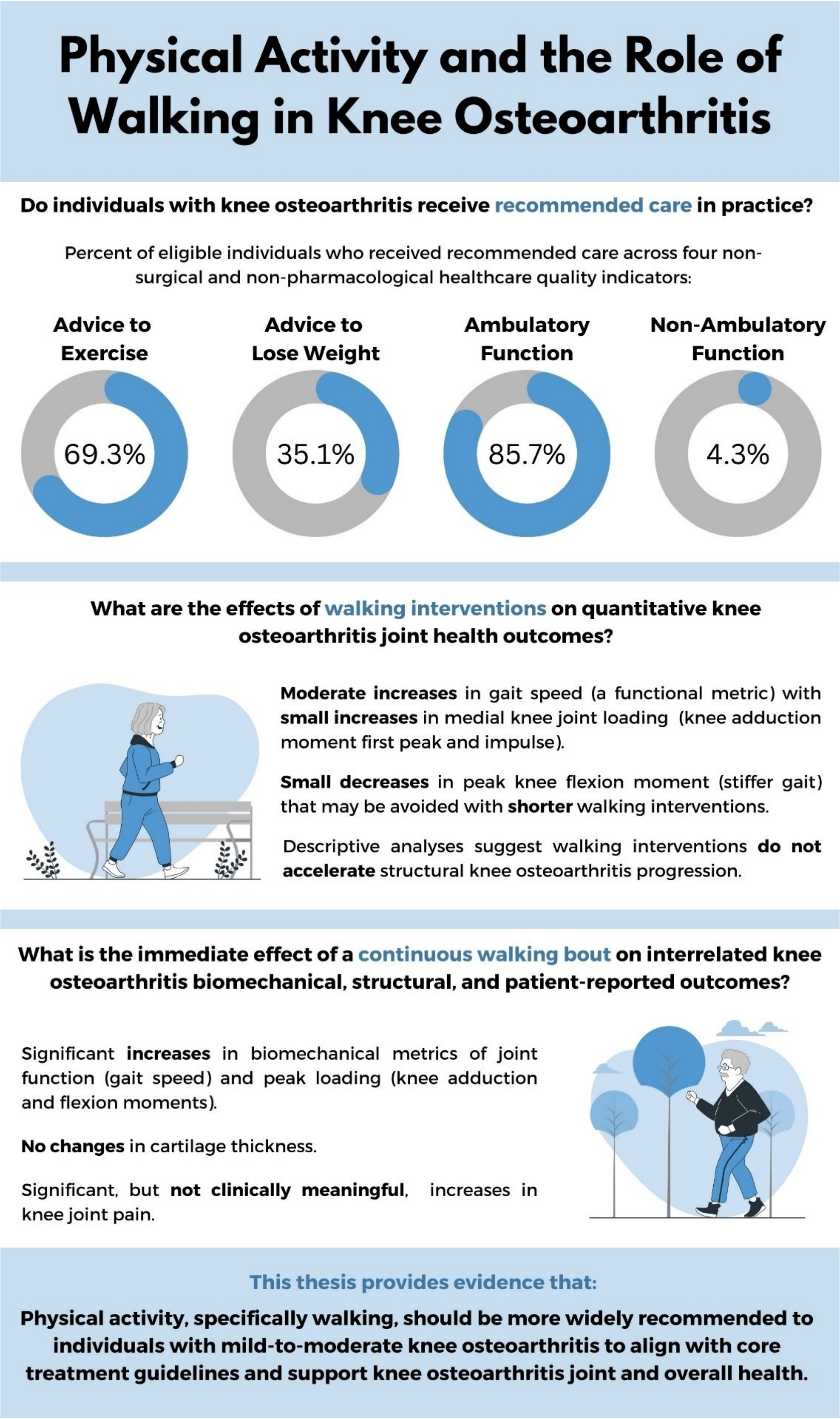
6.1.3 Summary of Chapter 5

Chapter 5 addressed the third objective of this thesis, which was to determine the immediate effect of a 30-minute continuous walking bout on biomechanical, structural, and patient-reported outcomes in individuals with knee osteoarthritis. Chapter 5 contributed to the overall purpose of this thesis by examining the immediate effects of walking on biomechanical, structural, and patient-reported knee osteoarthritis outcomes, thus adding to our current understanding of the effects of walking on quantitative joint health. This chapter was motivated by the gaps in the literature identified in Chapter 4, where very few studies have reported the immediate quantitative effects of walking on knee osteoarthritis joint health or concurrent biomechanical and structural findings. This study also adds to the current literature by evaluating patient-reported and cardiovascular outcomes, particularly pain response and heart rate, during and following a continuous bout of walking, and examines relationships with quantitative joint health outcomes.

Results from Chapter 5 demonstrate that a continuous 30-minute bout of walking increased gait speed and peak knee joint loading, but not total loading exposure, for individuals with mild-to-moderate knee osteoarthritis. These biomechanical changes were accompanied by a significant, but non-clinically meaningful, increase in pain and no changes in cartilage thickness measured using ultrasound or MRI. This mild-to-moderate knee osteoarthritis group achieved the recommended moderate exercise intensity threshold while walking at their self-selected speed based on age-adjusted heart rate data. Sub-group analyses revealed that participants who increased pain following the 30-minute walk had higher knee adduction moment impulse at baseline, and those who exhibited higher peak knee flexion angles and moments following continuous walking underwent more ultrasound-measured medial cartilage deformation. Findings from the sub-group analyses suggest potential relationships between biomechanical, structural, and patient-reported outcomes. Additionally, Bland-Altman plots indicated that within-person ultrasound-measured cartilage thickness changes are comparable to MRI findings, but a measurement offset may exist. Overall, findings from Chapter 5 indicate that a 30-minute continuous bout of walking immediately increases gait speed and peak knee joint loading, but not total loading exposure, does not meaningfully increase pain, and does not influence cartilage thickness measures.

6.2 Implications and Clinical Significance

Knee osteoarthritis is a multifactorial condition that results from interactions between mechanical, inflammatory, and biological components, influencing patient symptoms and knee joint structure. Core treatments, including physical activity and therapeutic exercise, are widely recommended to manage knee osteoarthritis illness (i.e., clinical symptoms) and disease (i.e., joint-level structural change) components. Walking represents a type of core treatment that can be incorporated as a form of physical activity (i.e., during activities of daily living to increase overall physical activity levels) or therapeutic exercise (i.e., prescribed within a walking bout) to improve interrelated knee osteoarthritis outcomes. By examining healthcare quality and quantitative walking intervention outcomes, this thesis provides evidence for the suitability of walking as a form of physical activity or therapeutic exercise in individuals with knee osteoarthritis, incorporating biomechanical, structural, and patient-reported outcomes. Findings from Chapter 3 demonstrate that healthcare quality requires improvements to align with recommended core treatment, and not all individuals with mild-to-moderate knee osteoarthritis receive advice to exercise. Moderate pass-rates for advice to exercise, as well as low pass rates for advice to lose weight, represent key healthcare delivery factors requiring more attention. Individuals with knee osteoarthritis should be encouraged to participate in exercise, and clinicians should prescribe exercise, including walking, to align with best practice guidelines and improve patient outcomes including joint health (Figure 6.1).



Physical Activity and the Role of Walking in Knee Osteoarthritis

Do individuals with knee osteoarthritis receive recommended care in practice?

Percent of eligible individuals who received recommended care across four non-surgical and non-pharmacological healthcare quality indicators:

Advice to Exercise	Advice to Lose Weight	Ambulatory Function	Non-Ambulatory Function
69.3%	35.1%	85.7%	4.3%

What are the effects of walking interventions on quantitative knee osteoarthritis joint health outcomes?

Moderate increases in gait speed (a functional metric) with **small increases** in medial knee joint loading (knee adduction moment first peak and impulse).

Small decreases in peak knee flexion moment (stiffer gait) that may be avoided with **shorter** walking interventions.

Descriptive analyses suggest walking interventions **do not accelerate** structural knee osteoarthritis progression.

What is the immediate effect of a continuous walking bout on interrelated knee osteoarthritis biomechanical, structural, and patient-reported outcomes?

Significant **increases** in biomechanical metrics of joint function (gait speed) and peak loading (knee adduction and flexion moments).

No changes in cartilage thickness.

Significant, but **not clinically meaningful**, increases in knee joint pain.

This thesis provides evidence that:

Physical activity, specifically walking, should be more widely recommended to individuals with mild-to-moderate knee osteoarthritis to align with core treatment guidelines and support knee osteoarthritis joint and overall health.

Figure 6.1. Infographic summary of findings from thesis chapters 3, 4, and 5.

Moderate pass-rates for advice to exercise may be driven by the lack of clear exercise prescription guidelines for knee osteoarthritis populations (61,62,115,257,258). Although general aerobic physical activity (24,45,47,48,67) and walking (265) guidelines exist, they are primarily based on patient-reported and cardiovascular improvements and do not consider quantitative joint health outcomes. Evidence suggests that aerobic exercise is currently inadequately prescribed to individuals with knee osteoarthritis to elicit optimal cardiovascular and systemic health benefits (266). Accordingly, walking prescription parameters varied across the literature for studies reporting quantitative biomechanical or structural outcomes in Chapter 4. A 30-minute bout of walking was the most prescribed duration across both single-bout and repeated walking exposures, which aligns with current recommendations (24,45,47,48,67). Chapter 5 findings suggest that 30-minutes of continuous walking is likely beneficial for quantitative functional, biomechanical, and structural outcomes, and does not exacerbate knee pain. Specific walking bout parameters (e.g., bout duration, frequency) were not shown to contribute to observed changes in biomechanical joint health outcomes in meta-regressions in Chapter 4. This thesis adds to the current evidence directly comparing the effect of different walking parameters on knee osteoarthritis outcomes (79,80,96,274); however, the optimal walking dosage remains unknown (21,63,64). More evidence is needed to compare the effect of varying walking parameters on biomechanical, structural, and patient-reported knee osteoarthritis outcomes to inform disease-specific physical activity and exercise prescription guidelines (21).

Individuals with knee osteoarthritis generally do not achieve recommended physical activity levels (58,360). Physical activity may be limited by patient-reported fears of joint damage or increased knee pain as a result of physical activity, despite individuals with knee osteoarthritis acknowledging the physical and psychological benefits of physical activity (116,280,343,500). Walking is a simple and accessible way of engaging in physical activity, and has been deemed a safe, low-cost aerobic activity for individuals with knee osteoarthritis (18,46,264). It remains difficult to draw conclusions about how knee osteoarthritis populations can safely engage in walking as a form of activity due to the low amount of evidence quantifying disease-specific outcomes, large variability in walking prescriptions, and diverse outcomes reported across the literature. Chapter 4 suggests that walking interventions do not accelerate structural changes, although patient-reported outcomes (e.g., pain) fell outside the scope of the systematic review. Nevertheless, Chapter 5 findings demonstrate no structural changes after a single bout of walking, with minimal-to-no increases in knee joint pain. Importantly, a sub-group of participants reported no changes or decreases in pain, signifying that pain response to continuous walking may be patient-specific rather than a universal adverse response. Observed pain responses are consistent with previous work that stated not all individuals with knee osteoarthritis increase pain following a bout of walking, and patient-specific response may be related to biomechanical, neuromuscular, or inflammatory factors (81,111,112,291). A best-evidence synthesis of the effect of walking interventions on patient-reported knee osteoarthritis outcomes would inform the efficacy of walking for knee pain in addition to the current findings. Translation of findings is needed to address patient fears of engaging in physical activity and contribute to patient education to support increased physical activity levels.

Quantitative biomechanical and structural effects of walking exercise interventions were examined within the current literature (Chapter 4) and immediately following a 30-minute continuous bout of walking (Chapter 5) to better understand the effects of walking on knee osteoarthritis joint health. Findings suggest that biomechanical and structural changes following an acute bout of walking are largely consistent with observed changes following repeated walking interventions, which may indicate that a single bout of walking is an appropriate model to infer more longitudinal effects of repeated walking programs. Although Chapter 5 is a first step toward addressing the limitations in the literature identified in Chapter 4, additional research is needed to confirm the relationships between the acute and longitudinal effects of walking interventions for knee osteoarthritis to thoroughly inform prescription and improve healthcare quality (Chapter 3).

Biomechanical results from Chapters 4 and 5 illustrate that walking, both following single-bout and repeated exposures, stimulates faster gait speeds and small increases in first peak knee adduction moment. Chapter 4 denotes a small increase in knee adduction moment impulse following repeated walking interventions, although few studies reported this outcome, and no increase in knee adduction moment impulse was observed following the walking bout in Chapter 5. Knee adduction moment impulse reflects both the magnitude and duration of loading per step; therefore, these findings suggest a small increase in peak loading, but potentially not total loading exposure, in the medial tibiofemoral compartment. Increases in knee adduction moment peak and impulse have been previously linked to clinical and structural knee osteoarthritis progression (90–95), indicating potentially negative effects of walking. However, the increases in first peak knee adduction moment may be explained by the concurrent increases in gait speed (415). Indeed, these changes may indicate a net positive effect of walking exercise because despite higher peak medial compartment loading, faster walking reduces overall loading exposure in the medial compartment (416). Therefore, the functional improvements in gait speed may offset the potentially negative increases in peak medial knee joint loading following prolonged walking. Biomechanical changes following continuous walking, particularly immediate changes, illustrate increased peak loading, but not total loading exposure, partnered with functional improvements and minimal-to-no increases in knee joint pain. Along with previously reported improvements in general health following walking interventions (277,310,361,362), the results of this thesis support the prescription of walking to improve functional biomechanical knee osteoarthritis outcomes.

Further, peak knee flexion moment increased immediately following continuous walking (Chapter 5). The external knee flexion moment is indicative of the net muscle contribution to joint loading (408,409), is associated with prolonged muscle activity (501), and contributes to medial knee contact forces (236,237,410). However, this increase in sagittal plane loading may represent a positive effect of walking exercise given that it was paired with an increase in peak knee flexion angle during stance, suggesting improved knee joint function, and that lower peak knee flexion moments have been associated with knee osteoarthritis progression (90,91). Conversely, these improvements were not sustained following repeated walking interventions (Chapter 4), where small decreases in peak knee flexion moments were observed, indicative of lower joint loading and a stiffer-knee gait pattern. Meta-regression results suggest that shorter walking interventions may attenuate the potential negative effects of walking interventions on peak knee flexion moments. Previous research has suggested that shorter walking durations (i.e., interval walking) mitigate potentially negative effects of continuous walking on joint contact forces, cartilage oligomeric matrix protein (COMP) concentrations, a serum biomarker linked to cartilage breakdown, and knee pain (79,80,96). Chapter 5 reports no significant increases in pain at

10- or 20-minutes of walking, and walking for 10-minutes per day has been deemed effective for providing cardiovascular benefits without exacerbating knee pain (277). Therefore, current and previous evidence supports the prescription of shorter walking bouts or interventions to improve cardiovascular health, not exacerbate knee pain, achieve immediate functional benefits (Chapter 5), and avoid potentially deleterious acute or more longitudinal effects of walking exercise on knee joint health (Chapter 4).

Noted changes in biomechanical outcomes did not result in structural changes, further supporting the efficacy of walking exercise for knee osteoarthritis populations. Findings suggest that a continuous bout of walking does not result in immediate structural effects (Chapter 5). Additionally, minimal-to-no structural effects were noted following repeated walking interventions (Chapter 4), and changes did not exceed previously established natural progression thresholds (298,427). Structural imaging responders and non-responders were identified in Chapter 5. Although cartilage deterioration is traditionally considered the hallmark of the disease, cartilage responsiveness to walking exercise is not consistent among individuals with knee osteoarthritis. Exploratory analyses indicated potential biomechanical contributions to structural imaging responder sub-groups, and future work should build on these findings by investigating patient-specific biomechanical and structural response to walking. Whether other structural findings that have been associated with knee pain, including effusion and synovitis (222–225), osteophytes (224), cartilage lesions (223,227), bone marrow lesions (222,225), or meniscal tears (223), may better explain patient-reported or biomechanical findings warrants consideration. This thesis provides encouraging evidence that walking does not negatively influence knee osteoarthritis joint structure or accelerate structural disease processes.

Chapter 5 was the first study to our knowledge to examine the clinical utility of ultrasound compared to MRI findings in knee osteoarthritis populations following an acute bout of walking. The results suggest that ultrasound may be a valid clinical tool to assess immediate changes in knee cartilage morphology compared to MRI. However, the absolute agreement between imaging modalities is questionable and may be attenuated by different imaging planes or anatomical regions. These findings are consistent with previous work comparing ultrasound- and MRI-measured cartilage thickness in healthy populations that reported poor absolute agreement between modalities (444). In contrast to Chapter 5 findings that demonstrated ultrasound measures were 0.5 mm to 0.7 mm larger than MRI, previous work reported ultrasound measures were 1.9 mm to 2.8 mm smaller than MRI in healthy individuals (444). These offsets represent similar magnitudes since they represent approximately 50% of baseline cartilage thickness. More work is needed to improve the criterion validity of baseline cartilage thickness measures obtained using ultrasound compared to MRI in healthy and osteoarthritic populations. Nevertheless, ultrasound represents a valid clinical tool to quantify within-person changes that are comparable to MRI and could be used to reliably measure intervention effectiveness or aspects of disease progression within an individual. Considering the clinical and point-of-care accessibility afforded by ultrasound imaging compared to MRI, clinicians may be encouraged to use ultrasound as a preliminary tool to estimate knee osteoarthritis cartilage health.

Knee osteoarthritis is a progressive disease often beginning with mild knee pain or other symptoms and minimal structural changes (502), culminating with severe pain, functional limitations, and end-stage joint failure. Interventions employed earlier in the disease process offer the highest potential to slow or stop knee osteoarthritis progression

(41–44). Walking for physical activity or therapeutic exercise reflects core treatment that is recommended for almost all individuals with knee osteoarthritis (18–25) and may contribute to lowering other risk factors for progression (e.g., weight gain) or comorbidities that worsen prognosis (74,503). Results from this thesis suggest that walking is appropriate for individuals with mild-to-moderate knee osteoarthritis. However, Chapter 4 is limited by a lack of consistent reporting of disease severity across walking intervention studies. This omission poorly aligns with what is already understood about progressively worsening gait biomechanics associated with increasing knee osteoarthritis severity (84,234) that implies different severity groups may respond to walking interventions differently. Further, Chapter 3 and previous evidence (36) suggested potential associations between patient-reported outcomes and healthcare quality, collectively indicating that knee osteoarthritis severity may influence both provision of and response to interventions. It is imperative to examine the effectiveness of core treatments as they can be suitably recommended for all individuals with knee osteoarthritis. More knowledge on core treatments, including walking as a form of physical activity or prescribed as a bout of therapeutic exercise, would determine whether these treatments can be further optimized for specific severity levels as knee joint symptoms and structural changes progress.

Chapter 4 highlights potentially different biomechanical effects of isolated walking interventions compared to multi-modal exercise. Isolated walking exercise provided no significant effects to discrete biomechanical metrics, whereas multi-modal exercise provided a small increase in knee adduction moment impulse, small decrease in peak knee flexion moment, and moderate increase in gait speed. Interestingly, a recent network meta-analysis deemed multi-modal exercise the least effective exercise type for patient-reported outcomes, whereas aerobic activities were most beneficial for pain and physical performance measures (344). Therefore, isolated walking exercise is likely an effective activity type to improve pain with minimal effects on joint loading. Although it is outside the scope of this thesis to directly compare joint loading across different types of activities, previous research has quantified the biomechanical effects of different aerobic activities. For instance, evidence suggests that walking results in lower knee joint loading than running (504), but higher than cycling or aquatic walking (505,506). Additionally, tai chi elicits lower peak knee adduction moment but longer time to achieve peak loading than walking (507). These results collectively suggest that other land- or water-based aerobic activities may alter knee joint loading magnitudes and patterns compared to walking, which may have implications for knee osteoarthritis joint health. However, walking is an accessible activity that can be done anywhere without specialized equipment, whereas other activities require special facilities (e.g., pool), equipment (e.g., bicycle), or training (e.g., tai chi expertise), and may be less appropriate for many individuals. Clinical practice guidelines state no clear preference between types of activities for improving pain and physical function (19,22,65,244); thus, exercise prescription should be based on patient preference to improve adherence (352) and increase physical activity levels.

This thesis addresses three of the key research recommendations provided by the ACR to improve exercise-based management of knee osteoarthritis (21). The first recommendation noted that there is currently insufficient evidence to prescribe the ideal exercise type and dosage (i.e., duration, intensity, and frequency) for knee osteoarthritis populations, and called for direct measurement of different exercise parameters on joint health. This thesis adds to the current literature by summarizing the prescribed walking intervention parameters for knee osteoarthritis (Chapter 4) and investigating the effects of 30-minutes of continuous walking, the most recommended duration of walking exercise, on direct measures of joint health (Chapter 5). The second recommendation stated that exercise-based research should consider disease location and severity, as well as exercise intensity, to optimize individualized exercise prescription. This thesis focused on a mild-to-moderate knee osteoarthritis group (Chapters 3, 4, and 5), summarized walking intensities prescribed within existing interventions (Chapter 4) and monitored clinical exercise intensity within a continuous walking bout (Chapter 5). Finally, the third recommendation noted that pre and post intervention measurement of cardiovascular and musculoskeletal fitness is needed. This thesis objectively monitored heart rate before, during, and after the continuous walking bout (Chapter 5) and found that a self-selected walking speed for individuals with knee osteoarthritis is sufficient to achieve moderate exercise intensity. Therefore, this thesis addresses noted gaps in the current literature and adds to our understanding of the effects of walking bouts and interventions on knee osteoarthritis joint health.

Overall, findings from this thesis suggest that physical activity, specifically walking, should be more widely recommended to individuals with mild-to-moderate knee osteoarthritis to align with core treatment guidelines and improve knee osteoarthritis joint health. Walking is an accessible, widely implemented activity that can be prescribed within structured bouts of aerobic exercise or implemented more broadly to increase physical activity levels and improve overall health and knee osteoarthritis outcomes. Results of this thesis can be used to address patient fears of engaging in physical activity by providing evidence that walking exercise provides functional benefit by increasing gait speed, does not structurally damage the joint, and does not exacerbate knee pain for most individuals. Additional pre and post walking interventions are needed to test the effects of differing walking parameters on various severities of knee osteoarthritis to thoroughly inform disease-specific walking prescription guidelines for knee osteoarthritis populations (21).

6.3 Limitations and Future Directions

Restrictions from the COVID-19 pandemic impacted participant recruitment for this thesis. The timing of the healthcare quality survey (sent in 2020) likely contributed to the low survey response rate in Chapter 3. Therefore, the large variability and relatively small sample size compared to other previous Canadian healthcare quality surveys (34,36) likely contributed to the lack of statistically significant findings. Further, research and healthcare restrictions interrupted and negatively influenced participant recruitment for Chapter 5; the resulting small sample size drove the descriptive approach. Nevertheless, the noted trends within these study chapters align with previous literature. Current findings should be confirmed with larger sample sizes and used to inform future studies on the effects of physical activity and walking exercise on knee osteoarthritis outcomes.

This thesis primarily focused on individuals with mild-to-moderate knee osteoarthritis. Participants were identified as having mild-to-moderate knee osteoarthritis based on patient-reported questionnaire responses that indicated relatively low levels of pain and physical dysfunction, along with moderate-to-high physical activity levels (Chapters 3 and 5), or through radiological grading (Chapter 4). Though relatively healthy individuals with knee osteoarthritis represent an important target group for earlier intervention, these sample groups represent a less clinically severe cohort compared to the wider Canadian population with knee osteoarthritis (508). Thus, results from this thesis may have limited generalizability but should not downplay the importance of optimizing disease management earlier in the disease course. Findings should be confirmed with groups of participants who have more baseline cartilage damage or severe pain, factors that have been shown to predict structural disease progression in conjunction with higher physical activity levels (305,509). Incorporating more diverse samples to determine the effects of walking on individuals with knee osteoarthritis may further aid in prescribing physical activity and exercise across emerging osteoarthritis phenotypes (510–513).

This thesis found that females may be more likely to receive recommended care compared to males but did not evaluate sex-specific walking effects. However, evidence suggests that females and males with knee osteoarthritis may differ biomechanically, structurally, and by pain response. Biomechanically, females, compared to males, have been shown to walk with smaller knee adduction moment features, including peaks (514–516), impulse (515), and overall magnitude (517). Additionally, recent work demonstrated sex differences in response to a 30-minute continuous walk where males, but not females, increased knee adduction moment first peak and impulse (112). Structurally, females, compared to males, have smaller cartilage volume (518–520), thickness (520), and surface area (521), and higher T1-rho relaxation times, indicating worse cartilage composition and lower proteoglycan content (515). In a healthy population, at baseline in females but not males, thinner anterior femoral cartilage was associated with higher resting COMP concentrations, although COMP response and cartilage deformation following continuous walking were not sex-specific (119). Finally, females, compared to males, typically report higher pain intensities (268,522–524), more widespread pain (524,525), and greater sensitivity to experimental pain (112,525). Although no sex differences were observed

Chapter 5, females, but not males, have also demonstrated decreased pain sensitization following a 30-minute walk (112). These findings collectively suggest sex differences at baseline and following continuous walking, whereby females may exhibit healthier gait patterns but have worse structural findings, as well as higher pain at baseline with more improvements following walking. Therefore, future research should aim to further examine sex differences in biomechanical, structural, and pain responses, and determine whether there are sex-specific relationships between interrelated knee osteoarthritis outcomes at baseline or following a continuous bout of walking. Knowledge on sex-specific walking effects could be used to inform, or confirm the need for, sex-specific walking guidelines.

Although Chapter 5 investigated morphological cartilage changes following a continuous bout of walking, it did not consider changes in cartilage composition that may drive changes in morphology. Cartilage response to loading has been proposed as a surrogate measure of cartilage composition (101), although changes in cartilage composition can be measured directly using MRI via T1-rho or T2 relaxometry. Direct changes in cartilage composition have been examined following a bout of running in individuals with knee osteoarthritis (526) and healthy populations (215,304,373,526), but Chapter 4 identified that compositional metrics have not yet been investigated in knee osteoarthritis populations following single-bout or repeated walking. Changes in cartilage composition occur pre-morphologically and have been associated with longitudinal structural disease progression (104,105); therefore, compositional changes represent important markers of cartilage health, particularly at early stages of knee osteoarthritis. Examining the acute effects of continuous walking on cartilage composition may provide a more in-depth analysis of physiological cartilage response and may augment Chapter 5 findings by further informing compositional changes associated with structural responder sub-groups. Concurrent morphological and compositional changes examined in response to continuous walking would further add to our understanding of how prolonged loading activities comprehensively influence knee osteoarthritis cartilage health and may be associated with structural disease progression.

The discrete biomechanical metrics examined in Chapter 5 were selected to align with previous work highlighting relationships between discrete knee adduction and flexion moment features and structural knee osteoarthritis progression (91,93,95). The discrete metrics also align with metrics most frequently reported in the literature following walking interventions, as summarized in Chapter 4. However, the inconsistent relationship between knee adduction moment first peak and impulse in Chapters 4 and 5 indicates that other features of the knee adduction moment waveform may contribute to total medial compartment loading exposure. Previous work has examined patterns (rather than discrete metrics) of knee joint loading. A primary pattern, higher knee adduction moment overall magnitude, is highly indicative of increased knee adduction moment impulse (527). This pattern and others, including larger early to midstance difference (90,93), as well as smaller knee flexion-extension moment difference (90), have been shown predict clinical and structural knee osteoarthritis progression. Recent evidence suggested that individuals with knee osteoarthritis improved their walking patterns after a 30-minute walk, and those who increased pain following the walk had worse baseline walking patterns (111). Exploring gait patterns and how they change after an acute bout of walking may better inform the potential associations with pain and structural responses. Additionally, neuromuscular activation patterns, including higher and prolonged quadriceps and hamstrings muscle activity (93,366,528), have also been linked to clinical and structural knee osteoarthritis progression. Acute effects of walking on neuromuscular outcomes could help understand exercise intensity and exertion if muscle activity increases in this population.

6.4 Conclusion

In conclusion, individuals with mild-to-moderate knee osteoarthritis receive sub-optimal healthcare quality in the Maritime provinces, and physical activity, particularly walking, should be more widely recommended to align with recommended core treatment and support knee osteoarthritis joint and overall health outcomes. This thesis provides encouraging evidence that walking exercise elicits minimal-to-no effect on biomechanical metrics indicative of increased joint loading, or structural progression measures. A continuous 30-minute walking bout at participant self-selected speed increased overground gait speed and biomechanical outcomes indicative of increased joint loading, with minimal-to-no effect on structural imaging measures and a non-clinically meaningful increase in knee joint pain. Therefore, walking is likely a suitable activity for individuals with mild-to-moderate knee osteoarthritis because it acutely improves how individuals walk and outcome responses were not suggestive of detrimental knee osteoarthritis pain increases or markers of structural progression.

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Appendix A: Study 1 Research Ethics Board Approval (File # 1025913)

Nova Scotia Health Research Ethics Board
Centre for Clinical Research, Room 118
5790 University Avenue
Halifax, Nova Scotia, Canada B3H 1V7
shelleyl.macdonald@nshealth.ca

August 24, 2020

Dr. Rebecca Moyer
Medicine\Surgery\Orthopedic Surgery
5869 University Avenue
PO Box 15000
School of Physiotherapy, Room 316
Halifax NS B3H 4R2

Delegated Review
Full Approval Letter
(August 24, 2020 to August 24, 2021)

Dear Dr. Moyer:

RE: Current Management and Health Care Quality for Patients with Knee and Hip Osteoarthritis Across the Maritime Provinces

REB File #: 1025913

Thank you for your response regarding your proposed study.

Document Name	Comments	Version Date
Investigator Response/Revisions	Cover Letter	2020/08/17
Consent Form	Non Interventional Informed E-consent Form	2020/08/11
Supporting Materials	Appendix: Oxford Hip Score	1996/01/01
Supporting Materials	Appendix: Oxford Knee Score	1998/01/01
Supporting Materials	Appendix: BC Arthritis Survey	2020/08/11

I have reviewed these documents on behalf of the Nova Scotia Health Research Ethics Board and note that all requested changes have been incorporated.

I am now pleased to confirm the Board's full approval for this research study, effective today. This includes approval / favorable opinion for the following study documents:

Document Name	Comments	Version Date
Researcher's Checklist for Submission	Researcher Checklist	2017/02/17
Investigator Response/Revisions	Cover Letter	2020/08/17
Letter of Support	PI Department Letter	2020/06/17
Review Comments/Correspondence	Reviewer Comments	2020/06/17
Review Comments/Correspondence	Reviewer Comments	2020/06/17
Review Comments/Correspondence	Reviewer Comments	2020/06/17
Consent Form	Non Interventional Informed E-consent Form	2020/08/11
Research Protocol	Research Protocol	2020/06/29
Supporting Materials	Appendix: Oxford Hip Score	1996/01/01
Supporting Materials	Appendix: Oxford Knee Score	1998/01/01
Supporting Materials	Appendix: BC Arthritis Survey	2020/08/11
Supporting Materials	Appendix: ICOAP Hip	2007/11/19
Supporting Materials	Appendix: ICOAP Knee	2007/11/19
Supporting Materials	Appendix: EQ5D	2020/06/29
Supporting Materials	Appendix: KOOS	2020/06/29
Supporting Materials	Appendix: Email Template	2020/06/29
Supporting Materials	Appendix: HOOS	2020/06/29
Certificate of Completion TCPS 2: CORE	TCPS2: CORE Certificate	2014/04/17
Curriculum Vitae (CV)	Abbreviated PI CV	2020/01/24
Initial Letter - REB Use Only		2020/08/05

Continuing Review

1. The Board's approval for this study will expire one year from the date of this letter **August 24, 2021.** To ensure continuing approval, submit a Request for Annual Approval to the Board 2-4 weeks prior to this date. If approval is not renewed prior to the anniversary date, the Board will close your file and you must cease all study activities immediately. To reactivate a study, you must submit a new Initial Submission (together with the usual fee) to the REB and await notice of re-approval.

2. Please be sure to notify the Board of any:
* Proposed changes to the initial submission (i.e., new or amended study documents or supporting materials),
* Additional information to be provided to study participants,
* Material designed for advertisement or publication with a view to attracting participants,
* Serious unexpected adverse reactions experienced by local participants,
* Unanticipated problems involving risks to participants or others,

* Sponsor-provided safety information,
* Additional compensation available to participants,
* Upcoming audits /inspections by a sponsor or regulatory authority,
* Premature termination / closure of the study (within 90 days of the event).

3. Approved studies may be subject to internal audit. Should your research be selected for audit, the Board will advise you and indicate any other requests at that time.

Important Instructions and Reminders

1. Submit all correspondence to Ethics Coordinator, Shelley MacDonald at the address listed at the top of this letter (do not send your response to the REB Chair or Co-Chair).
2. Login to the Research Portal; click Applications (Post Review), browse through files to locate the study in which you wish to make revisions to; click the Events Button and choose the type of revision you wish to make from the table provided; complete the electronic form and attach document under the attachments tab if required and Click on the Submit button.
3. Be sure to reference the Board's assigned file number, 1025913, on all communications.
4. Highlight all changes on revised documents, and remember to update version numbers and/or dates.

Best wishes for a successful study.

Sincerely,

Gredi Patrick, RN, BSc, MSN, MHSA, CHE

Co-Chair, Research Ethics Board

This statement is in lieu of Health Canada's Research Ethics Board Attestation:
The Research Ethics Board for Nova Scotia Health operates in accordance with:
- Food and Drug Regulations, Division 5 "Drugs for Clinical Trials Involving Human Subjects"
- Natural Health Products Regulations, Part 4 "Clinical Trials Involving Human Subjects"
- Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2)
- ICH Good Clinical Practice: Consolidated Guideline (ICH-E6)

cc: Research & Innovation

Appendix B: Replicating the British Columbia Osteoarthritis Survey

Methods: *Statistical Analysis*

Binary logistic regressions were used to determine associations between each quality indicator and four categorical independent variables: (2) age group (in years: <54, 55-64, 65-74, ≥75 [reference group]) (1) sex (female, male [reference group]), (3) education level (university degree, trade certificate, high school diploma [reference group], less than high school), and (4) employment (employed, unemployed/retired, retired due to medical reasons [reference group]). Models began with the number of comorbidities (maximum 12) and all two-way interactions between the four independent variables. Backward elimination was used to remove all non-significant terms, and the final models included the significant terms along with the independent variables and total WOMAC score. Outcomes are reported as unadjusted and adjusted odd's ratios (OR) and 95% confidence intervals (CI). An OR greater than 1 indicates a higher likelihood of the specified group receiving recommended care compared to the reference group. Statistical testing was performed using SPSS (IBM SPSS Statistics for Windows, Version 28.0.1.1 Armonk, NY), with an alpha value of 0.05 to represent statistical significance.

Results

There were no significant differences between age group, sex, education level, or employment factors for individuals who did, or did not, receive advice to exercise or advice to lose weight using the British Columbia Osteoarthritis Survey criteria (Table B.1) based on the analyses conducted by Li et al. (36).

Table B.1: Logistic regression models for advice to exercise and advice to lose weight.

Independent Variable	n (received care) / n (needed care)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Advice to exercise (no. eligible for analysis = 199) *			
Age, years (reference: ≥ 75)			
≤ 54	5/8	1.11 (0.23, 5.41)	0.97 (0.16, 5.95)
55-64	38/56	1.44 (0.60, 3.47)	1.60 (0.56, 4.58)
65-74	59/101	0.95 (0.44, 2.08)	0.94 (0.40, 2.21)
≥ 75	20/34	1	1
Sex (reference: Male)			
Female	97/153	1.22 (0.63, 2.35)	1.42 (0.66, 3.02)
Male	28/46	1	1
Education (reference: High school)			
University degree	72/99	2.25 (0.97, 5.21)	2.06 (0.85, 5.01)
Trade certificate	37/70	0.93 (0.39, 2.17)	0.74 (0.29, 1.85)
High school diploma	16/30	1	1
Employment (reference: Unemployed/retired)			
Employed	51/78	1.16 (0.63, 2.14)	0.94 (0.46, 1.92)
Retired for medical reasons	15/23	1.24 (0.48, 3.20)	1.88 (0.59, 6.04)
Unemployed/retired	59/98	1	1
WOMAC total score	-	0.98 (0.96, 1.00)	0.99 (0.97, 1.01)
Advice to lose weight (no. eligible for analysis = 139)			
Age, years (reference: ≥ 75)			
≤ 54	1/4	1.42 (0.12, 17.5)	2.04 (0.13, 31.2)
55-64	20/46	3.43 (0.89, 13.2)	4.26 (0.91, 19.9)
65-74	19/69	1.89 (0.50, 7.16)	1.91 (0.48, 7.65)
≥ 75	3/20	1	1
Sex (reference: Male)			
Female	34/103	1.40 (0.60, 3.26)	1.49 (0.57, 3.91)
Male	9/36	1	1
Education (reference: High school)			
University degree	18/57	1.20 (0.43, 3.32)	1.13 (0.37, 3.43)
Trade certificate	18/57	1.12 (0.40, 3.10)	0.79 (0.26, 2.45)
High school diploma	7/25	1	1
Less than high school	0/1	-	-
Employment (reference: Unemployed/retired)			
Employed	20/60	1.49 (0.68, 3.25)	0.75 (0.29, 1.97)
Retired for medical reasons	8/22	1.54 (0.55, 4.26)	0.87 (0.25, 3.09)
Unemployed/retired	15/57	1	1
WOMAC total score	-	1.00 (0.98, 1.03)	1.00 (0.98, 1.03)

Note: OR = Odds ratio. CI = confidence interval. * Number of comorbidities was significant for advice to exercise and remained in the model.

Appendix C: Full Systematic Review Search Strategy for Each Database

CINAHL

S1 (MH “Osteoarthritis, Knee”)

S2 (MH “Osteoarthritis+”)

S3 TI (osteoarthr* OR arthrosis OR arthritis OR gonarthrosis OR “degenerative joint disease” OR “musculoskeletal disease” OR “degenerative arthritis”)

S4 AB (osteoarthr* OR arthrosis OR arthritis OR gonarthrosis OR “degenerative joint disease” OR “musculoskeletal disease” OR “degenerative arthritis”)

S5 (S2 OR S3 OR S4)

S6 (MH “Knee”)

S7 (MH “Knee Joint+”)

S8 TI knee* OR AB knee*

S9 (S6 OR S7 OR S8)

S10 (S5 AND S9)

S11 (S1 OR S10)

S12 (MH “Exercise”)

S13 (MH “Physical Activity”)

S14 (MH “Walking”)

S15 (MH “Aerobic Exercises”)

S16 TI (exercis* OR physical activit* OR walk* OR aerobic*)

S17 AB (exercis* OR physical activit* OR walk* OR aerobic*)

S18 (S12 OR S13 OR S14 OR S15 OR S16 OR S17)

S19 (S11 AND S18)

Embase

1. 'knee osteoarthritis'/exp OR 'knee osteoarthritis'
2. 'osteoarthritis'/exp OR 'osteoarthritis'
3. osteoarthr$:ti,ab,kw OR arthrosis:ti,ab,kw OR arthritis:ti,ab,kw OR gonarthrosis:ti,ab,kw OR 'degenerative joint disease':ti,ab,kw OR 'musculoskeletal disease':ti,ab,kw OR 'degenerative arthritis':ti,ab,kw
4. #2 OR #3
5. 'knee'/exp OR knee
6. knee$:ti,ab,kw
7. #5 OR #6
8. #4 AND #7
9. #1 OR #8
10. 'exercise'/de OR 'exercise'
11. 'physical activity'/de OR 'physical activity'
12. 'walking'/exp OR 'walking'
13. 'aerobic exercise'/de OR 'aerobic exercise'
14. exercise$:ti,ab,kw OR 'physical activit$':ti,ab,kw OR walk$:ti,ab,kw OR aerobic$:ti,ab,kw
15. #10 OR #11 OR #12 OR #13 OR #14
16. #9 AND #15
17. #16 AND ('article'/it OR 'article in press'/it OR 'conference paper'/it)

PubMED

((("Osteoarthritis, Knee"[Mesh]) OR ((("Osteoarthritis"[Mesh]) OR (Osteoarthr*[Title/Abstract]) OR (arthrosis[Title/Abstract]) OR (arthritis[Title/Abstract]) OR (gonarthrosis[Title/Abstract]) OR (“degenerative joint disease” [Title/Abstract]) OR (“musculoskeletal disease” [Title/Abstract]) OR (“degenerative arthritis” [Title/Abstract])) AND ((“Knee joint”[Mesh]) OR (“Knee”[Mesh]) OR (knee*[Title/Abstract])))) AND (("Walking"[Mesh]) OR ("Exercise"[Mesh]) OR (Exercis*[Title/Abstract]) OR (“physical activit*”[Title/Abstract]) OR (Walk*[Title/Abstract]) OR (Aerobic*[Title/Abstract])))

SportDiscus

S1: SU Osteoarthritis

S2: TI osteoarthr* OR arthrosis OR arthritis OR gonarthrosis OR ‘degenerative joint disease’ OR ‘musculoskeletal disease’ OR ‘degenerative arthritis’

S3: AB osteoarthr* OR arthrosis OR arthritis OR gonarthrosis OR ‘degenerative joint disease’ OR ‘musculoskeletal disease’ OR ‘degenerative arthritis’

S4: S1 OR S2 OR S3

S5: SU Knee

S6: TI knee* OR AB knee*

S7: S5 OR S6

S8: S4 AND S7

S9: SU Exercise

S10: SU Physical activity

S11: SU Walking

S12: SU Fitness walking

S13: SU Aerobic exercises

S14: TI exercis* OR ‘physical activit*’ OR walk* OR aerobic*

S15: AB exercis* OR ‘physical activit*’ OR walk* OR aerobic*

S16: S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15

S17: S8 AND S16

Scopus

1 TITLE-ABS-KEY (“knee osteoarthritis”)

2 TITLE-ABS-KEY (osteoarthr* OR arthrosis OR arthritis OR gonarthrosis OR “degenerative joint disease” OR “musculoskeletal disease” OR “degenerative arthritis”)

3 TITLE-ABS-KEY (knee*)

4 #2 AND #3

5 #1 OR #4

6 TITLE-ABS-KEY (exercis* OR physical activit* OR walk* OR aerobic*)

7 #5 AND #6

Appendix D: Study 3 Research Ethics Board Approval (File #1024411)

Subject: Approval re: Amendment Submission - REB FILE #: 1024411

Nova Scotia Health Research Ethics Board
Centre for Clinical Research, Room 121
5790 University Avenue
Halifax, Nova Scotia, Canada B3H 1V7
jennifer.macvicar@nshealth.ca

July 15, 2022

Rebecca Moyer
Medicine\Surgery\Orthopedic Surgery
5869 University Avenue
PO Box 15000
School of Physiotherapy, Room 316
Halifax NS B3H 4R2

Dear Moyer:

RE: Do walking patterns influence the effect of a 30-minute continuous walk on imaging markers of disease progression in patients with knee osteoarthritis?

REB FILE #: 1024411

On behalf of the Nova Scotia Health Research Ethics Board, I have examined the proposed amendment to this research study. I am pleased to confirm the Board's approval of this amendment request, effective July 15, 2022.

The following denotes new items approved with this amendment:

Document Name	Comments	Version Date
Consent Form - paper version	Consent Form - Paper v6	2022/07/14
Consent Form - electronic version	Consent Form - Electronic v6	2022/07/14
Research Protocol	Research Protocol v4	2022/07/14
Supporting Materials	Appendix Q v0	2022/07/14

Supporting Materials	Appendix B v2	2022/07/14
Supporting Materials	Appendix C v2	2022/07/14
Supporting Materials	Appendix A v4	2022/07/14
Supporting Materials	Appendix F v5	2022/07/14

Sincerely,

Dr. Chris MacKnight, Executive Chair

This statement is in lieu of Health Canada's Research Ethics Board Attestation:
The Research Ethics Board for Nova Scotia Health operates in accordance with:

- Part C Division 5 of the *Food and Drug Regulations* or with the definition in the *Interim Order Respecting Clinical Trials for Medical Devices and Drugs Relating to COVID-19*
- *Natural Health Products Regulations, Part 4 "Clinical Trials Involving Human Subjects"*
- *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2)*
- *ICH Good Clinical Practice: Consolidated Guideline (ICH-E6)*

Appendix E: Magnetic Resonance Imaging Screening Questionnaire

Question	Desired Answer	Answer/ Comments
Have you had a previous MRI exam?	N/A	
Is there a chance that you may be pregnant?	No	
Have you ever had an injury of any kind from a metal object such as a bullet, BB, shrapnel, or metal shavings?	No	
Have you ever had metal in your eye?	No	
Do you have glaucoma?	No	
Do you have a cardiac pacemaker?	No	
Do you have any surgical clips or staples?	No	