Cumulative Occupational Physical Load as a Risk Factor for Knee Osteoarthritis in Men and Women

by

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Abstract

Objective: To determine the association between cumulative occupational physical load (COPL) to the knee and the presence of symptomatic osteoarthritis (SOA) and magnetic resonance imaging–defined osteoarthritis (MRI-OA).

Methods: Cross-sectional analyses of symptomatic and asymptomatic (n=327) individuals were performed. Inclusion criteria for the symptomatic participants were: 1) having pain, aching, or discomfort in or around the knee on most days of the month at any time in the past; 2) having any pain, aching, or discomfort in or around the knee in the past 12 months. Asymptomatic participants responded "no" to both knee pain questions. COPL was calculated using a self-reported level of activity (five levels) and participation in knee bending/kneeling tasks (three levels) for each occupation held. SOA was defined by the Kellgren Lawrence x-ray grade $\geq$2, plus the presence of knee pain, as defined by the study inclusion pain criteria. MRI-OA was defined using the criteria specified by Hunter and associates. Logistic regression analyses, adjusted with population weights, were used to examine the associations between COPL (reference group=the lowest COPL quarter) and the presence of SOA and MRI-OA, respectively, after controlling for age, female sex, body mass index, and two-way interactions.

Results: Participants (women=167, men=160) were on average 58.5 (SD=11.0) years old with a BMI of 26.3 (SD=4.7). Of those, 102 (31.2%) participants had SOA. For SOA, a monotonic statistically significant relationship was found between COPL 4 (highest quarter; odds ratio (OR)=8.16; 95% CI=1.89, 35.27) and COPL 3 (OR=5.73; 95% CI=1.36, 24.12) versus COPL 1. For MRI-OA, monotonic and statistically significant associations were found in COPL 4 versus 1 (OR=9.54; 95% CI=2.65, 34.27); COPL 3 versus 1 (OR=9.04; 95% CI=2.65, 30.88); COPL 2 versus 1 (OR=7.18; 95% CI=2.17, 23.70).

Conclusion: COPL is a significant risk factor for knee OA. Dose response relationships between COPL and both SOA and MRI-OA were found. This study provides new insight into the role of occupation in knee OA, although the results should be interpreted cautiously due to limitations associated with the cross-sectional study design.

Preface

This thesis contains the work of a research study conducted by Allison M. Ezzat under the supervision of Dr. Linda Li with guidance from Dr. Jolanda Cibere, Dr. Mieke Koehoorn, and Dr. Eric C. Sayre. This study was a secondary analysis based on data collected from two cohorts at the Arthritis Research Centre of Canada: Model for the Diagnosis of Early Knee Osteoarthritis (MoDEKO) between 2002 and 2004 and Asymptomatic Cohort for Early Knee Osteoarthritis (ACE-KOA) between 2008 and 2009. The study design, data analysis, and writing of the manuscript were primarily the work of the candidate.

This research has been presented at the following conferences:

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Selections from this thesis will be submitted for publication in peer-reviewed journals in the future.

Ethical approval for this research study was provided by the University of British Columbia Clinical Research Ethics Board. (MoDEKO: H02-70200; ACE-KOA: H07-00793)

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List of Abbreviations

95% CI	95% Confidence Interval
A	COPL score for “Activity Level”
ACE-KOA	Asymptomatic Cohort for Early Knee Osteoarthritis
ACL	Anterior Cruciate Ligament
ACR	American College of Rheumatology
BLOKS	Boston-Leeds Osteoarthritis Knee Score
BMI	Body Mass Index
BML	Bone Marrow Lesion
COOS	Cumulative O*NET Occupational Score
CPFI	Cumulative Peak Force Index
COPL	Cumulative Occupational Physical Load
EULAR	European League Against Rheumatism
K	COPL score for “Knee Bending/Kneeling”
K&L	Kellgren-Lawrence Scale
MoDEKO	Model for the Diagnosis of Early Knee Osteoarthritis
MRI	Magnetic Resonance Imaging
MRI-OA	Magnetic Resonance Imaging–Defined Osteoarthritis
OA	Osteoarthritis
OAI	Osteoarthritis Initiative Study
O*NET	Occupational Information Network
OOS	O*NET Occupational Score
OPL	Occupational Physical Load
OR	Odds Ratio
PA	O*NET Score for “General Physical Activity”

Pre-OA	Pre-radiographic Osteoarthritis
QCOPL	Quarter of Cumulative Occupational Load
ROA	Radiographic Osteoarthritis
RR	Relative Risk
SOA	Symptomatic Osteoarthritis
TSK	O*NET Score for “Time Spent Kneeling, Crouching, Stooping, Crawling”
Y	COPL score for “Years in Occupation”

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1 Literature Review

1.1 Introduction

Osteoarthritis (OA) is the most common form of arthritis and joint disease in the world.[1] As the leading cause of chronic pain and disability worldwide, it represents a major public health problem. Affecting 10-15% of adults, OA may become symptomatic during mid-adulthood, with the incidence and prevalence rising with age.[2] The hallmark symptoms of pain and stiffness can result in mobility disability with ramifications for quality of life and work productivity.[3-5] Restricted mobility and lower physical activity may contribute to the development of other health concerns including cardiovascular disease and diabetes.[6]

The knee, hip, hand, and spine are the joints most frequently affected by OA. A recent definition of OA suggests it is the result of failed repair of damage caused by excessive mechanical stress on joint tissues, where the body's innate mechanisms for repair are no longer effective in overwhelming mechanical abnormality.[7] There is disruption of the normal articular cartilage processes of degradation and synthesis, which affects the structural and functional integrity of the entire joint, with pathological changes to the subchondral bone, cartilage, and synovium. This in turn impairs the peripheral nervous system and sends nociceptive signals from the joint and surrounding tissues to inhibit muscles and impair function.[8, 9] Local joint pain, hypomobility, crepitus, and variable joint swelling characterize clinical OA. X-rays can be used to detect intra-articular changes, such as joint space narrowing, osteophyte formation, and subchondral sclerosis.[9]

The economic burden of osteoarthritis in Canada in 2010 was estimated at $27.5 billion, of which $17.3 billion was attributed to indirect costs, including work absenteeism and disability.[3] With no known cure or effective treatments to halt the progression of the

disease, analgesic medications, physical activity modification, exercise, and weight-loss strategies are the first-line treatments in managing OA symptoms.[10, 11] Joint replacement surgery as a last resort is extremely effective, but also costly.[12] Given this, combined with the increasing age of our population, the identification of risk factors and prevention strategies is essential. Without breakthroughs in disease prevention, it is estimated that cases of OA in Canada's population will more than double over the next 30 years, with the cumulative indirect costs expected to reach $909 billion in that time.[3]

1.2 Knee Osteoarthritis

The knee is the joint most commonly affected by OA, and is a major reason for loss of independence in older adults.[13] Knee OA can be defined in numerous ways, and it is likely neither feasible nor desirable to rely on a single definition.[14] While pain and disability are most relevant to patients, the considerations of underlying biological changes may inform researchers and clinicians about important clues for disease prevention and treatment.

A number of definitions exist for categorizing knee OA. It can be defined via imaging tools, such as radiographs[15] or magnetic resonance imaging (MRI)[16]; or clinically, using internationally developed guidelines.[17, 18] Within these different definitions, there has been an acknowledged discordance between radiographic changes and clinical symptoms such as pain.[19, 20] Bedson and Croft performed a systematic search and summary of the literature in this area, and found studies reported between 15% and 81% of those with radiographic OA (ROA) also had knee pain.[21] It appears that only severe disease shows good agreement between advanced radiographic changes and knee pain.[22, 23]

Symptomatic OA (SOA) is defined as the presence of both radiological signs and clinical symptoms. Usually this requires individuals to have had knee pain on most days of a

recent month to qualify as having symptoms. Numerous studies have found the presence of knee pain as having prognostic significance for radiographic progression.[24, 25] The current effectiveness of treatment options for individuals with SOA is limited. Therefore, from a public health perspective, it is logical that these individuals should be important targets for new research and interventions. Those with SOA are most likely utilizing health services and will be the most likely to progress to advanced disease which often culminates in costly joint replacement surgery.[13]

1.2.1 Prevalence of Knee Osteoarthritis

The prevalence of knee OA varies greatly between ROA and SOA. Population-based studies in the United States have produced estimates for knee ROA prevalence that are between 28% and 37% and knee SOA that are between 7% and 17%.[4, 22, 26] Using administrative data from visits to health professionals and hospitals covered by the British Columbia Medical Services Plan, Kopec et al.[27] found 11% of the population had a physician diagnosis of knee OA. Both knee OA definitions show prevalence rates that rise consistently with age and are more common in women than men.[4, 22, 26] In the Framingham heart study cohort, knee OA was reported in 27% of people below age 70; the prevalence rose to 44% among those who were aged 80 and older.[22] The same study also found a higher levels of OA in women compared with men using both definitions (ROA=34% vs. 31%; SOA=11% vs. 7%).

1.2.2 Clinical Knee Osteoarthritis

Clinical criteria for the classification of knee OA were first developed in 1986 by the American Rheumatism Association, now the American College of Rheumatology (ACR).[17] These criteria have been updated recently by the European League Against Rheumatism

(EULAR).[18] They state that the probability of having OA increases incrementally with the presence of each of the following six symptoms and signs: persistent knee pain, limited morning stiffness, reduced function, crepitus, restricted movement, and boney enlargement. The likelihood of a person having OA who meets all six criteria is 99%. However, one shortcoming of using these criteria is their limitations in identifying those individuals with early disease who may have milder joint damage and fewer functional limitations, but who also may be more amenable to treatment.[28]

1.2.3 Radiographic Knee Osteoarthritis

The radiographic classification and grading for knee OA described by Kellgren and Lawrence (K&L) in 1957 (Table 1.1) is the most widely used grading scale for identifying ROA.[15, 29] It defined ROA within five grades (0=normal; 4=severe) based on the following changes in the knee joint: a.) formation of osteophytes at the joint margins or ligamentous attachments, b.) narrowing of the joint space associated with sclerosis of the subchondral bone, c.) cystic areas with sclerotic walls situating in the subchondral bone, and d.) altered shapes of the bone ends. The original article reported high inter-observer and intra-observer reliability for the K&L classification for the knee (both, r=0.83).[15] However, descriptions for each grade in the original article have been criticized as vague and inexact, thus creating challenges for interpretation.[29] Schiphof et al. found five distinct descriptions of the K&L classification used in epidemiological cohorts.[29] There is reported confusion distinguishing between various grades, especially for grade 2, which is problematic as it is often used as the cut-off point to determine the presence of ROA. Despite the challenges with this grading system, the World Health Organization continues to use these criteria as the standard radiological classification for knee ROA in epidemiological studies.[30]

Table 1.1: Kellgren and Lawrence Criteria

Grade	Description
Grade 0	Definite absence of x-ray changes
Grade 1	Doubtful narrowing of joint space and possible osteophytic lipping
Grade 2	Definite osteophytes and possible narrowing of joint space
Grade 3	Moderate multiple osteophytes, definite narrowing of joint space and some sclerosis, and possible deformity of bone ends
Grade 4	Large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone ends

1.2.4 Magnetic Resonance Imaging-Defined Osteoarthritis

While radiography remains the most widely applied imaging technique to quantify OA outcomes, magnetic resonance imaging (MRI) technology is being increasingly implemented in research settings and this is reflected in the increased number of publications involving MRI applications in OA.[31] MRI has advantages over radiography in its ability to visualize a large variety of structures believed to be related to the functional integrity of a joint and pathophysiology of OA. These include cartilage morphology, subchondral bone marrow lesions (BML), cysts, synovitis, and meniscal or ligament lesions in joints before radiographic abnormalities are visible.[32, 33] MRI has become a useful tool in a research setting to detect and quantify early signs that may be indicative of OA.

MRI has been used for examining the role of BML and knee pain associated with joint changes. In a population-based study of participants with knee pain, Ip et al. found BML in 11% of those with no OA, 38% of those with pre-radiographic OA (pre-ROA; K&L <2, with visible MRI cartilage damage), and 71% of those with ROA.[34] A separate study of women aged 35-55 with knee pain, but normal radiographs, found that 55% had MRI-visible cartilage lesions.[33] These authors suggested that quantifying BML and cartilage defects using MRI would facilitate studying the association between joint pain and these

cartilage defects in the absence of radiographic findings, and this may be a method to detect early stages of joint disease.[33] While hyaline cartilage does not have pain fibres, bone is rich in nociceptive fibres. BML and edema could cause increased intra-osseous pressure and heightened pain. Compared with those without joint pain, individuals with pain had significantly more frequent large lesions greater than 1 cm and bone marrow defects penetrating to subchondral bone. Studying BML with MRI could facilitate identification of those with painful, but early joint disease.

Cibere et al. suggested that those with pre-ROA may have early manifestations of OA and may be progressing towards full symptomatic disease.[35] Their Model for the Diagnosis of Early Knee Osteoarthritis (MoDEKO) study examined the risk factors associated with ROA and pre-ROA. They found that ROA was significantly associated with age, body mass index (BMI), frequency and duration of pain, regular sports activity after age 20, and history of severe knee injury, as well as the presence of abnormal gait, effusion, crepitus, flexion contracture, and reduced flexion. Similar factors were also identified in pre-ROA, including age, regular participation in sports after age 20, and the presence of knee effusion and flexion contractures.

The literature has shown little uniformity in the definition of OA using MRI.[16, 36] Recently, a group of leading OA experts led by Hunter et al. undertook a Delphi process to develop an MRI definition of structural OA.[16] This evidence-based multi-stage process produced 11 propositions, including 9 preamble statements to provide context, and 2 parts to the definition of OA (Table 1.2).

Table 1.2: Hunter Definition of Osteoarthritis Using Magnetic Resonance Imaging

Tibiofemoral OA on MRI The presence of both group A features or one group A and two or more of Group B features:	
Group A	Group B
Definite osteophyte formation	Subchondral bone marrow lesion or cyst not associated with meniscal or ligamentous attachments
Full thickness cartilage loss	Meniscal subluxation, maceration, or degenerative tear
	Partial thickness cartilage loss
	Bone attrition
Patellofemoral OA on MRI All of the following involving the patella and/or anterior femur:	
Definite osteophyte formation	
Partial or full thickness cartilage loss	

The diagnostic performance of the MRI definition was compared to the radiographic reference standard of a K&L $\geq$2 in 160 participants from the progression sub-cohort of the Osteoarthritis Initiative study (OAI).[37] The osteophyte volume was assessed using Dual Echo Steady State MRI sequences done in a former study[37] that investigated cartilage morphometry changes in participants from the OAI database. For this analysis, osteophyte volume in the tibiofemoral joint was defined as the sum of osteophyte volume at the medial and lateral tibia as well as the medial and lateral femur. The following cut-points were used for osteophyte volume: 50 mm^3, 100 mm^3, and 200 mm^3. Full thickness cartilage loss was also examined using Dual Echo Steady State MRI sequences acquired by OAI, which provided a complete high-resolution view of the knee cartilage tissue with good contrast between fluid, cartilage, meniscus, and bone. After image segmentation, the following were analyzed: cartilage volume, normalized cartilage volume (volume normalized to bone surface interface area), and denuded area (area of bone where full thickness cartilage loss has occurred). For cartilage loss the denuded area was used with the following cut-points: 0 mm^2 and 10 mm^2. BML were imaged using the sagittal intermediate-weighted Turbo Spin Echo fat-supressed images and were deemed present when an irregular hyperintense signal

in the subchondral bone, proximal to the epiphyseal line, was seen. BML size was evaluated using Boston-Leeds Osteoarthritis Knee Score (BLOKS; ranging from 0 to 3)[38] in each of the following locations: medial and lateral weight-bearing femur and medial and lateral tibia. BML were classified as present in any region (>0) and those with BLOKS score >1 in any region. The presence of degenerative meniscus tears was evaluated with sagittal intermediate-weighted Turbo Spin Echo fat-supressed images. The meniscal integrity was scored using the Whole-Organ Magnetic Resonance Imaging Score grading system.[39] The anterior horn, body segment, and posterior horn of each medial and lateral meniscus were graded from 0 to 4 based on both sagittal and coronal images: 0=intact; 1=minor radial tear or parrot-beak tear; 2=non-displaced tear; 3=displaced tear or partial resection; 4=complete maceration/destruction or complete resection. Meniscal abnormality was scored as present in any region (>0) and also with a score $\geq$2, with cut-points of 0 and 2.

Lastly, a composite model was done using the most discriminatory cut-points from each of these previous described features. It included the osteophyte threshold of 200 mm^3, a cartilage loss cut-point of 10 mm^2, BML of >1, and meniscus tear of >2. The overall composite C statistic was 0.59. The authors recognized that the sample had only a small number of people without radiographic OA (16%), which was not ideal for testing this MRI-OA definition. Compared with the radiographic standard, the specificity of the MRI composite model was 1, indicating that all the participants who were diagnosed with OA using the radiographic standard were also diagnosed with OA with the new definition, resulting in no false positives or type I errors. However, sensitivity of the MRI-OA definition was 0.46, likely due to MRI's ability to detect earlier disease compared with the radiographic standard. The study authors concluded that their new definition requires further validation, especially in cohorts with early disease. They also suggested that using an MRI-OA definition would facilitate recruitment of a study sample with early pre-OA

disease, where preventive interventions could be applied and tested in a realistic manner.[16]

From a research perspective there is immense value in using multiple knee OA outcomes, such as SOA, ROA, and MRI-OA when studying this chronic disease. Each OA definition can provide a discrete perspective, insight, and knowledge into the overall disease continuum, such as the implementation and evaluation of early prevention strategies for MRI-OA or the links between disability, pain, and function in the more advanced disease state of SOA. Therefore, the current study analyzed data using all three OA outcomes to gain these varied perspectives, as well as providing the unique opportunity to make comparisons between these OA outcomes within the same study.

1.3 Risk Factors for Osteoarthritis

The pathophysiology of OA is undoubtedly multi-factorial, and thought to evolve from the complex interaction of multiple factors, both systemic (e.g., age, sex, body weight) and local (e.g., previous injury, alignment, abnormal loading).[40] It is likely that the systemic factors increase the vulnerability of the joint to local biomechanical and loading factors. Understanding all major risk factors will help to clarify the disease process and contribute to prevention strategies before the outcome of synovial joint failure is reached.

1.3.1 Systemic Factors

Age, sex, and body weight are the three important established risk factors for knee OA. Contrary to popular belief, OA is not a inevitable part of aging, although age is a prominent risk factor.[2, 41] With aging there is time for the development of underlying local joint risk factors, such as injury and abnormal loading, to evolve through cumulative exposure. OA has a long induction period before symptoms begin, and joint changes are

likely occurring much earlier in life even though symptoms may not manifest until later. As well, other natural processes of aging, such as decreased muscle strength, cartilage thinning, and reduced proprioceptive abilities likely make the joint less resilient to abnormal forces.[42] Age will be included as a covariate in this thesis.

With the population aging, the increasing prevalence of OA has been shown to be greater in women than men. Most epidemiological studies show that women are 1.5 to 2.0 times more likely to develop knee OA.[13, 43] As well, women tend to have more severe progression of the disease and report more pain compared with men.[44, 45] Zhang and Jordan hypothesize that hormonal changes at menopause may play a role, as the imbalance in the number of women compared with men diagnosed with knee OA is accentuated around this time point.[42] However, overall the evidence in this area remains conflicted. The role of sex will be explored in detail in this thesis and being female will be controlled for in the main analysis.

Excess body weight is one of the most established risk factors for knee OA.[41, 42, 46] Being classified as obese (BMI: >30) or overweight (BMI: 25-30)[47] has been shown to increase the risk of both the onset and progression of knee OA, independent of age and sex.[48, 49] In the Rotterdam study, 3,585 people were followed for an average of 6.6 years to investigate the relationship between BMI and knee OA incidence and progression. Those with a BMI over 27.5 at baseline had increased odds of incident knee OA by 3.3 (95% Confidence Interval (CI)=2.1, 5.3) and progression of knee OA by 3.2 (95% CI=1.1, 9.7).[48] Another prospective cohort in the Framingham study demonstrated that women who lost about 5 kg had a 50% decreased risk of developing symptomatic knee OA.[50]

Two plausible explanations have been raised regarding the relationship between obesity and knee OA. Firstly, excess weight increases biomechanical strain on the knee by increasing the adductor moment on the joint, which results in breakdown of cartilage and

supporting structures.[41, 51] This was illustrated in a 2010 case-control study involving 622 participants. Vrezas et al. found that those with a BMI over 24.92 were 2.5 times [95% CI=1.5, 4.3] more likely to have SOA, compared with those with a lower BMI, after adjusting for age, geographic region, and physical activity.[52] Secondly, there may be an inflammatory or metabolic link leading to the presence of a low-grade systemic inflammation.[40] With obesity, there is evidence of increased blood glucose, C-reactive protein levels, and other pro-inflammatory markers such as cytokines.[53, 54] This systemic aspect of obesity as a risk factor for OA is also supported by its apparent association to OA in the hand, a non-weight bearing joint.[55]

Previous research has also shown an interaction between BMI and physical workload.[52, 56] In the above-mentioned study by Vrezas et al., their final model had a multiplicative interaction between BMI and squatting or kneeling with an OR of 5.3 (95% CI=2.4, 11.5), after adjusting for age, geographic region, and physical activity.[52] With the rising levels of obesity in North America, the interaction between these two risk factors is an area that deserves further study, and will be examined in this thesis.

1.3.2 Local Factors

Several local factors influence how dynamic load is transmitted and distributed across the articular surface of the knee joint. These include previous injury and joint alignment. There is evidence from both in vitro and epidemiological studies suggesting that cyclical mechanical loading is beneficial and necessary for cartilage homeostasis stimulating anabolic processes and regulating chondrocyte activity.[9] This dynamic loading may come from participation in physical activity, including sports and occupation. However, if this loading is done on a compromised joint, or the loading becomes overly intense, these same processes may become catabolic, leading to OA.

Knee joint injuries, including ligament disruption, intra-articular fracture, and cartilage or meniscus tears, have all been found to be strongly associated with future development and accelerated progression of knee OA.[57] These injuries have the potential to alter load absorption and distribution, as well as mechanical function within the joint.[40] Muscle inhibition and altered joint position sense may also occur. The anterior cruciate ligament (ACL) is the most commonly injured ligament in the knee, and this injury usually occurs before the age of 30. Unfortunately, once the ACL is torn joint health is severely compromised. For example, in one study involving soccer players, approximately 80% of those who had sustained an ACL injury had ROA of the knee within 12 to 14 years and 70% had functional limitations regardless of whether they had had surgery or conservative management.[58, 59]

Lower limb alignment (i.e., hip–knee-ankle angle) affects how the loading force is distributed across medial and lateral tibiofemoral compartments. A shift from neutral alignment into varus (bowed knees) or valgus (knock knees) redistributes load to the medial or lateral compartment, respectively. A 4-6% increase in varus alignment shifts the load-bearing moment axis of the knee medially and increases the load on this compartment by up to 20%.[60] Research conducted in this area has largely focused on the role of knee alignment in OA progression rather than OA onset.[42]

Mechanical loading of the knee occurs with all types of physical activity, which encompasses the domains of sport, household activity, and occupation. Musculoskeletal and joint health are included in the innumerable benefits of physical activity.[6] Physical activity promotes increases in bone mass in childhood which persist into adulthood.[61] Cartilage homeostasis relies on cyclical bouts of mechanical stress provided through moderate physical activity to regulate anabolic activities[9] such as increasing proteoglycan content and cartilage thickness.[62] Healthy knee joints without increased vulnerability to OA from

the presence of underlying risk factors, such as previous injury, will respond to loading in a favourable way. Participation in recreational sports, including running, does not appear to increase the risk of knee OA. In fact, it may play a protective role.[63] However, an increased prevalence of knee OA has been found in elite athletes with a history of intense participation in sports with high impact and torsion forces, such as soccer and running.[64] For the majority of individuals, participation in sport represents a relatively small proportion of their total joint loading. This has recently been quantified in a study by Ratzlaff et al., who found that occupations and household tasks made up the majority of both joint force on the knee and energy expenditure over the lifespan.[65] Ratzlaff et al. also reported that women had slightly higher total scores for joint loading force than men.

Broadly, occupation is what people do to occupy themselves with some regularity or consistency by contributing to the productivity of their communities through engagement in the workforce or home.[66] However, the literature often refers to "occupation" as paid employment outside the home.[1, 67] Both research and labour policy have classified activities that involve heavy lifting, kneeling, and stair climbing as occupational tasks.[68, 69] Current evidence suggests there is a relationship between physically demanding occupational activities and knee OA.[67, 69-71] This has led some countries to classify knee OA as an occupational disease.[68] For example, Denmark recognizes "degenerative arthritis of the knee joint (arthrosis genus)" as an occupational disease in individuals whose jobs involve kneeling or squatting work for many years.[69] However, there remains a need to accurately quantify lifetime exposure to occupational joint loading, and examine its role using a variety of classifications of knee OA. Furthermore, a broader definition of occupation should be explored to include the role of homemaker as a valid occupation to ensure the completeness of this exposure measurement, especially in women.

1.4 Cumulative Occupational Physical Load and Knee Osteoarthritis: A Literature Review

For the purposes of the current study, I conducted a literature review by searching Medline and EMBASE databases using the terms "knee osteoarthritis," "occupational exposure," and "occupational disease." Eligible articles included those published between 1946 and April 2011 which met the following criteria: 1) included adults reporting on their employment history; 2) measured individuals' exposure to work-related activities with heavy loading in the knee joint, such as lifting, kneeling, and stair climbing; 3) measured the presence of ROA, or MRI-identified cartilage defects associated with knee OA, or joint replacement surgery. The methodological quality of studies was rated using a standardized protocol used in a previous review in this area.[69]

The initial search yielded 2 reviews[67, 69] and 32 articles[1, 15, 32, 52, 56, 68, 72-97] from 31 unique studies, of which 16 were deemed high quality (Table 1.3).[1, 32, 56, 73, 80, 82-84, 86, 90-95, 98] During my literature synthesis, two additional reviews were published.[70, 71] This section will summarize the findings of the four systematic reviews and present the findings from my own review pertaining to the following exposure subgroups: 1) heavy lifting, 2) kneeling, 3) combined heavy lifting and kneeling. My results examining occupational load and knee OA separately in men and women will also be discussed.

1.4.1 Systematic Reviews

In the first narrative review published in 1997, Maetzel et al. identified nine observational studies published between 1966 and 1995 as fitting their inclusion criteria of having a comparison group and radiologically diagnosed knee OA.[67] Separate analyses were done for men and women. Based on three high-quality studies,[1, 73, 77] this review concluded that there was a strong positive relationship between exposure to jobs that

involved knee bending and knee OA in men, with an odds ratio (OR) varying between 1.4 and 6.0. Three studies examined occupational exposure and knee OA separately in women;[1, 73, 99] however, only one reported a significantly positive association.[73] Maetzel et al. hypothesized that not assessing occupational exposure in "housewives" contributed to the non-significant results in the other two studies.

A best evidence synthesis review was published in 2008 by Jensen et al.[69] and included 25 epidemiological studies published up to 2004 on knee OA and physical work demands. Separate analyses were done for each of the four tasks: 1) heavy lifting, 2) kneeling, 3) climbing stairs, 4) combined kneeling and lifting, as well as for exposure by occupational titles. The study authors concluded there was moderate evidence that activities involving kneeling and heavy lifting were associated with knee OA (kneeling: OR=2.20-6.90; heavy lifting: OR=1.90-7.31). Based on study design, exposure and outcome ascertainment, and statistical analysis, six of the kneeling studies were rated as high quality,[1, 56, 73, 82-84] as were six of the lifting studies.[1, 56, 73, 82-84] Jensen et al. found the strongest positive association in studies examining combined kneeling or squatting and heavy lifting. All four studies, one cohort and three case-control studies, showed an association with knee OA with OR ranging from 2.20 to 5.40.[1, 56, 81, 100] However, only two studies were rated high quality, suggesting further investigation in this area was strongly warranted.[1, 81] Jensen et al. found a discrepancy in the quantity and quality of studies conducted with women when compared with those with men. They concluded that the evidence on the relationship between occupational exposure and knee OA in women was obscure.[69] This made them unwilling to suggest specific recommendations or interventions for women.

Two more reviews have been published this past year.[70, 71] Fransen et al.[71] examined the role of occupational factors in knee pain, and reported a significant

association between each of the following exposures and SOA: heavy lifting with OR varying from 1.4 to 5.0; kneeling with OR varying from 1.5 to 2.5; and combined heavy lifting and kneeling with OR varying from 2.4 to 3.4. This review did not include a quality assessment and had broader inclusion criteria than the previous two reviews, using either a clinical or radiographic OA definition. The final review by McWilliams et al.[70] was a meta-analysis with 51 observational studies assessing the relationships between occupational factors (i.e., heavy work, kneeling activity, elite sports participation, job titles) and knee OA. This meta-analysis found a statistically significant association between occupational physical loading and knee OA with an overall OR of 1.61 (95% CI=1.45, 1.78); however, the methodological quality of the studies was not assessed. The authors acknowledged noticeable heterogeneity among studies and the evidence of publication bias. They also discussed the disparity between sexes in the numbers of participants (446,057 men; 63,666 women) when studies were combined. Yet increased risks of knee OA were similar between sexes, with men at 1.53 times (95% CI=1.36, 1.73) greater risk of knee OA and women 1.61 times (95% CI=1.42, 1.82) more likely to have knee OA after occupational exposure.

1.4.1 Heavy Lifting

In my review, I found 18 articles that examined the relationship between heavy lifting and knee OA. The study designs included 3 cohort studies,[1, 75, 76] 12 case-control studies,[52, 56, 68, 74, 81-87, 94] and 3 cross-sectional studies.[73, 95, 98] Of these, 11 papers[52, 68, 73, 75, 82-86, 94, 98] showed a significant association between heavy lifting and knee OA, with ORs between 1.4 and 7.3.

Ten studies[1, 56, 73, 82-84, 86, 94, 95, 97] were rated high quality (Table 1.3), four[86, 94, 95, 98] of which were completed after the most recent review published prior to my literature search. In 2006, Yoshimura et al.[86] conducted a small case-control study

on 74 Japanese men with a mean age of 70. A significant relationship was found between having physical work as a principal occupation and knee OA, with OR=6.20 (95% CI=1.40, 27.50) after controlling for heaviest reported weight and previous knee injury. In a cross-sectional study of 2,729 participants (933 men, 1,796 women), Allen et al.[98] found no association between any occupational physical loading task and ROA. However, lifting over 10 lb at work was significantly associated with a 1.42 times greater risk of SOA (95% CI=1.13, 1.80). Teichtahl et al.[95] performed a cross-sectional analysis with 96 women without OA symptoms. MRI was used to assess tibial and patellar cartilage volume and defects. After controlling for age, BMI, and frontal plane knee alignment, they found a trend suggesting an association between occupations involving heavy lifting and patellar knee cartilage defects (OR=1.8; 95% CI=1.0, 3.1). In another large case-control study with 301 men and 438 women, Klussmann et al.[94] reported a 2.1 greater odds of SOA in women who performed occupational lifting and carrying tasks (95% CI=1.1, 4.0), after adjusting for sports participation, obesity, malalignment, and smoking history. He failed to find this same association in men. The response rate in this study was about 70% for both cases and controls. However, as cases were recruited from hospitals, selection bias may be present because only those who sought medical treatment were included.

The findings of the most recent studies concurred with those included in the previous reviews, suggesting that heavy lifting was associated with knee OA. Out of the 10 high-quality studies, 7 found a significant association. Therefore, based on the overall study design and methodological quality, my review concluded there was a moderate level of evidence that occupations consisting of heavy lifting were associated with knee OA.

1.4.2 Kneeling or Knee Bending

Sixteen articles were found examining the association between kneeling or knee bending and knee OA. These included 2 cohort studies,[1, 76] 10 case-control articles from 9 studies,[52, 56, 68, 78, 81, 83-85, 87, 94] and 4 cross-sectional studies.[73, 80, 92, 95] Eleven of these showed a significant positive association between kneeling/knee bending and knee OA, with ORs varying between 1.5 and 6.9.[52, 56, 68, 73, 78, 80, 81, 83-85, 94] However, this did not include either of the cohort studies. Nine studies received a high quality score (Table 1.3)[1, 56, 73, 80, 83, 84, 92, 94, 95]; four of these were published after Jensen's review.[69] Two of these studies have already been discussed under heavy lifting.[94, 95] Their results for kneeling or knee bending are as follows: 1) Klussmann et al.,[94] women: OR=2.52; 95% CI= 1.35, 4.68; men: OR=2.47; 95% CI=1.41, 4.32; and 2) Teichtahl et al.,[95] OR=1.8; 95% CI=1.0, 3.1. The remaining two high-quality studies will be discussed below.[80, 92]

To calculate a dose-response relationship between kneeling and squatting at work and knee OA, Jensen[80] analyzed the work activities of 150 floor layers, carpet layers, and composers by administering a questionnaire (80% response rate) and videotaping particpants' workdays. The amount of knee strain was then quantified for each occupational task, and exposure was calculated by analyzing for how long each task was performed. After controlling for age, BMI, smoking, and sports activities, he found a significant association between knee-straining work activities and knee OA in the highest-exposure group compared with the unexposed group (OR=4.92; 95% CI=1.1, 21.9). In another study, Bernard et al.[92] used a questionnaire to assess work exposure to squatting, jolting of the legs, and stair climbing in "the job you had for most of your life" in 3,436 people in the United States (average age=63.4 years.) After adjusting for age, sex, and BMI, they failed to find a significant association between squatting and knee OA (men: OR=1.56, 95% CI=0.89,

2.75; women: OR=0.89, 95% CI=0.50, 1.6). The variety of recruitment strategies employed for this study, including television and radio advertisements and seminars with local community groups, limited the ability of the researchers to calculate a true response rate.

Out of 16 papers, 9 case-control and cross-sectional articles received high quality scores. However, only six of these showed a significant association between kneeling or knee bending and knee OA. In my review, I concluded there was limited-level evidence for a significant relationship between knee bending/kneeling tasks and knee OA.

1.4.3 Combined Heavy Lifting and Kneeling

My review found that combined heavy lifting and kneeling as a risk factor for knee OA was investigated in six studies. These included one cohort study,[1] three case-control designs,[56, 68, 81] and two cross-sectional studies.[32, 95] Five studies showed an increased risk for knee OA, with OR varying from 1.8 to 7.9.[1, 32, 56, 68, 81] Four of the six studies were rated as high quality (Table 1.3).[1, 32, 56, 95] Two of these studies have been discussed previously; their results for this subgroup are: 1) Felson et al.,[1] men: OR=2.22; 95% CI=1.38, 3.58; women: OR=0.36; 95% CI=0.09, 1.40); 2) Teichthal et al.,[95] OR=1.8; 95% CI=1.0, 3.1. The remaining high-quality studies are presented below.

Coggon et al.[56] conducted a case-control study with 518 patients awaiting total joint replacement surgery matched by age and sex with individuals from the same communities. After assessing lifetime exposure to various occupational tasks through interviews, they found men with exposure to combined kneeling and lifting had 2.7 greater odds of knee OA compared with those unexposed, after controlling for BMI, Heberden's nodes, and previous injury (95% CI=1.1, 7.1). The results for women failed to reach statistical significance (OR=0.3; 95% CI=0.03, 4.1). In a cross-sectional study, Amin et al.[32] examined the relationship between occupational exposure to frequent squatting or kneeling

and lifting, and cartilage morphology based on MRI imaging in 192 men (mean age=69). Compared with those who were not exposed to these tasks at work, a statistically significant relationship was found in men who held jobs that required frequent squatting/kneeling plus lifting and cartilage defects in the patellofemoral joint (OR=1.8, 95% CI=1.1, 3.2), after controlling for age, BMI, and history of previous injury. Results for cartilage defects in the tibiofemoral joint did not reach statistical significance.

Although fewer studies investigated the role of combined heavy lifting and kneeling, five out of six showed a significant relationship[1, 32, 56, 68, 81] and four of these had high methodological quality.[1, 32, 56, 95] Therefore, I concluded that there was moderate-level evidence of knee OA in relation to these combined occupational physical loading tasks.

1.4.4 Occupational Physical Loading by Sex

Twenty-two articles reported results on the relationship between occupational physical loading tasks and knee OA separately in men. The study designs included 3 cohort studies,[1, 75, 89] 11 case-control studies, resulting in 12 papers,[32, 52, 56, 68, 82-84, 86, 88, 91, 93, 94] and 7 cross-sectional studies.[72, 73, 77, 79, 80, 92, 101] Twenty studies reported statistically significant findings favouring the relationship between occupational physical loading and knee OA, with OR varying from 1.4 to 7.9. Thirteen studies received high quality scores, all of which reported statistically significant positive results (Table 1.3).[1, 32, 56, 73, 80, 82-84, 86, 91-94] All three cohort studies reported significant results for men: 1) Felson et al.[1] measured knee bending and lifting with heavy demands compared with sedentary jobs and light demands, OR=2.22; 95% CI=1.38, 3.18; 2) Vingard et al.[75] examined high versus low exposure to lifting in 45–55-year-olds, OR=1.4; 95% CI=1.1, 1.9); 3) Jarvholm et al. analyzed heavy loading occupations (such as floor layers, brick layers, plumbers) and found increased risk, with OR varying from 2.1 to 4.7, compared

with more sedentary jobs. Considering the consistent results from these cohort studies combined with the large number of significant results in high-quality case-control and cross-sectional studies, I concluded that there was moderate-level evidence for a relationship between occupational joint loading and knee OA in men.

Fifteen studies examined the relationship between occupational physical loading tasks and knee OA in women. They included two cohort studies,[1, 75] nine case-control studies, [56, 82-85, 87, 88, 93, 94] and four cross-sectional studies.[73, 92, 95, 96] Nine studies showed a significantly positive association between an occupational exposure and knee OA in women, with OR varying between 1.4 and 7.3.[1, 56, 73, 75, 83-85, 94, 95] Ten studies were rated high quality (Table 1.3)[1, 56, 73, 82-84, 92-95]; seven of these showed a statistically significant relationship.[56, 73, 82-84, 94, 95] Of the two large cohort studies, one high-quality study by Felson et al.[1] did not find a significant association between any physically demanding tasks and knee OA in women. The other, lower-quality cohort study, by Vingard et al.,[75] found an association in women aged 45-55, (OR=1.9; 95% CI=1.3-2.9), but not in women aged 55-75. This registry-based study risked exposure misclassification, as occupational loading was quantified only by job title at one time point by occupational health physicians. As well, cases were selected from hospitals, creating possible selection bias, and age and residence were the only covariates controlled for in the analysis. Given the methodological limitations and the ambiguity in results for this sex, I believed that there was limited-level evidence upon which to draw a conclusion about the association between occupational knee joint loading and OA in women.

1.5 Significance of the Current Project

Overall, based on the evidence from four systematic reviews and my own review, occupations involving heavy lifting and combined heavy lifting and kneeling appear to be

risk factors for knee OA in men. The evidence regarding these same relationships in women is limited, which may be due to methodological challenges of measuring exposure in women or to true biological differences. This project attempted to provide further insight into this area.

Direct observation of occupational exposure in large-scale epidemiological studies is neither financially feasible nor time-efficient. Therefore, many challenges emerge in measuring this exposure accurately, whether investigators elect to use self-reported measures, ergonomist ratings, or job titles. Currently, there is no accepted gold standard for measuring occupational exposure to joint loading. To comprehensively examine combined heavy lifting and kneeling tasks, it is necessary to use a lifetime method of exposure measurement that can illustrate whether increased amounts of exposure translate into increased levels of risk, thereby facilitating the calculation of a dose-response relationship. This would contribute to the goal of determining a threshold where cumulative exposure to loading becomes detrimental to the knee joint. To this end, this project introduced a new lifetime joint loading measure called cumulative occupational physical load (COPL), which is designed to measure combined lifting and kneeling over an adult's life up to the time of reporting.

Previous studies have used a variety of methods to quantify knee OA, including participant self-reporting, physician diagnosis, radiography, and MRI. Each OA outcome has its own advantages and values. Few studies have examined multiple OA outcomes when investigating occupational exposure in a single cohort. This would allow insight into distinct aspects of each disease classification. This thesis will use three separate OA outcomes (SOA, ROA, MRI-OA) to examine COPL to the knee.

The use of MRI is a novel technique in epidemiological research and it is regarded as the gold standard for studying cartilage defects non-invasively. Its ability to allow

researchers a glimpse into earlier disease than more traditional OA quantification methods has triggered interest in its application for studying early OA, a disease subgroup that has historically received less attention than more advanced and severe disease states. The first comprehensive definition of OA based on MRI findings was published recently.[16] This thesis will utilize the new MRI-OA outcome in one analysis, facilitating comparison with other established OA definitions and addressing a gap in the literature surrounding early OA and occupational loading. From a public health perspective, utilizing this new MRI-OA definition as a measure of early disease offers the potential to identify individuals amenable to early interventions and prevention strategies to be tested in future studies.

Table 1.3: Occupational Physical Loading and Knee Osteoarthritis: High-Quality Study Characteristics

Reference	Study Sample	Study Design	Exposure Measurement	Adjusted for Covariates	Outcome	Results: OR (95% CI)[1]
Anderson & Felson ,1988 [73] (United States)	n=5193 Men: 2428 Women: 2765 Age: 35-74 years old	Cross-sectional	Current occupation used to compute physical demands from the US Dictionary of Occupational Titles (DOT) by professionals	Ethnicity, BMI[3], education	Knee OA: KL scale ≥2	Knee Bending: Men 45-54 years old: OR=0.82 (0.32, 2.11) *Men 55-64 years old: *OR=2.45 (1.21, 4.97) Women 45-54 years old: OR=2.07 (0.71, 6.08) *Women 55-64 years old: *OR=3.49 (1.22, 10.52) Heavy lifting: Men 45-54 years old: OR=1.05 (0.45, 2.4) Men 55-64 years old: OR=1.88 (0.88, 4.0) Women 45-54 years old: OR=1.09 (0.31, 3.5) *Women 55-64 years old: OR=3.13 (1.04, 9.4)
Felson et al., 1991 [1] (United States)	n=1831 Men: 745 Women: 1086 Age: mean=73 years old	Cohort	Interview	Age, smoking, BMI[3], history of knee injury, education	Knee OA: KL scale ≥2	Lifting: Men OR=0.96 (0.49, 1.87) Women OR=2.53 (0.82, 7.85) Knee bending / light demands: Men OR=1.07 (0.53, 2.17) Women OR=1.43 (0.77, 2.63) Knee bending and lifting med, heavy, very heavy: *Men OR=2.22 (1.38, 3.58) Women OR=0.36 (0.09, 1.40)

Reference	Study Sample	Study Design	Exposure Measurement	Adjusted for Covariates	Outcome	Results: OR (95% CI)[1]
Coggon et al., 2000 [56] (England)	n=1036 (Cases=518, Controls=518) Men: 410 Women: 626 Age: mean=71.5 years old, range 47-93 years old	Case-control	Interview regarding occupations held for >1 year	Cases waiting for surgery secondary to knee OA	Cases waiting for surgery secondary to knee OA	Lifting >10 kg for 10 years, 10x per week vs. no lifting: Men OR=1.9 (1.0, 3.3) Women OR=1.5 (1.0, 2.3) Lifting >25 kg: Men OR=1.7 (0.9, 3.0) Women OR=1.7 (1.0, 2.8) Lifting >50 kg: Men OR=1.7 (0.9, 3.2) Women OR=1.2 (0.6, 2.4) Kneeling/squatting >1 hour/day: 1-9.9 years *Men OR=3.0 (1.4, 6.1) *Women OR=2.8 (1.4, 5.5) 10-19.9 years Men OR=1.3 (0.5, 3.2) Women OR=0.8 (0.3, 2.0) >20 years Men OR=1.7 (0.7, 4.0) Women OR=3.2 (0.8, 13.0) Kneeling/squatting & lifting: *Men OR=2.7 (1.1, 7.1) Women OR=0.3 (0.03, 4.1) Climbing ladder/stairs: *Men OR=2.3 (1.3, 4.0) Women OR=0.7 (0.3, 1.6)
Sandmark et al., 2000 [83] (Sweden)	n=1173 (Cases=625 Controls=548) Men: 589 Women: 584 Age: range 55-70 years old	Case-control	Questionnaire and interview	Age, BMI[3], sports	TKR[4] surgery	Lifting: *Medium Men OR=2.5 (1.5, 4.4) Medium Women OR=1.2 (0.7, 1.9) *High Men OR=3.0 (1.6, 2.9) High Women OR=1.7 (1.0, 2.9)

Reference	Study Sample	Study Design	Exposure Measurement	Adjusted for Covariates	Outcome	Results: OR (95% CI)[1]
						<u>> Work 10 years in heavy jobs:</u> *Men OR=2.5 (1.7, 3.6) *Women OR=2.5 (1.6, 3.9) <u>Squatting/knee bending:</u> Med. Men OR=1.3 (0.8, 2.2) *High Men OR=2.9 (1.7, 4.9) Med Women OR=1.2 (0.7, 1.9) High Women OR=1.1 (0.6, 1.9) <u>Kneeling:</u> Med. Men OR=1.4 (0.9, 2.2) *High Men OR=2.1 (1.4, 3.3) Med. Women OR=1.5 (1.0, 2.3) High Women OR=1.5 (0.9, 2.4) <u>Climbing stairs:</u> Medium exposure: Men OR=1.2 (0.8, 1.9) *Women OR=1.7 (1.1, 2.5) High exposure: Men OR=1.2 (0.7, 2.1) Women OR=1.4 (0.8, 2.3) Men: *Construction OR=3.1 (1.5, 6.4), *Farmers OR=3.2 (2.0, 5.2), Forestry OR=2.1 (1.0, 4.6) Women: *Farmers OR=2.4 (1.4, 4.1)
Lau et al., 2000 [82] (China)	n=1316 (Cases=658, Controls=658) Men: 332 Women: 984	Case-control	Interview	Age, sex	28% TKR[2] 15% waiting for TKR[4] 57% knee OA: KL[2] scale 3-4	<u>Lifting 10 kg 1-10x/week:</u> Men OR=1.5 (0.6,3.5) Women OR=1.2 (0.7,2.0) <u>Lifting >10x/week</u> *Men OR=5.4 (2.4,12.4) *Women OR=2.0 (1.2, 3.1)

Reference	Study Sample	Study Design	Exposure Measurement	Adjusted for Covariates	Outcome	Results: OR (95% CI)[1]
						Climbing > 15/flights stairs: Men: OR=2.5 (1.0, 6.4) *Women: OR=5.1 (2.5, 10.2)
Manninen et al., 2002 [84] (Finland)	n=805 (Cases=281, Controls=524) Men: 195 Women: 610 Age: 69.2 ±5.4, range 55-75 years old	Case-control	Computer-assisted telephone interview	BMI[3], knee injury, exercise	Arthroscopic surgery for knee OA	Physical Workload: Med. Men OR=2.23 (0.64, 7.72) Med. Women OR=1.60 (0.83, 3.06) High Men OR=1.53 (0.42, 5.56) *High Women OR=2.03 (1.03, 3.99) Lifting: Med. Men OR=1.35 (0.57, 4.16) Med. Women OR=0.90 (0.55, 1.50) High Men OR=0.92 (0.50, 2.39) High Women OR=1.11 (0.71, 1.75) Kneeling/squatting >2hours: Men OR=1.68 (0.66, 4.28), *Women OR=1.81 (1.11, 2.95) Climbing stairs: *Med Men OR=3.06 (1.25, 7.5) Med Women OR=1.08 (0.71, 1.63) High Men OR=2.79 (0.96, 8.2) High Women OR=1.50 (0.81, 2.77)
Jensen ,2005 [80] (Denmark)	n=149 Men: 149 Age: range 26-72 years old	Cross-sectional	Questionnaire and video recording of knee straining work	Age, BMI[3], sports, smoking	Knee OA: KL[2] scale ≥2	Kneeling or squatting: Low/mod OR=2.96 (0.5, 17.2) Med/high OR=4.20 (0.6, 27.9) *High/very high OR=4.92 (1.1, 21.9)
Yoshimura et al., 2006 [86] (Japan)	n=74 (Cases=37, Controls=37) Men: 74 Age: 70.0 ±6.6 years old	Case-control	Questionnaire	Heaviest weight, knee injury	Knee OA: KL[2] Scale ≥3	Physical work as principal job *Men OR=6.20 (1.40, 27.5)
Amin, 2008 [32] (United States)	n=192 Men: 192 Age: 69 ±9 years old	Cross-sectional	Validated questionnaire	Age, BMI[3], history of injury/surgery	MRI cartilage changes ≥grade 2; osteophyte	Squatting, lifting, & kneeling: *PF joint=OR 1.8, (1.1, 3.2] Medial TF joint=OR 1.6 (0.9, 3.0)
Mounach et al., 2008 [90]	n=190 (Cases=95, Controls=95)	Case-control	Questionnaire and interview	Obesity, age, sex	Symptomatic radiographic knee	Climbing stairs (>50/day) *Men and Women: OR=0.48, (0.26,

Reference	Study Sample	Study Design	Exposure Measurement	Adjusted for Covariates	Outcome	Results: OR (95% CI)[1]
(Moroco)	Men: 52 Women: 138 Age: 59.7 ±8.5 years old, 37-76 years old				OA: KL scale ≥3 for <1 year	0.91)
Rytter et al., 2009 [91] (Denmark)	n=254 (Cases=134, Controls=120) Men: 254 Age: 52.6 years old (cases), 57.9 years old (controls)	Case-control	Questionnaire	BMI[3], knee straining sports	Knee OA: Ahlback score ≥1	Floor layers vs. graphic designers ≤49 years old: TF OR=1.1 (0.1, 13.1) PF OR=0.1 (0.01, 1.3) 50-59 years old: *TF OR=3.6 (1.1, 12.0) PF OR=1.3 (0.5, 3.8) ≥60 years old: TF OR=1.9 (0.4, 7.8) PF OR=0.1 (0.01, 1.1)
Allen et al., 2010 [98] (United States)	n=2637 Men: 933 Women: 1796 Age: 63.8 ±10.8 years old	Cross-sectional	Interview administered questionnaire	Age, race, gender, BMI[3], prior knee injury, household tasks, smoking	Radiographic knee OA: KL[2] scale >2 Symptomatic knee OA: Criteria for Radiographic knee OA, plus pain, aching, and stiffness most days	Radiographic knee OA No association with any occupational task Symptomatic knee OA: Lifting >10 lb: *Men and Women: 1.42 (1.13, 1.80) Heavy work *Men and Women: 1.44 (1.03, 2.02)
Bernard et al., 2010 [92] (United States)	n=3436 Men: 1098 Women: 2450 Age: 63.4 ±10.9 years old (men), 61.4 ±10.7 years old (women)	Cross-sectional	Questionnaire	Age, sex, BMI[3]	Knee OA: KL[2] scale ≥grade 2	Stair Climbing: *Men: OR=1.61 (1.11, 2.32) Women: OR=1.14 (0.87, 1.49) Squatting: Men OR=1.56 (0.89, 2.75) Women OR=0.89 (0.50, 1.61)
Franklin et al., 2010 [93] (Iceland)	n=2490 (Cases=1408, Controls=1082) Men: 1066 Women: 1424 Age: 73.9 ±6.5	Case-control	Questionnaire	Age, sex, BMI[3], recreational activity	TKR[4]	Men: *Farmer OA=5.1 (2.1, 12.4) *Fisherman OA=3.3 (1.3, 8.4) Women: No occupations increased risk.

Reference	Study Sample	Study Design	Exposure Measurement	Adjusted for Covariates	Outcome	Results: OR (95% CI)[1]
	(men), 73.5 ±7.2 (women)					
Klussmann et al., 2010 [94] (Germany)	n=1310 (Cases=739, Controls=571) Men: 569 Women: 741 Age: 62 ±9.6 years old (women), range 25-75 years old	Case-control	Standardized questionnaire and semi-structured interview	BMI[3], sports, malalignment, genetics, childhood knee pain, smoking	Symptomatic Radiographic Knee OA: KL[2] scale >2 or arthroscopic surgery + pain	Cumulative lifting/carrying: >1,088 tons/life *Women:OR=2.13 (1.14, 3.98) Cumulative kneeling: >8,934 hours/life *Women:OR=2.52 (1.35, 4.68) 3,574 – 12,244 hours/live *Men: OR=.16 (1.24, 3.77) >12,244 hours/live *Men: OR=2.47 (1.41, 4.32)
Teichtahl et al., 2010 [95] (Australia)	n=96 Women: 96 Age: 46.5 ±9.1 years old, range 26-62 years old	Cross-sectional	Questionnaire	Age, BMI[3], frontal knee plane alignment	MRI measured tibial and patellar cartilage volume and defects	Patellafemoral joint: Heavy lifting/bending/squatting Women: OR=1.8 (1.0, 3.1) Knee bending: Women: OR=1.8 (1.0, 3.1) Stair climbing: *Women: OR=2.9 (1.4, 6.0)

OR (95% CI)[1]: Odds Ratio 95% Confidence Interval
KL[2]: Kellgren-Lawrence
BMI[3]: Body Mass Index
TKR[4]: Total Knee Replacement
***Statistical Significance**

1.6 Aim, Objectives, and Hypotheses

The current study aimed to provide new insight into the understanding of occupational risks factors in knee OA. First, lifetime exposure to occupational tasks was measured using a detailed questionnaire. This facilitated examining the cumulative effects of jobs with high activity levels combined with kneeling or knee-bending tasks regardless of how often individuals changed careers over their lifetime. The agreement of this self-report occupational exposure score was compared with an ergonomist-based rating system prior to performing the analyses. Next, to prevent gender bias and to obtain the most accurate quantification of occupational exposure, the occupations of homemaker, student, and retired person were included as valid occupations on the questionnaire. Finally, using a new definition of OA based on MRI, occupational risk was assessed in a population-based cohort that included people from across the spectrum of OA. As such, findings from this study provide novel implications about the role of occupational activities at the early stage of OA.

The overarching goal of this study was to determine the association between cumulative occupational physical load (COPL) to the knee and the presence of knee OA across the spectrum of disease in a cohort of men and women. COPL refers to an individual's lifetime total work activity, which includes the following potentially knee-straining tasks performed in an occupation: heavy lifting, carrying, knee bending, and kneeling.

The primary objective of this study was to examine the association between COPL to the knee and the presence of SOA. Next, I explored this relationship separately in men and women.

My secondary objective was two-fold. First, I examined the association between COPL to the knee and the presence of MRI-OA, using the new definition of MRI-OA by Hunter et al.[16] Second, I assessed the association between COPL to the knee and the presence of ROA. I hypothesized a priori that:

1. There would be a statistically significant association between COPL score and SOA of the knee.
    a. There would be a statistically significant association between COPL score and SOA of the knee in men.
    b. There would be a statistically significant association between COPL score and SOA of the knee in women.
2. There would be a statistically significant association between COPL score and MRI-OA of the knee.
3. There would be a statistically significant association between COPL score and ROA of the knee.

2 Methods

This chapter describes the methodology employed to examine the role of occupational activities as a risk factor for the development of knee osteoarthritis (OA). While moderate mechanical loading is necessary to stimulate anabolic processes in the joint to maintain healthy articular cartilage, overloading a joint with too much intensity and for too long, and undertaking particular types of physical activity can turn this same process catabolic and destructive. This study explored one source of knee joint loading in men and women: occupational activity; specifically, the tasks of heavy lifting or carrying, kneeling, and knee bending.

2.1 Research Design

This cross-sectional analysis was done with two cohorts of participants recruited from the Greater Vancouver area in British Columbia. The first cohort, the Model for the Diagnosis of Early Knee Osteoarthritis (MoDEKO), was a nine-year population-based longitudinal study that aimed to develop a clinical prediction model to identify early knee OA using combinations of clinical tests, imaging techniques, and biomarkers. MoDEKO recruited a stratified sample of 255 people with knee pain; of those, 163 completed a three-year follow-up. The six-year follow-up was underway during the current study. This cohort comprised people across all stages of disease. A previous publication regarding this cohort reported that 13% had no OA, 49% had pre-radiographic osteoarthritis (pre-ROA), and 38% had radiographic osteoarthritis (ROA).[35]

The second cohort, Asymptomatic Cohort for Early Knee Osteoarthritis (ACE-KOA), consisted of a stratified population-based sample of 73 people from the Greater Vancouver area without knee pain. Recruitment of ACE-KOA participants began in 2008. The current

study used baseline data collected from MoDEKO between 2002 and 2004, and from ACE-KOA between 2008 and 2009.

2.2 Participants and Recruitment

Individuals eligible for MoDEKO: 1) were between 40 and 79 years old; 2) had experienced pain, aching, or discomfort in or around the knee on most days of the month at any time in the past; and 3) had experienced pain, aching, or discomfort in or around the knee in the past 12 months. Previous research that evaluated knee pain with respect to determining prevalence and associations with disability and structural change in the community recommended these specific criteria for use in recruiting participants for population studies where the burden of pain was the relevant variable of interest.[102] It showed the most sensitivity, ($\geq$grade II osteophyte=72.2%) compared with two discrete variations of similar questions.[102] The presence of any of the following conditions or situations made individuals ineligible for the study: inflammatory arthritis or fibromyalgia, knee arthroplasty, knee injury or surgery within the past six months, knee pain referred from the hips or back (determined by clinical exam), or inability to undergo MRI. To ensure appropriate distribution, recruitment was organized into eight strata by sex and decade (age 40-49 years; 50-59 years; 60-69 years; 70-79 years), with each stratum capped at 34 participants.

A random list of households, including addresses and telephone numbers, was generated from the telephone directory listings. Recruitment followed a multi-stage screening process (Figure 2.1). Initially, invitation letters were mailed to these households (n=8,523), followed by a standardized telephone screening conducted by an independent marketing agency, Pulse Research Limited. Seven call attempts were made over the next three weeks before a number was excluded because contact could not be established

(n=2,337). Other households were excluded because residents could not speak English (n=955). Of the 5,231 English-speaking people who were reached by telephone, 3,269 people consented to the screening survey. The recruiter interviewed the person who answered the telephone; if that person was not eligible, the recruiter asked if there was another household member who would fit the criteria. If this included multiple people, the person with the next birthday was selected. If necessary, the same procedure was repeated for a third household member. From this screening, 265 individuals met the eligibility criteria and were invited to the study centre to participate in a physical assessment and complete a detailed questionnaire. At the centre, a further 10 individuals were excluded for the following reasons: 1) missing assessment appointment (n=5); 2) failing to give consent (n=1); 3) failing to complete an MRI (n=1); 4) not having knee pain (n=1); and 5) other reasons (n=2). Therefore, 255 eligible individuals were included in the MoDEKO cohort.

The ACE-KOA cohort was recruited from the same population as MoDEKO using a similar multi-stage protocol (Figure 2.2). Eligible participants: 1) were between 40 and 79 years old; and 2) had responded "no" to both questions regarding knee pain, which were used in MoDEKO. The remaining exclusion criteria and stratum organization by age and sex were identical to those of MoDEKO, except that each age and gender stratum was capped at 12 and each age stratum was capped at 22. The enrolment target for ACE-KOA was determined by sample size calculations completed by researchers prior to recruitment. Invitation letters were mailed to a randomly generated list of households (n=4,300). These letters were followed by a standardized telephone screening call conducted by a research assistant from The Arthritis Research Centre of Canada. Five call attempts were made over the next three weeks and two messages left before a number was excluded because contact could not be established (n=1,745). Other households were excluded because residents could not speak English (n=200). Of the 2,355 English-speaking people who were reached

by telephone, 1,091 people consented to the screening survey. The research assistant interviewed the person who answered the telephone; if that person was not eligible, they asked if there was another household member who would fit the eligibility criteria. If this included multiple people, the person with the next birthday was selected. If necessary, the same procedure was repeated for a third household member.

From this screening, 104 individuals met the eligibility criteria and were invited to participate in a physical assessment and complete a detailed questionnaire at the study centre. At the centre, a further 31 individuals were excluded for the following reasons: 1) knee pain (n=13); 2) not willing to participate (n=7); 3) failing to complete an MRI (n=5); 4) missed appointment (n=5); and 5) having a rheumatologic condition (n=1). The recruitment process resulted in the ACE-KOA cohort containing 73 participants.

Figure 2.1: Study Recruitment for MoDEKO Cohort

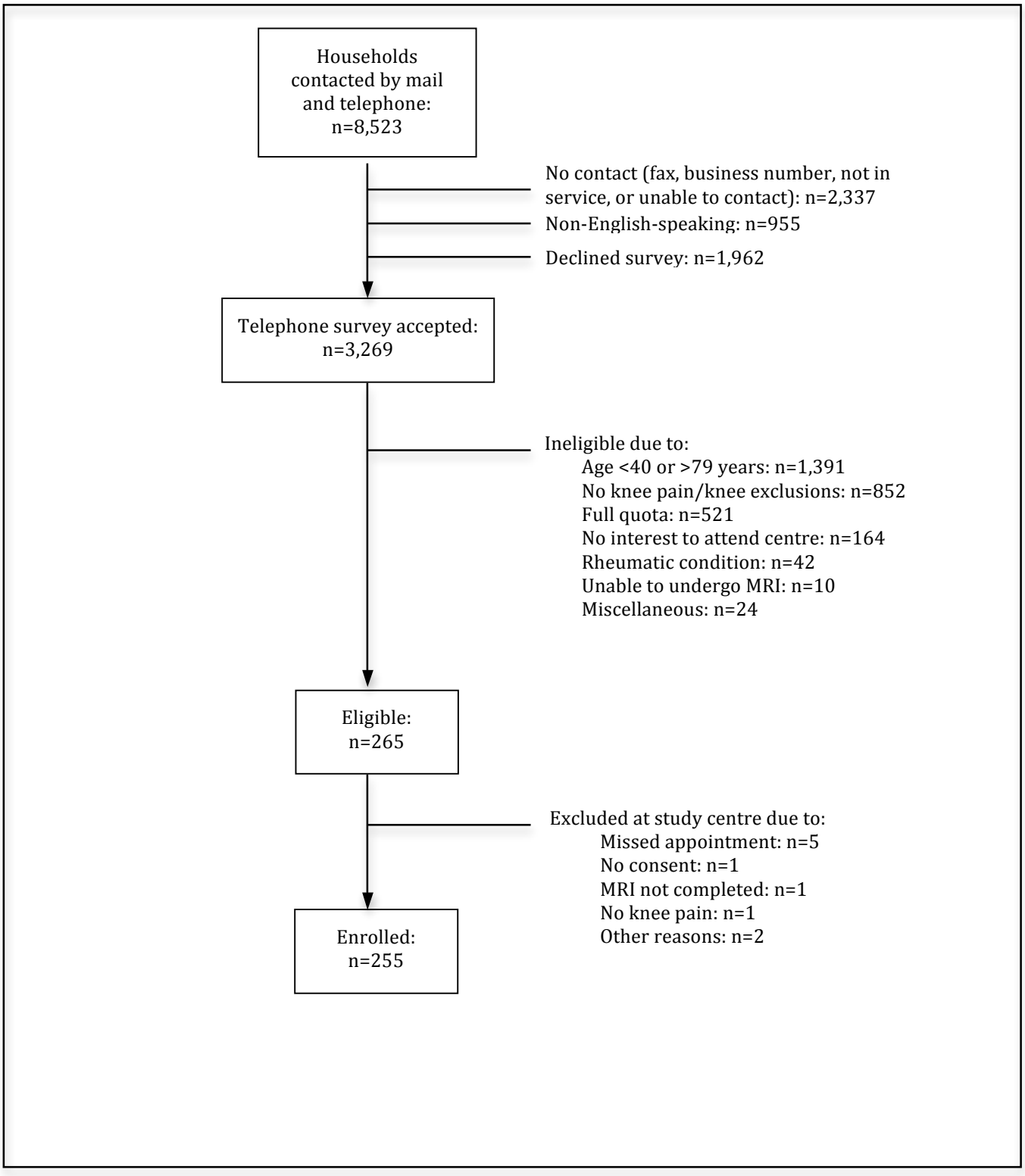
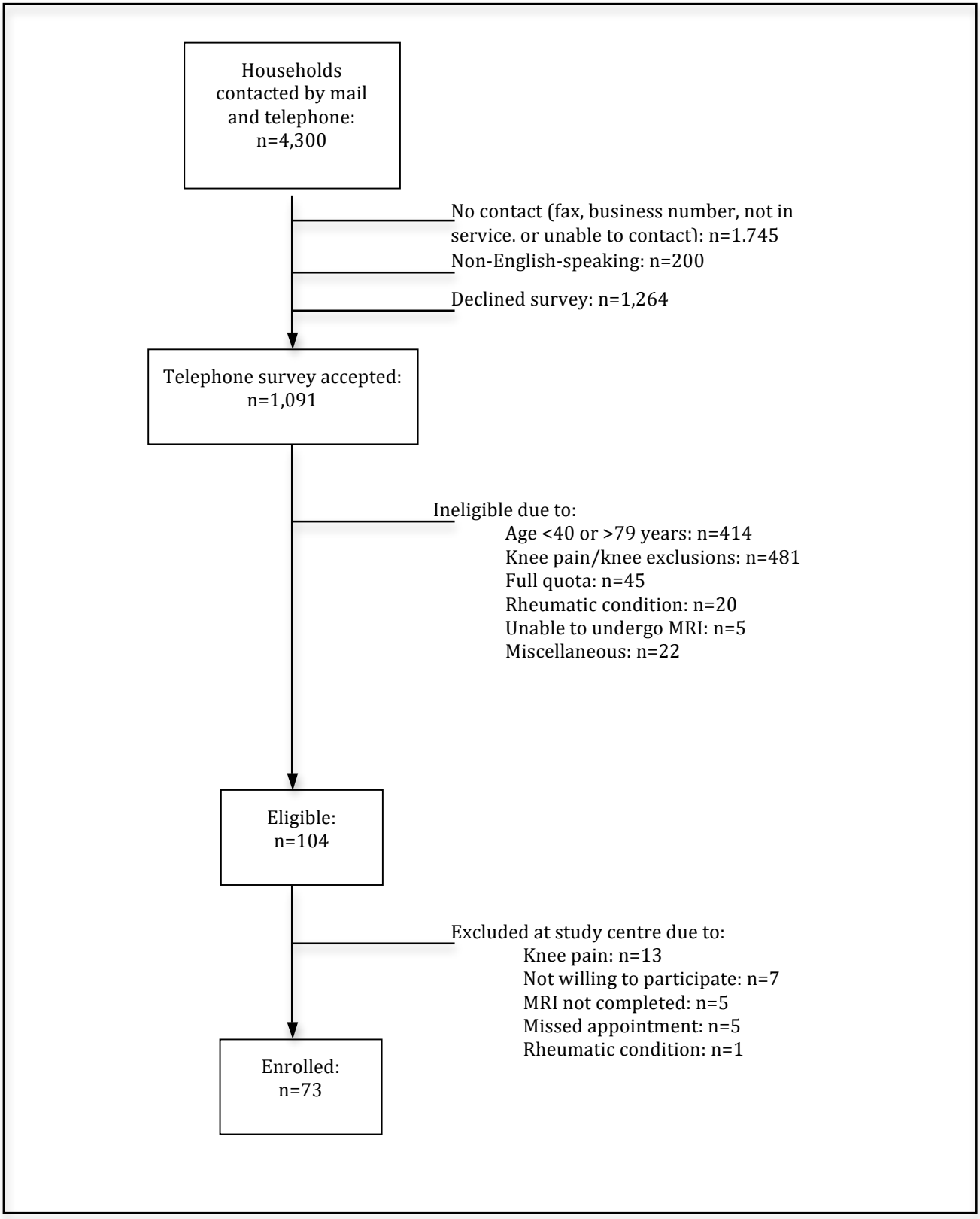


Figure 2.2: Study Recruitment for ACE-KOA Cohort



2.3 Study Procedure

At the study centre, all participants (n=328) received a standardized knee assessment, completed two self-administered questionnaires, and underwent knee radiographs and an MRI. The standardized knee examination, shown to have high inter-rater reliability in 10 domains (reliability co-efficient=0.67-0.99),[103] was performed by a rheumatologist. It included assessments for malalignment and gait by inspection, quadriceps atrophy and strength, effusion, bony swelling, general passive crepitus, and range of motion measurement with a goniometer. Participants completed the Western Ontario and McMaster Universities Osteoarthritis Index, a validated instrument for assessing the condition of people with knee OA.[104] A comprehensive questionnaire was used to gather demographic details, information regarding OA risk factors, and knee symptoms. Data were collected on the following items: 1) participant information, such as age, ethnicity, marital status, and education; 2) knee symptoms, including pain location, duration, and intensity; 3) medical history, including co-morbid conditions, smoking status, and previous surgery; 4) use of medication and non-pharmacological treatments for knee pain and other purposes, including oral contraceptive or hormone replacement therapy; 5) self-reported weight and height, at the time of the assessment and at age 25; 6) history of severe knee injury (required a walking aid for at least one week) or mild knee injury (no walking aid for at least one week); 7) regular sports activities that were performed at least once weekly after age 20 and current physical activities; 8) family history of osteoarthritis; and 9) occupational history, defined as all occupations held for at least 12 months after the age of 18, including occupations such as student, homemaker, or retiree.

Participants were asked to list all previous occupations, the number of years in that position, and their starting age. For each occupation, they rated the activity level on a five-point scale (Table 2.1) and then reported whether the job involved knee bending or

kneeling, with “Never”=0, “Occasionally”=1, and “Frequently”=2. In addition, participants received radiographs and MRI assessments within one month of the study centre visit. Knee radiographs were done using a fixed flexion technique with the SynaFlexor positioning frame in weight bearing and a skyline view in a supine position. Two independent readers, blinded to clinical and MRI information, scored the radiographs on the Kellgren & Lawrence (K&L) scale of 0-4.[15]

Table 2.1: Occupational History: Activity Level Score

Activity Level	Description
1-Sedentary	Lifting of 10 lb maximum with occasional walking or standing
2-Light	Lifting of 20 lb maximum with frequent lifting or carrying of up to 10 lb; frequent walking or standing
3-Medium	Lifting of 50 lb maximum with frequent lifting or carrying of up to 25 lb
4-Heavy	Lifting of 100 lb maximum with frequent lifting and carrying of up to 50 lb
5-Very Heavy	Lifting of over 100 lb with frequent lifting or carrying over 50 lb

The MRI was performed on a GE 1.5T magnet using a transmitter-receiver extremity knee coil. The protocol involved four MRI sequences: 1) fat-saturated T1-weighted three-dimensional spoiled gradient-recalled acquisition in the steady state sequence with images obtained in the sagittal plane with reformat images in the axial and coronal planes (repetition times [TR] 52 msec, time to echo [TE] 10 msec, flip angle 60, field of view [FOV] 12 cm matrix 256 x 128, section thickness 1-1.5 mm, with 1 signal averaged); 2) fat-saturated T2-weighted fast spin-echo (FSE) sequence with images obtained in the coronal plane (TR 3,000 msec, TE54 msec, echo train length [ETL] 8, FOV 14 cm matrix 256 x 128, section thickness 4 mm, with an intersection gap of 1 mm with two signals averaged); 3) T1-

weighted FSE sequence with images obtained in the oblique sagittal plane (TR 450 msec, TE minimum full, ETL 2, bandwidth 20 Hz/pixel, FOV 16 cm, matrix 384 x 224, section thickness 4 mm, with an intersection gap of 1 mm with two signals averaged); 4) T2-weighted FSE sequence with images obtained in the oblique sagittal plane (TR 4,025 msec, TE 102 msec, ETL 17, bandwidth 20 Hz/pixel, FOV 16 cm, matrix 320 x 288, sectional thickness 3 mm with an intersection gap of 0 mm with four signals averaged).

The following six areas were scored: medial and lateral tibial plateaus, medial and lateral femoral condyles, patella, and trochlear groove. MRI was scored by one reader, blinded to radiographs and clinical exams, for the presence of the following: cartilage (Table 2.2), osteophyte formation (Table 2.3), bone marrow edema or subchondral cysts (Table 2.4), and anterior, body, or posterior meniscal pathology (Table 2.5).

Table 2.2: Semi-Quantitative Assessment of Cartilage*

0	Normal cartilage
1	Abnormal signal without cartilage contour defect
2	Cartilage defect ≤50%
3	Cartilage defect >50% but <100%
4	Cartilage defect 100% with subjacent bone signal abnormality

*Scale adapted from Disler et al.[105]

Table 2.3: Assessment of Osteophytes

0	Absent
1	Small beak-like osteophyte
2	Intermediate-size osteophyte
3	Proliferative or mushroom-like osteophyte

Table 2.4: Assessment of Bone Marrow Edema and Subchondral Cysts

	Bone Marrow Edema	Subchondral Cysts
0	Absent	Absent
1	Mild	≤2 small cysts
2	Moderate	>2 small cysts or 1 large cyst
3	Severe	≥2 large cysts

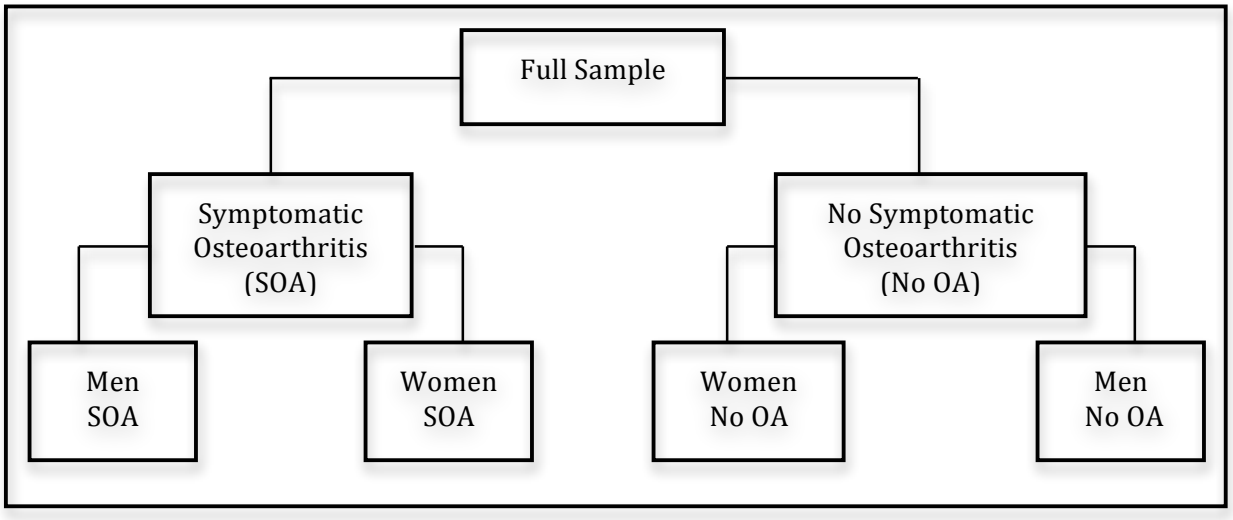
Table 2.5: Assessment of Meniscus

0	Normal
1	Intra-substance increased signal intensity
2	Increased signal intensity extending to articular surface (i.e., tear)

2.4 Outcome Variables

For the first study hypothesis, participants were classified into one of two groups based on K&L scores (Table 1.1) from radiographs and clinical symptoms: Symptomatic Osteoarthritis (SOA) or No SOA (Figure 2.3). These subgroups were defined based on previous literature and by consensus of MoDEKO researchers: 1) SOA=K&L grade $\geq$2 and knee pain, as defined by the two study inclusion pain criteria; and 2) No SOA=K&L grade <2 or no pain. Participants were then further subdivided by sex.

Figure 2.3: Participant Classification for the Primary Objectives



For the second study hypothesis, participants were reclassified into 1) MRI-OA, or 2) No MRI-OA using the semi-quantitative MRI data. Each component of the MRI-OA definition created by Hunter et al.[16] (Table 1.2) was matched closely with the current MRI data, except for bone attrition, with the assistance of MoDEKO researchers experienced with

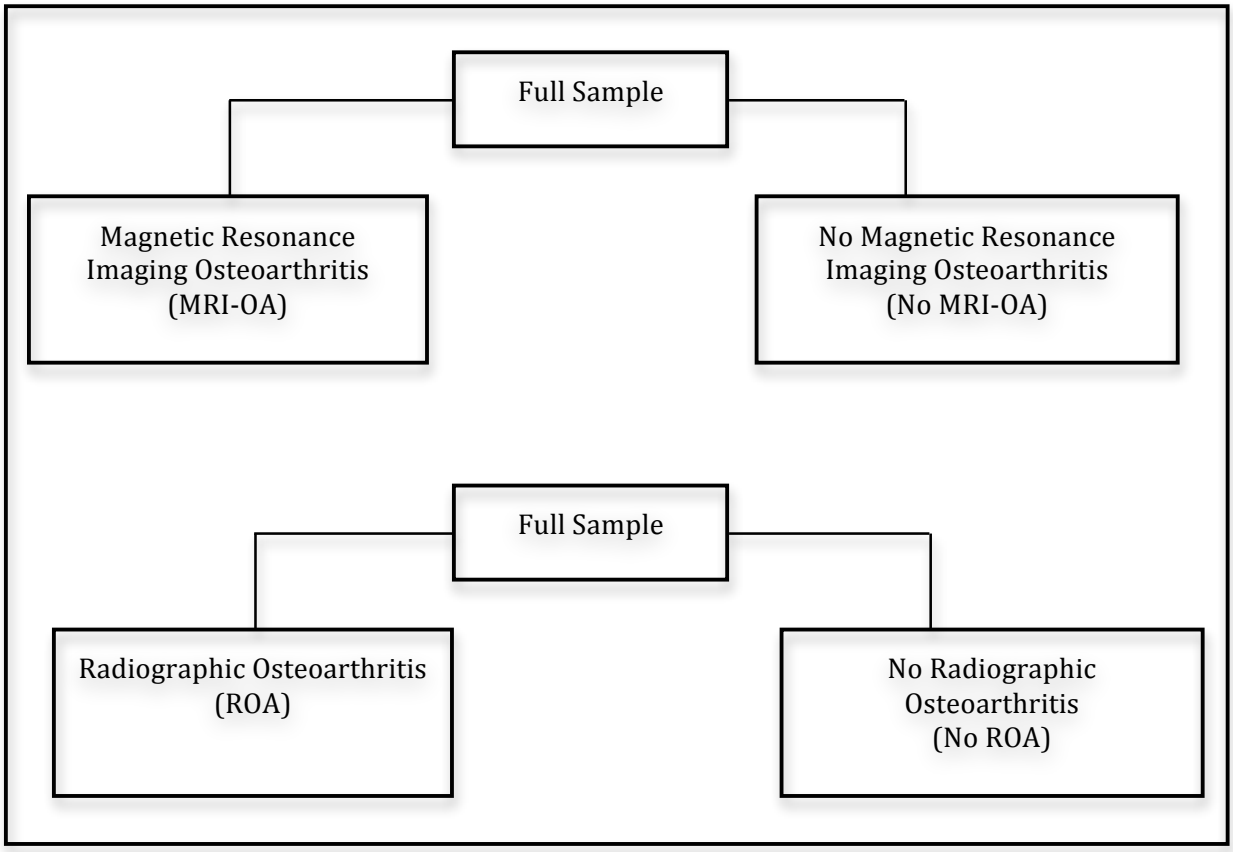
this data set (Table 2.6). To assess tibiofemoral OA the medial and lateral tibial plateaus and femoral condyles were assessed, whereas for patellofemoral OA the patella and trochlear grooves were assessed. If participants met either the tibiofemoral or patellofemoral OA definition, they were classified as MRI-OA. If they met neither tibiofemoral nor patellofemoral OA, they were classified as No MRI-OA.

For the final hypothesis, participants were redistributed into two groups based on only radiograph results: 1) Radiographic osteoarthritis (ROA)=KL grade ≥2; 2) No ROA=KL grade <2.

Table 2.6: Magnetic Resonance Imaging–Defined Osteoarthritis

<table>
<tr><th colspan="2">MRI-OA (Tibiofemoral)
The presence of both group A features or one group A and two or more of Group B features:</th></tr>
<tr><td>Group A</td><td>Group B</td></tr>
<tr><td>Definite osteophyte formation: score of ≥2 on osteophyte assessment (see Table 2.3)</td><td>Subchondral bone marrow lesion or cyst: Score of ≥1 on bone marrow edema or subchondral cyst (see Table 2.4)</td></tr>
<tr><td rowspan="3">Full thickness cartilage loss: score of 4 on cartilage assessment (see Table 2.2)</td><td>Meniscal subluxation, maceration, or degenerative tear: score of 2 on assessment of meniscus (see Table 2.5)</td></tr>
<tr><td>Partial thickness cartilage loss: score of 2 or 3 on cartilage assessment (see Table 2.2)</td></tr>
<tr><td>Bone attrition: not scored</td></tr>
<tr><th colspan="2">MRI-OA (Patellofemoral)
All of the following involving the patella and/or anterior femur:</th></tr>
<tr><td colspan="2">Definite osteophyte formation: score of ≥2 on osteophyte assessment (see Table 2.3)</td></tr>
<tr><td colspan="2">Partial or full thickness cartilage loss: score of ≥2 on cartilage assessment (see Table 2.2)</td></tr>
</table>

Figure 2.4: Participant Classification for the Secondary Objectives



2.5 Exposure Variable: Cumulative Occupational Physical Load

The occupational physical load (OPL) of each job was calculated by multiplying the number of years in each job (Y) by the activity level (A) and by the knee-bending or kneeling score (K) for each occupation for each participant. The knee-bending score was recoded to the following: 1=never, 2=occasionally, and 3=frequently, to avoid a "0" score in the OPL calculation. This equation was illustrated as:

$$OPL = Y * A * K$$

The COPL for each participant was the sum of the OPL for every occupation reported. If a participant reported multiple concurrent jobs, OPL for each occupation was adjusted proportionally with respect to the overlapping time period. For example, if a participant reported three concurrent occupations, then one-third of the OPL for each was included. The COPL equation was:

$$COPL = \sum_{i=1}^{n} (OPL)_i$$

2.5.1 Cumulative Occupational Physical Load Agreement Analysis

Exposure to occupational activities in relation to knee OA has been quantified in many ways;[1, 32, 81] however, no gold standard has been developed as yet. Before proceeding with my objectives, I assessed the agreement between the COPL measure and scores calculated based on data from the Occupational Information Network (O*NET) database.[106] O*NET is the primary source of occupational information in the United States. The current version was an update of the 1991 Dictionary of Occupational Titles, by the US Department of Labor/Employment and Training Administration. It is maintained by the National Center for O*NET Development and regularly updated by job incumbents, occupational experts, and occupational analysts. Most recently updated in July 2011, O*NET consists of a database containing more than 900 occupations. Detailed descriptions of required tasks, knowledge level, skills, abilities, and qualifications, as well as information about wages and employment trends are given for each occupation. For this agreement analysis, scores were used from the section called "work context," where each occupation is given a score out of 100 for "performing general physical activities" and "time spent kneeling, crouching, stooping, or crawling."

The O*NET Occupational Score (OOS) was calculated by multiplying the number of years in each job (Y) by the O*NET score for "general physical activity" (PA) and "time spent kneeling, crouching, stooping or crawling" (TSK) for each occupation that participants reported:

$$OOS = Y * PA * TSK$$

The cumulative O*NET occupational score (COOS) for each participant was calculated by summing the OOS scores for every occupation that participants reported. In participants who held concurrent multiple jobs, each OOS score for those occupations was weighted by half for the overlapping time period:

$$COOS = \sum_{i=1}^{n} (OOS)_i$$

O*NET does not provide data on homemakers as an occupation and so we used the occupation of patrolman as a proxy. Previous research analyzing the composition of homemakers' duties found that the physical demands of homemaking were similar to those of a patrolman.[107] In that study, 48 homemakers were interviewed using the Position Analysis Questionnaire. Results indicated that being a homemaker was personally demanding and required sensitivity to oneself and one's environment, as well as a variable activity schedule; all of which are similar to the requirements of a patrolman's duties. The occupational roles of student or retired person were excluded from this agreement assessment, due to the large individual variability of loading tasks for these occupational roles.

For this agreement analysis, I calculated COPL and COOS scores for a subset of 60 participants randomly selected from the MoDEKO database. The Pearson correlation

coefficient (Y) was used to assess the correlation between the two scores and a Bland Altman plot was used to illustrate the relationship between the two scores.

2.6 Power Calculation

Power calculations were performed a priori to ensure sufficient sample sizes for addressing the current objectives and hypothesis. The sample was hypothetically divided into four equal-sized quarters based on occupational exposure, a reference category with the lowest exposure, then moderate, high, and highest exposure categories.

2.6.1 Primary Objectives

To examine the relationship between exposure to COPL and SOA, the entire sample was used (n=327); among those, 102 (31.2%) had SOA. Each exposure quarter contained 81 or 82 participants. Based on this information, I assumed that 21% of those who experienced the lowest occupational exposure (Quarter 1) have SOA (n=17), and 41%, or 33 people, with the highest exposure (Quarter 4) have SOA. The literature in this field suggests that a relative risk (RR) of 2 is commonly used to compare two exposure groups in a power calculation.[68, 94] In the current study, if I compared the highest quarter with the lowest quarter of exposure, we would have 74.2% power to detect an RR=2.0 and 82.6% power for an RR=2.1.

The next analysis was the relationship between exposure to COPL and the presence of SOA in men (n=160) and women (n=167) separately. There were 45 (28.1%) men with SOA. I assumed that 12% of those who experienced the lowest occupational exposure (Quarter1) had SOA (n=5) and 44% of those with the highest occupational exposure (Quarter 4) had SOA (n=18). Comparing the highest quarter with the lowest quarter of exposure, I had 85.0% power to detect an RR=3.7 at alpha=0.05. There were 58

(34.1%) women with SOA. I assumed that 18% of those who experienced the lowest occupational exposure (Quarter 1) had SOA (n=8) and 50% of those with the highest occupational exposure (Quarter 4) had SOA (n=21). Comparing the highest quarter with the lowest quarter of exposure, we had 82.9% power to detect an RR=2.8 at alpha=0.05.

2.6.2 Secondary Objectives

Firstly, to investigate the relationship between exposure to COPL and MRI-OA in the overall sample (n=327), I found that 40.1%, or 131 participants, had MRI-OA. Each quarter contained 81 or 82 participants. I assumed that 27% of those who experienced the lowest occupational exposure (Quarter 1) had MRI-OA (n=22) and 53% of those in the highest occupational exposure (Quarter 4) had MRI-OA (n=43). Comparing the highest with the lowest quarter of exposure, I had 90.7% power to detect an RR=2.0 (alpha=0.05).

Secondly, to investigate the relationship between exposure to COPL and ROA in the overall sample (n=327), it was calculated that 33.3%, or 109 participants, had ROA. The same exposure quarters were used as with MRI-OA. I assumed that 22% of those who experienced the lowest occupational exposure (Quarter 1) had ROA (n=18) and 44% of those with the highest occupational exposure (Quarter 4) had ROA (n=36). Comparing the highest with the lowest quarter of exposure, I had 81.3% power to detect an RR=2.0 (alpha=0.05).

2.7 Statistical Analysis

Descriptive demographic data including sex, ethnicity, marital status, education, smoking status, and family history of OA were described by frequency (%) for the full sample, by sex, and for each of the OA subgroups (SOA/No SOA; MRI-OA/No MRI-OA; ROA/No ROA). Age, BMI, and COPL were also summarized in means with standard

deviations (SD) for each of the OA subgroups and by sex. The continuous exposure variable, COPL, was grouped into a categorical variable called QCOPL, with 25% of participants in each quarter to allow for possible non-linearity in the statistical models. The lowest quarter was deemed the reference group.

For the remainder of the analyses, a population-based stratum-sampling weight was applied to the data to allow for greater generalizability of results to the population of the Greater Vancouver area. This weight was originally calculated for each cohort (MoDEKO and ACE-KOA) separately and then recalculated when the two cohorts were combined. An overall weighted mean COPL score and SD were calculated, as well as the weighted mean COPL and SD for each quarter for all OA and gender subgroups. Box plots (unweighted) were used to identify extreme or outlier results.

The variables of age, BMI, and female sex were important covariates to include in this analysis. I adjusted for them as potential confounders, and also examined possible interactions between each variable and COPL. Age was considered a potential confounder as the literature suggests that it is a predictor of the presence of knee OA.[13] To the best of my knowledge, there is no study that examines the association between age and the amount of OPL for an individual; however, it is reasonable to believe that older individuals will have accumulated greater cumulative OPL throughout their lifetime than younger people. While BMI has been shown to be an independent risk factor for knee OA,[46, 108] previous research has also shown an interaction between BMI and physical workload.[52, 56] Female sex is also associated with higher frequency of OA,[13] and OPL has been found to be higher in men.[65] Before constructing the final models for each analysis, uni-variable logistic regression was performed for QCOPL, age, BMI, and female sex (as appropriate), versus each OA outcome. The final multi-variable model was adjusted for age, BMI, and female sex as well as any statistically significant interaction terms.

To address the primary objectives, two separate analyses were done. First, logistic regression was used to assess the association between QCOPL and the presence of SOA, after adjusting for female sex, age, and BMI. Two-way interactions between age, BMI, and female sex with QCOPL were examined. Second, logistic regression was used to explore the association between QCOPL and the presence of SOA, in men and women separately, after adjusting for the same covariates and two-way interactions.

A sensitivity analysis was done to examine how uncertainty in the model output can be attributed to uncertainty in the model input. With this in mind, COPL scores were recalculated, excluding homemakers as a source of occupational exposure. COPL quarters, QCOPL, were recalculated using the new score. The model for the primary objective was re-run using the revised COPL scores and the output was compared with the original model, which included homemakers.

Two separate analyses were done to address the secondary objectives. First, logistic regression was used to examine the association between QCOPL and the presence of MRI-OA, after adjusting for age, BMI, and female sex. Second, logistic regression was used to explore the association between QCOPL and the presence of ROA, after adjusting for age, BMI, and female sex. The level of statistical significance was set at $p \leq 0.05$. All analyses were performed using SAS version 9.2.

3 Results

Two population-based cohorts, MoDEKO (n=255) and ACE-KOA (n=73) were combined into one cohort (n=328) for the current study. One participant was excluded due to incomplete occupational data. The remaining participants (n=327) made up the full sample. Unweighted demographic data and characteristics are presented in Table 3.1. Participants were on average 58.5 years old (standard deviation SD=11.0) with a BMI of 26.3 (SD=4.7). The majority of participants were married (n=198; 60.6%), with others single (n=44; 13.5%), divorced (n=42; 12.8%), widowed (n=30; 9.2%), or separated (n=13; 4.0%). There were more women (n=167; 51.1%) than men (n=160; 48.9%), and Caucasian was the most common ethnicity (n=257; 78.6%), followed by Asian (n=44; 13.5%). University education was achieved by 128 (39.1%) participants. Just under half of participants had a history of knee injury (n=145), just under half had a family history of osteoarthritis (OA) (n=152; 44.3%), and just over half had a smoking history (n=172; 52.6%). The average COPL score was 194.2 (SD=137.8).

The average age of men was 58.1, (SD=10.9) and of women was 58.9 (SD=11.0) (Table 3.1). BMIs were similar (men 26.4, SD=3.4; women 26.2, SD=5.6.) A higher percentage of men were married (73.8%) compared with women (47.9%), and more men had attended university (men: 46.3%; women: 32.3%). A history of knee injuries was reported by 48.8% of men compared with 40.1% of women, and more men than women reported smoking (58.8% vs. 46.7%). Conversely, a greater proportion of women had a family history of OA (59.2%) compared with men (33.1%). Average COPL scores for the two sexes were 204.6 (SD=144.7) for men and 184.2 (SD=130.6) for women.

To convert COPL from a continuous variable to a categorical variable (QCOPL), quartiles of COPL were calculated using the unweighted full sample (n=327). The 25th

Table 3.1: Participant Characteristics: Full Sample and by Sex (Unweighted)

Subgroup	Full Sample (n=327)	Men (n=160)	Women (n=167)
Age, years mean, SD	58.5 (11.0)	58.1 (10.9)	58.9 (11.0)
Sex, women (%)	167 (51.0)	0	167 (100)
Ethnicity (%)			
Caucasian	257 (78.6)	122 (76.3)	135 (80.8)
Asian	44 (13.5)	23 (14.4)	21 (12.6)
Black	2 (0.61)	2 (1.3)	0
First Nation	3 (0.92)	0	3 (1.8)
Hispanic	2 (0.61)	1(0.63)	1 (0.6)
Other	19 (5.8)	12 (7.5)	7(4.2)
Marital Status (%)			
Married	198 (60.6)	118 (73.8)	80 (47.9)
Divorced	42 (12.8)	11 (6.9)	31 (18.6)
Separated	13 (4.0)	8 (5.0)	5 (3.0)
Widowed	30 (9.2)	3 (1.9)	27 (16.2)
Single	44 (13.5)	20 (12.5)	24 (14.4)
Type of Post-Secondary Education (%)			
High school	73 (22.3)	26 (16.2)	47 (28.1)
Trades training	19 (5.8)	13 (8.1)	6 (3.4)
College	58 (17.7)	23 (14.4)	35 (21.0)
University	128 (39.1)	74 (46.3)	54 (32.3)
Other	18 (5.5)	7 (5.5)	11 (6.6)
Missing data	31 (9.4)	17 (10.6)	14 (8.4)
Body Mass Index (SD)	26.3 (4.7)	26.4 (3.4)	26.2 (5.6)
Knee Injuries (%)	145 (44.3)	78 (48.8)	67 (40.1)
Family History OA (%)			
No	159 (48.6)	97 (60.6)	62 (37.1)
Yes	152 (46.5)	53 (33.1)	99 (59.2)
Missing data	16 (4.9)	10 (6.3)	6 (3.6)
Smoking Ever			
No	155 (47.4)	66 (41.3)	89 (53.3)
Yes	172 (52.6)	94 (58.8)	78 (46.7)
Years, mean (SD)*	19.5 (13.4)	19.1 (13.5)	20.0 (13.5)
COPL, mean (SD)	194.2 (137.8)	204.6 (144.7)	184.2 (130.6)
QCOPL 1 (%)	81 (24.8)	37 (23.1)	44 (26.3)
QCOPL 2	82 (25.1)	38 (23.8)	44 (26.3)
QCOPL 3	82 (25.1)	39 (24.4)	43 (25.7)
QCOPL 4	82 (25.1)	46 (28.8)	36 (21.6)

*reported by former and current smokers only

percentile, 50th percentile, and 75th percentile QCOPL scores were 82, 157, and 282, respectively. Each quarter contained 25% of participants (n=81 in QCOPL 1, n=82 in QCOPL 2-4). The definition of QCOPL is: 1) QCOPL 1: less than 82; 2) QCOPL 2: 82 to 156; 3) QCOPL 3: 157 to 281; 4) QCOPL 4: greater than 281. A boxplot confirmed programming and QCOPL calculations by showing no overlap between quarters and no extreme outliers (Figure 3.1). The distribution of COPL using the weighted sample was also calculated and resulted in the following counts and percentages per quarter: QCOPL 1: n=118.4 (36.2%); QCOPL 2: n=92.8 (28.4%); QCOPL 3: n=69.3 (21.1%); QCOPL 4: n= 46.5 (14.2%). The unweighted quarters were used for the definition of QCOPL in order to avoid unequal statistical power across different comparisons. The weighted COPL scores varied from 12 to 729 and the mean (SD) weighted COPL score was 151.8 (124.0). The mean (SD) weighted COPL score by quarter is shown in Figure 3.2.

Figure 3.1: Boxplot of Mean Weighted COPL by QCOPL Level (Unweighted)

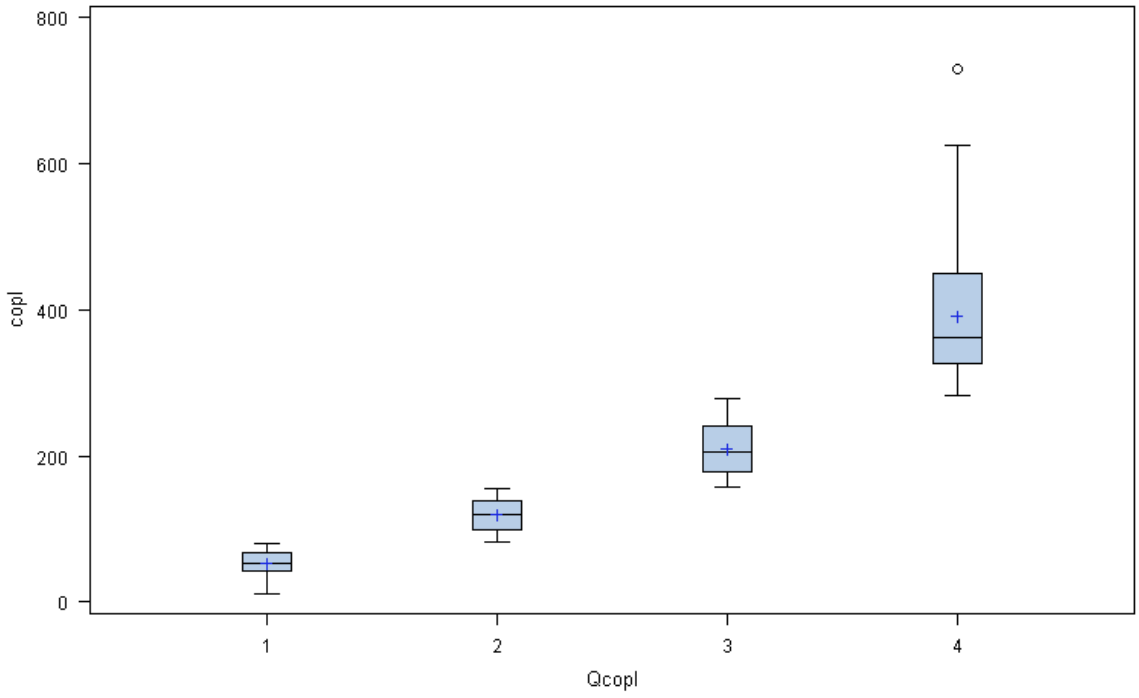
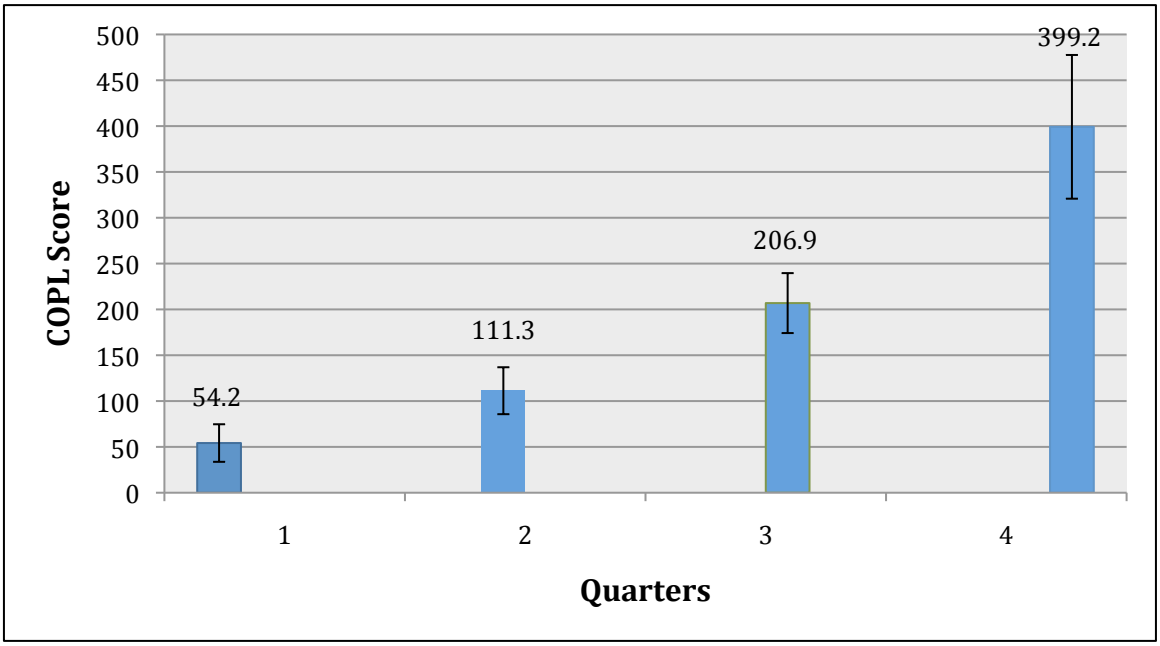


Figure 3.2: Mean (SD) Weighted COPL Score by Unweighted Quarter for Men and Women



3.1 Cumulative Occupational Physical Load Agreement Analysis

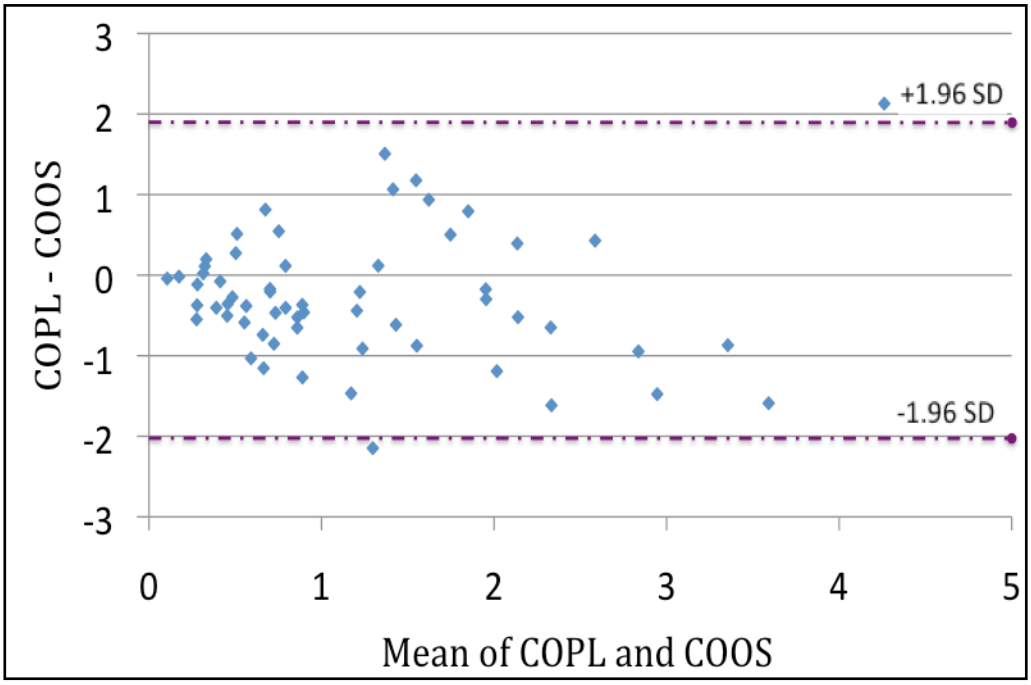
In a random sample, 60 participants from MoDEKO, 29 women and 31 men with an average age of 59.0 years old (SD=11.3), were selected for this sub-analysis (Table 3.2). Everyone had knee pain, but Kellgren-Lawrence (K&L) scores varied with K&L<2: n=42; K&L=2: n=7; and K&L>2: n=11. Based on two different scoring systems, the average COPL score was 191.8 (SD=141.7), and the average Cumulative O*NET Occupational Scores (COOS) was 27,970.2 (SD=25883.7). The Pearson correlation coefficient (ϒ) was 0.69 (95%CI=0.52, 0.80). The Bland Altman plot (standardized variables) was distributed around 0 and free of systemic patterns, indicating no consistent bias of one measure over the other (Figure 3.2).

Table 3.2: Participant Characteristics: Agreement Analysis (n=60)

Sex: women, n (%)	29 (48.3)
Age, mean (SD)	59.0 (11.3)
Knee OA Severity, n (%) KL <2 KL=2 KL >2	 42 (70.0) 7 (11.7) 11 (18.3)
COPL, mean (SD)	191.8 (141.7)
COOS, mean (SD)	27,970.2 (25,883.7)

KL: Kellgren-Lawrence Scale

Figure 3.3: Bland Altman Plot with Standardized Variables



3.2 Objective 1

3.2.1 Cumulative Occupational Physical Load as a Risk Factor for Symptomatic Osteoarthritis

In the full sample (n=327), there were 102 people with symptomatic osteoarthritis (SOA) (Table 3.3). Their average age (63.5 years old, SD=9.9) was higher than that of the 255 participants with No SOA (56.2 years, SD=10.7). The SOA group had proportionally more women than the No SOA group (55.9% vs. 48.9%), as well as a higher BMI (BMI=27.3; SD=5.3) than the No SOA group (BMI=25.8; SD=4.3). Other demographic details including ethnicity, marital status, education, and family history of OA were similar between groups. The SOA group's average COPL score of 249.0 (SD=137.4) was higher than the No SOA group's score of 169.3 (131.0).

For the analysis, a population-based weight was applied to the sample. Using the unweighted quartiles, the weighted sample was divided into QCOPL by COPL score with 81 participants in quarter 1, while quarters 2-4 had 82 participants. These quarters, along with the mean (SD) COPL score per quarter, are shown in Figure 3.2. The distribution of QCOPL among those with SOA was skewed to the left, with a greater proportion in QCOPL 3 and 4 (35.3% in each), compared with those with No SOA, who had only 20.4% in QCOPL 3 and in QCOPL.

Table 3.3: Participant Characteristics: Subgroups (Unweighted)

Subgroup	SOA[1] (n=102)	No SOA[2] (n=225)	MRI-OA[3] (n=131)	No MRI-OA[4] (n=196)	ROA[5] (n=109)	No ROA[6] (n=218)
Age, years mean, SD	63.5 (9.9)	56.2 (10.7)	62.0 (10.1)	56.1 (10.9)	63.6 (9.6)	55.9 (10.7)
Sex, women (%)	57 (55.9)	110(48.9)	62 (47.3)	105(53.6)	62 (56.9)	105 (48.2)
Ethnicity (%)						
Caucasian	80 (78.4)	177(78.7)	103 (78.6)	154 (78.6)	86 (78.9)	171 (78.4)
Asian	12 (11.8)	32 (14.2)	17 (13.0)	27 (13.8)	13 (11.9)	31(14.2)
Black	2 (2.0)	0	1 (0.76)	1 (0.51)	2 (1.8)	0
First Nation	3 (2.9)	0	3 (2.3)	0	3 (2.8)	0
Hispanic	0	2 (0.9)	1 (0.76)	1 (0.51)	0	2 (0.92)
Other	5 (4.9)	14 (6.2)	6 (4.6)	13 (6.63)	5 (4.6)	14 (6.4)
Marital Status (%)						
Married	64 (62.8)	134 (59.6)	78 (59.5)	120 (61.2)	67 (61.5)	131 (60.1)
Divorced	14 (13.7)	28 (12.4)	19 (14.5)	23 (11.7)	15 (13.8)	27 (12.4)
Separated	1 (1.0)	12 (5.3)	4 (3.1)	9 (4.6)	2 (1.8)	11 (5.1)
Widowed	15 (14.7)	15 (6.7)	16 (12.2)	14 (7.1)	16 (14.7)	14 (6.4)
Single	8 (7.8)	36 (16.0)	14 (10.7)	30 (15.3)	9 (8.3)	35 (16.1)
Type of Post-Secondary Education (%)						
High school	24 (23.5)	49 (21.8)	32 (24.4)	41 (20.9)	25 (22.9)	48 (22.0)
Trades	8 (7.8)	11 (4.9)	10 (7.6)	9 (4.6)	8 (7.3)	11 (5.0)
College	12 (11.8)	46 (20.4)	14 (10.6)	44 (22.4)	14 (12.8)	44 (20.2)
University	36(35.3)	92 (40.9)	45 (34.4)	83 (42.3)	40 (37.7)	88 (40.4)
Other	6 (5.9)	12 (5.3)	11 (8.4)	7 (3.6)	6 (5.5)	12 (5.5)
Missing Data	16 (15.7)	15 (6.7)	19 (14.5)	12 (6.1)	16 (14.7)	15 (6.9)
Knee Injuries (%)	44 (43.1)	85 (37.8)	73 (55.7)	72 (36.7)	61 (56.0)	84 (38.5)
Body Mass Index (SD)	27.3 (5.3)	25.8 (4.3)	27.3 (5.2)	25.6 (4.1)	27.1 (5.3)	25.5 (5.6)

Subgroup	SOA[1] (n=102)	No SOA[2] (n=225)	MRI-OA[3] (n=131)	No MRI-OA[4] (n=196)	ROA[5] (n=109)	No ROA[6] (n=218)
Family History OA (%)						
No	48 (47.1)	111 (49.3)	64 (48.8)	95 (48.4)	54 (49.5)	105 (48.1)
Yes	54 (43.1)	98 (43.6)	63 (48.1)	89 (45.4)	55(50.5)	97 (44.5)
Unsure	0	16 (7.1)	4 (3.1)	12 (6.1)	0	16 (7.3)
Smoking Ever						
No	58 (56.9)	97 (43.1)	67 (51.2)	88 (44.9)	61 (56.0)	94 (43.1)
Yes	44 (43.1)	128 (56.9)	64 (48.9)	108 (55.1)	48 (44.0)	124 (56.9)
Years, mean (SD)	23.4 (15.3)	18.2 (12.5)	22.9 (14.2)	17.5 (12.6)	23.2 (15.2)	18.1 (12.5)
COPL, mean (SD)	249.0 (137.4)	169.3 (131.0)	245.6 (140.6)	159.8 (125.0)	242.1 (136.5)	170.2 (132.4)
QCOPL 1 (%)	8 (7.8)	73 (32.4)	13 (9.9)	68 (34.7)	10 (9.2)	71 (32.6)
QCOPL 2	22 (21.6)	60 (26.7)	27 (20.6)	55 (28.1)	24 (22.0)	58 (26.6)
QCOPL 3	36 (35.3)	46 (20.4)	43 (32.8)	39 (19.9)	39 (35.8)	43 (19.7)
QCOPL 4	36 (35.3)	46 (20.4)	48 (36.6)	34 (17.3)	36 (33.0)	46 (21.1)

[1]Symptomatic Osteoarthritis
[2]No Symptomatic Osteoarthritis
[3]Magnetic Resonance Imaging Osteoarthritis
[4]No Magnetic Resonance Imaging Osteoarthritis
[5]Radiographic Osteoarthritis
[6]No Radiographic Osteoarthritis

The results of weighted bivariate analysis for each QCOPL, as well as for BMI, age, and female sex in relation to the odds of developing SOA versus No SOA for the full sample are shown in Table 3.4. QCOPL 4 and QCOPL 3 had the largest crude odds ratio (OR) at 10.56 (95% CI=2.58, 43.21) and 7.12 (95% CI=1.78, 24.44), respectively. The covariates of age (OR=1.07, 95% CI=1.03, 1.12) and BMI (OR=1.08; 95% CI=1.01, 1.17) were also significant. Non-linearity tests for age and BMI were non-significant. Weighted multi-variable analysis provided adjusted OR for QCOPL and covariates (Table 3.4). All interaction terms were non-significant. There was a monotonic relationship, with the odds of SOA for those in QCOPL 4 being 8.16 (95% CI=1.89, 35.27) times greater than those in QCOPL 1, and 5.73 (95% CI=1.36, 24.12) times greater for those in QCOPL 3, after adjusting for covariates. While QCOPL 2 did not reach statistical significance, the confidence interval trends to significance and fits the monotonic pattern. Age also remained significant with OR=1.05 (1.01, 1.09). No association was found for female sex or BMI for SOA.

Table 3.4: Crude and Adjusted Odds Ratios for Symptomatic Osteoarthritis vs. No Symptomatic Osteoarthritis

Independent Variable	Crude OR	95% CI	P-Value	Adjusted OR	95% CI	P-Value
QCOPL 2 vs. 1	3.16	0.74, 13.52	0.12	3.06	0.70, 13.39	0.14
QCOPL 3 vs. 1	7.12	1.78, 24.44	0.01	5.73	1.36, 24.12	0.02
QCOPL 4 vs. 1	10.56	2.58, 43.21	<0.01	8.16	1.89, 35.27	0.01
Age	1.07	1.03, 1.12	<0.01	1.05	1.01, 1.09	0.03
Female Sex	1.24	0.56, 2.75	0.59	1.56	0.67, 3.63	0.30
BMI	1.08	1.01, 1.17	0.04	1.07	0.98, 1.16	0.13

OR: odds ratio; 95% CI=95% Confidence interval; BMI=body mass index
* Population-based stratum-sampling weight was applied.

3.2.2 Cumulative Occupational Physical Load as a Risk Factor for Symptomatic Osteoarthritis in Men

The weighted sample was then divided into men (n=160) and women (n=167) for sub-analysis of COPL as a risk factor for SOA vs. No SOA adjusted for age and BMI. The same quartiles were used to make quarters of QCOPL as in the full analysis. For men this resulted in the following distribution of participants: QCOPL 1, n=37; QCOPL 2, n=38; QCOPL 3, n=39; QCOPL 4, n=46. Figure 3.4 shows the mean (SD) COPL per QCOPL for men. Weighted multi-variable logistic regression revealed no significant association between any QCOPL and SOA in men (Table 3.5) after adjustment for BMI and age.

Figure 3.4: Mean (SD) Weighted COPL by Unweighted Quarter in Men

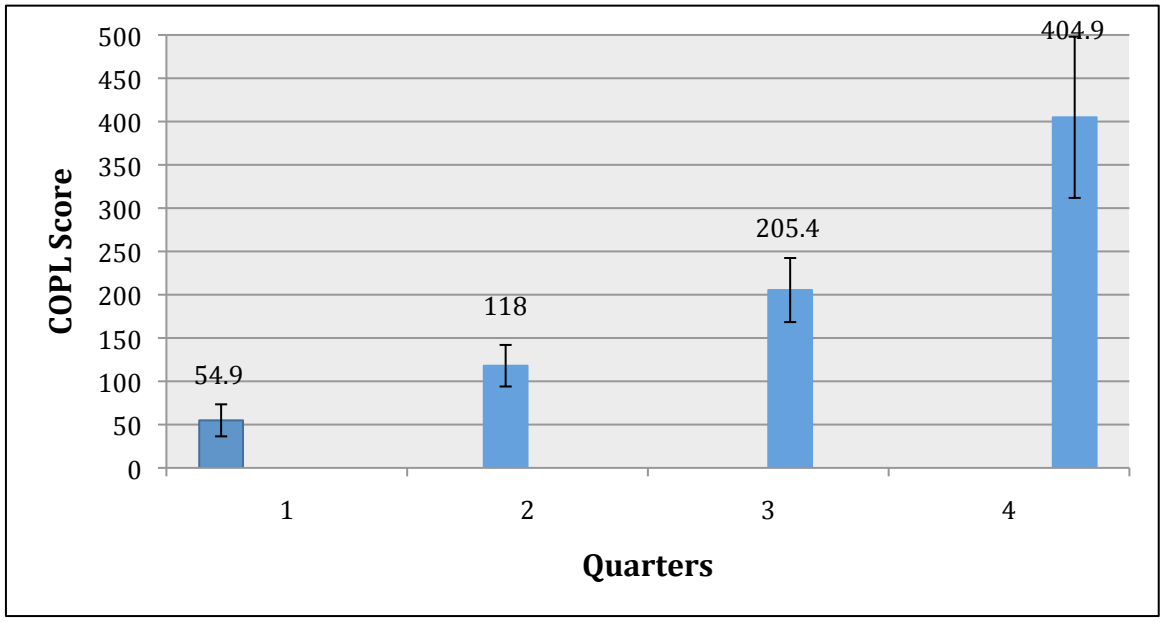


Table 3.5: Adjusted Odds Ratio for Symptomatic Osteoarthritis vs. No Symptomatic Osteoarthritis in Men

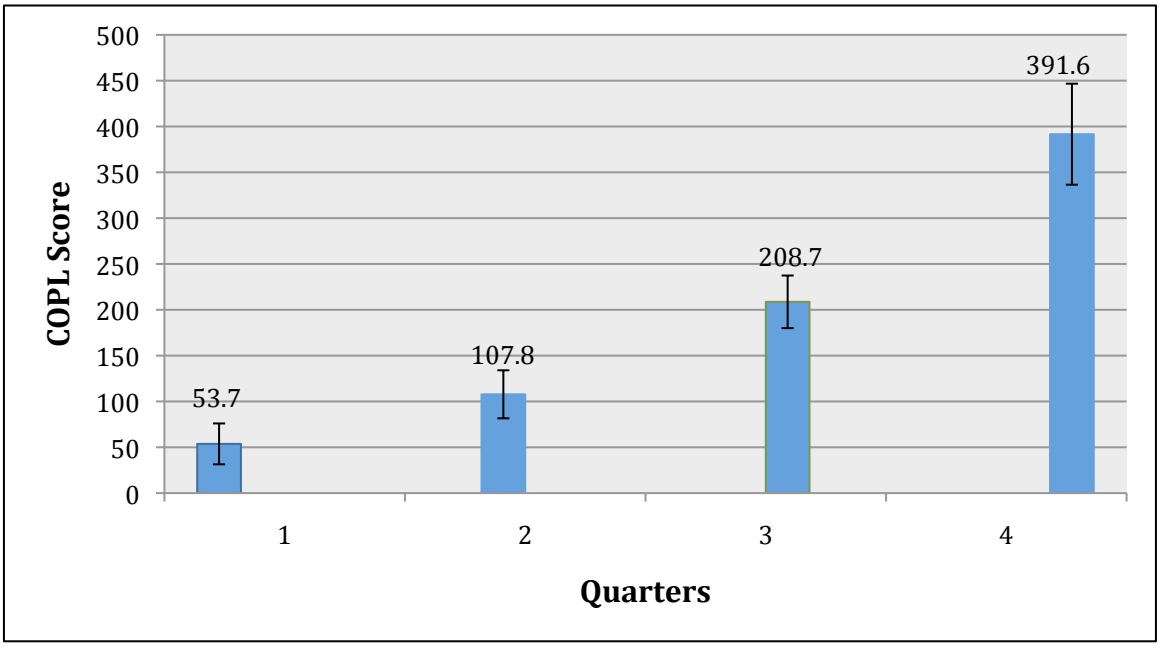
Independent Variable	Odds Ratio	95% CI	P-Value
QCOPL 2 vs. 1	2.50	0.21, 29.77	0.47
QCOPL 3 vs. 1	2.58	0.23, 29.38	0.45
QCOPL 4 vs. 1	4.93	0.45, 54.02	0.19
Age	1.05	0.99, 1.12	0.14
BMI	1.10	0.91, 1.33	0.32

OR: odds ratio; 95% CI=95% Confidence interval; BMI=body mass index
* Population-based stratum-sampling weight was applied.

3.2.3 Cumulative Occupational Physical Load as a Risk Factor for Symptomatic Osteoarthritis in Women

For women, 167 participants were distributed as follows: QCOPL 1, n=44; QCOPL 2, n=44; QCOPL 3, n=43; QCOPL 4, n=36. Mean (SD) COPL per QCOPL is shown in Figure 3.5.

Figure 3.5: Mean (SD) Weighted COPL by Unweighted Quarter in Women



In women, the same multi-variable analysis for the presence of SOA vs. No SOA provided evidence of a monotonic relationship: that QCOPL 4 (OR=9.69, 95% CI=1.44, 65.38) and QCOPL 3 (OR=8.24, 95% CI=1.32, 51.40) significantly increased risk for knee SOA (Table 3.6). QCOPL 2 was not significant, but the range of potential point estimates within this confidence interval supports the relationship between this level of COPL and SOA in women. Age and BMI failed to reach statistical significance.

Table 3.6: Adjusted Odds Ratio for Symptomatic Osteoarthritis vs. No Symptomatic Osteoarthritis in Women

Independent Variable	Odds Ratio	95% CI	P-Value
QCOPL 2 vs. 1	2.87	0.41, 19.93	0.29
QCOPL 3 vs. 1	8.24	1.32, 51.40	0.02
QCOPL 4 vs. 1	9.69	1.44, 65.38	0.02
Age	1.04	0.98, 1.11	0.16
Body Mass Index	1.06	0.96, 1.18	0.26

OR: odds ratio; 95% CI=95% Confidence interval; BMI=body mass index
* Population-based stratum-sampling weight was applied.

3.2.4 Cumulative Occupational Physical Load as a Risk Factor for Symptomatic Osteoarthritis: Sensitivity Analysis

Homemaker was removed from the data as an occupation, and COPL scores were recalculated (mean COPL=169.7; SD=133.8). Unweighted quartiles of COPL were calculated to create the categorical variable QCOPL with 25% of participants in each quarter (n=81 in QCOPL 1, n=82 in QCOPL 2-4). New weighted COPL scores varied between 0 and 729 with the 25th percentile, 50th percentile, and 75th percentile COPL scores = 64, 137, and 240, respectively. Therefore, the following COPL scores were contained in each quarter: 1) QCOPL 1=0-63; 2) QCOPL 2=64-136; 3) QCOPL 3=137-239; 4) QCOPL 4=240-729.

Adjusted OR from multi-variable analyses are shown in Table 3.7. No QCOPL was significant. The only variable predictive of increased risk of SOA was age (OR=1.06, 95% CI=1.02, 1.10).

Table 3.7: Sensitivity Analysis: Adjusted Odds Ratio for Symptomatic Osteoarthritis vs. No Symptomatic Osteoarthritis

Independent Variable	Odds Ratio	95% CI	P-Value
QCOPL 2 vs. 1	1.55	0.43, 5.64	0.51
QCOPL 3 vs. 1	2.40	0.70, 8.25	0.16
QCOPL 4 vs. 1	3.26	0.90, 11.81	0.07
Age	1.06	1.02, 1.10	0.01
Female sex	1.54	0.65, 3.65	0.33
BMI	1.07	0.98, 1.16	0.14

OR: odds ratio; 95% CI=95% Confidence interval; BMI=body mass index
* Population-based stratum-sampling weight was applied.

3.3 Objective 2

3.2.1 Cumulative Occupational Physical Load as a Risk Factor for Magnetic Resonance Imaging-Defined Osteoarthritis

In the full sample (n=327), there were 131 people with Magnetic Resonance Imaging-defined osteoarthritis (MRI-OA), leaving 196 participants with No MRI-OA (Table 3.3). When the same participants were reclassified by radiographic osteoarthritis (ROA), 109 participants fit this criteria with the remainder (n=218) in the No ROA group. The average age of groups with MRI-OA (62.0 years, SD=10.1) and ROA (63.6 years, SD=9.6) were similar, as were groups with No MRI-OA (56.1 years old, SD=10.9) and No ROA (55.9 years old SD=10.7). BMI showed the same pattern with the MRI-OA group and the ROA group having higher average BMI (27.3; SD=5.2 and 27.1; SD=5.3 respectively) compared with the No MRI-OA (25.6; SD=4.1) and the No ROA (25.5; SD=5.6). A larger proportion of participants suffered knee injuries in the MRI-OA (55.7%) and ROA (56.0%) groups versus the No MRI-OA (36.7%) and No ROA (38.5%) groups. The No MRI-OA group had

proportionally more women than the MRI-OA group (53.6% vs. 47.3%), whereas the ROA group had a greater proportion of women (56.9%) compared with the No ROA (48.2%) group. A larger proportion of participants attended university in the No MRI-OA group than in the other three groups. Ethnicity, marital status, and family history were similar across all four groups. Average COPL scores varied considerably: MRI-OA=245.6 (SD=140.6); No MRI-OA=159.8 (SD=125.0); ROA=242.1 (SD=136.5); No ROA=170.2 (132.4).

Unweighted quartiles were used to divide the weighted sample of MRI-OA and No MRI-OA into quarters called QCOPL 1-4 by COPL score (Figure 3.3). Eighty-one participants were in QCOPL 1, while QCOPL 2-4 had 82 participants. Of these participants, those with MRI-OA made up the following percentage of each quarter: QCOPL 1: 9.9%; QCOPL 2: 20.6%; QCOPL 3: 32.8%; and QCOPL 4: 36.6%.

Table 3.8 shows crude and adjusted OR for QCOPL 2, 3, and 4 as a risk factor for MRI-OA. Bivariate OR showed a large increased risk of MRI-OA for all three QCOPL levels with a monotonic relationship. There were increased odds of 12.01 (95% CI=3.46, 41.71) for QCOPL 4, 10.88 (95% CI=3.30, 35.88) for QCOPL 3, and 7.49 (95% CI=2.29, 24.49) for QCOPL 2 (Table 3.8). Older age also increased odds of MRI-OA (OR=1.05, 95% CI=1.02, 1.08). Non-linearity tests for age and BMI were non-significant. The strength of association remained high for all QCOPL with multi-variable logistic regression adjusted for age, female sex, and BMI. Adjusted OR were also monotonic: 1) QCOPL 4; OR=9.54 (95% CI=2.65, 34.26), 2) QCOPL 3; OR=9.04 (95% CI=2.65, 30.88), and 3) QCOPL 2 OR=7.18 (95% CI=2.17, 23.70). No other covariates or interaction terms were significant.

Table 3.8: Crude and Adjusted Odds Ratio for Magnetic Resonance Imaging Osteoarthritis vs. No Magnetic Resonance Imaging Osteoarthritis in Men and Women

Independent Variable	Crude OR	95% CI	P-Value	Adjusted OR	95% CI	P-Value
QCOPL 2 vs. 1	7.49	2.29, 24.49	<0.01	7.18	2.17, 23.70	<0.01
QCOPL 3 vs. 1	10.88	3.30, 35.88	<0.01	9.04	2.65, 30.88	<0.01
QCOPL 4 vs. 1	12.01	3.46, 41.71	<0.01	9.54	2.65, 34.27	<0.01
Age	1.05	1.02, 1.08	<0.01	1.03	1.00, 1.06	0.07
Female Sex	0.99	0.53, 1.77	0.92	1.17	0.61, 2.23	0.63
BMI	1.06	1.00, 1.13	0.05	1.06	0.99, 1.13	0.13

OR: odds ratio; 95% CI=95% Confidence interval; BMI=body mass index
* Population-based stratum-sampling weight was applied.

3.2.2 Cumulative Occupational Physical Load as a Risk Factor for Radiographic Osteoarthritis

To examine the relationship between COPL and the presence of ROA, the weighted sample was redistributed into ROA and No ROA, and divided into QCOPL by COPL score (Figure 3.3). Eighty-one participants were in QCOPL 1, while QCOPL 2-4 had 82 participants. Of these participants, those with ROA made up the following percentage of each quarter: QCOPL 1: 9.2%; QCOPL 2: 22.0%; QCOPL 3: 35.8%; and QCOPL 4: 33.0%. A weighted analysis was performed examining the multi-variable relationship between QCOPL 4, QCOPL 3, QCOPL 2, and ROA, with adjustment for age, female sex, and BMI (Table 3.9). Increased odds of ROA were found for QCOPL 4 with 3.15 (95% CI=1.02, 1.11) times greater risk of ROA, and QCOPL 3 with 4.19 (95% CI=1.55, 11.34) greater risk of ROA compared with those in QCOPL 1. The covariates of age and female sex were also significant with OR=1.07 (95% CI=1.04, 1.11) and 2.15 (95% CI=1.05, 4.39). No association was found for BMI and interaction terms were non-significant.

Table 3.9: Adjusted Odds Ratio for Radiographic Osteoarthritis vs. No Radiographic Osteoarthritis in Men and Women

Independent Variable	Adjusted Odds Ratio	95% CI	P-Value
QCOPL 2 vs. 1	2.35	0.86, 6.36	0.09
QCOPL 3 vs. 1	4.19	1.55, 11.34	<0.01
QCOPL 4 vs. 1	3.15	1.02, 9.70	0.05
Age	1.07	1.04, 1.11	<0.01
Female sex	2.15	1.05, 4.39	0.04
BMI	1.01	0.94, 1.09	0.79

OR: odds ratio; 95% CI=95% Confidence interval; BMI=body mass index

* Population-based stratum-sampling weight was applied.

4 Discussion

The purpose of this study was to determine the association between cumulative occupational physical load (COPL) to the knee and the presence of osteoarthritis (OA). In this study, I hypothesized that occupational tasks involving heavy lifting and kneeling were associated with the presence of knee OA. Physical activity, including performing occupational tasks, causes moderate mechanical loading to the joint that is necessary to stimulate intra-articular anabolic processes, which maintain healthy articular cartilage.[9] However, overloading a joint with too much intensity, for too long, or by particular types of physical activity can turn this same process catabolic and destructive.

The primary underlying mechanism for OA as being mainly mechanical or due to an inflammatory disease remains under debate among international researchers.[9, 109] Clearly, the theory behind occupational joint loading as a risk factor for knee OA is largely driven from the biomechanical perspective. The activities of walking, squatting, and climbing stairs are thought to increase tibiofemoral contact stresses by 3.1 times, 4.7-5.6 times, and 5.1 times body weight, respectively.[110, 111] Occupational tasks requiring significant knee flexion increase shear stress and retropatellar load which consequently may predispose an individual to patellofemoral pathology.[112] It has been recognized that women have different lower extremity biomechanics than men with altered muscle mass, knee alignment, and Q angles, all of which could influence the role of occupational physical loading in this sex.[95] As well as being an independent risk factor for OA, high BMI has been shown to interact with occupational exposure to increase risk by over five times.[52, 56]

In this study, using a population-based sample, COPL was quantified with a new self-report measure that was tested for agreement with an ergonomist expert-based ratings scale. Strong agreement was found with a Pearson Υ=0.69 (95% CI=0.52, 0.80). Pearson's

coefficients range from -1 to 1, and while the specific interpretation depends on context and purpose, conventional guidelines suggest the following for a positive correlation between variables: none = 0.0 to 0.09; small = 0.1-0.3; medium = 0.3 to 0.5; and strong = 0.5-1.0.[113] The Bland Altman plot was distributed around zero and free of systemic patterns indicating no consistent bias of one measure over the other.

This study took a novel approach by investigating the role of COPL using a variety of knee OA definitions as outcomes in the same population; namely, symptomatic osteoarthritis (SOA), magnetic resonance imaging OA (MRI-OA), and radiographic osteoarthritis (ROA). Strengths of this study were the comprehensive recruitment strategy used to obtain a cohort of individuals representing the full spectrum of OA, as well as the application of a population-based weight to the multi-variable analysis, which allowed the results to be extrapolated to the population of Greater Vancouver. For SOA and MRI-OA, the adjusted analysis revealed a statistically significant monotonic relationship between the level of COPL and the presence of OA. Odds ratios (OR) ranged between 5 times and almost 10 times greater risk for those who were exposed. The results for the ROA analysis were similar, although a monotonic relationship was not observed. Men and women were analyzed separately to explore the presence of potential differences between sexes. The results indicated that the two highest quarters of COPL significantly increased the odds of SOA in women, and although significant p-values were not found for men, the results showed the same trend with elevated point estimates and confidence intervals trending towards significance, suggesting an effect of COPL.

A sensitivity analysis was performed to examine the robustness of the results by altering the inclusion of the homemaker occupation in the calculation of COPL scores. The results revealed that the homemaker occupation had a large influence on the results. When this occupation was omitted, OR were no longer significant for any level of COPL. Given this

finding, as well as the cross-sectional nature of study design, these results should be interpreted cautiously. Nonetheless, they provide an important and novel insight into the role of lifetime occupational loading in knee OA, as this new MRI-OA definition has not previously been used to investigate modifiable risk factors associated with OA.

4.1 Measuring Occupational Exposure

In this study, a new self-report measure of COPL was used to quantify a person's lifetime occupational exposure to knee joint loading. It was unique in that it accounted for the time frame (i.e., number of years) that a person performed each historical occupation. It allowed for an investigation of a dose-response relationship between lifetime amount of COPL and the odds of knee OA. In previous literature, a wide variety of methods have been used to define and measure occupational exposure as one domain of physical activity. However, most validated methods assess physical activity in terms of energy expenditure and metabolic equivalents, rather than in respect to mechanical joint loading.[114] This is because these tools are designed to measure the benefits of physical activity, believed to be largely due to exposing the cardiovascular system to long duration activities with prolonged elevation of the heart rate, rather than to examine the potential detrimental effects of certain body positions, movements, and activities on the health of muscle, bone, and joints.[115]

Most early studies examining joint loading performed direct comparisons between physically demanding jobs such as mining,[101] floor-laying,[79] or farming[88] to more sedentary jobs, such as office work. However, this proved problematic as not all individuals were employed in one specific occupation over their entire working life, and if they did retain the same occupation, the amount and intensity of the physical activity, as well as the length of time over which it was performed, did not always stay the same, and thus the validity of this method has been questioned.[67, 69] This same flaw appeared when job

titles were rated, classified, and ranked by ergonomists to measure occupational load.[73, 116] Another creative, yet time-consuming method of measuring occupational exposure was to videotape workers while they performed their duties. For example, Jensen et al. recorded carpet layers and floor layers for 1,400 minutes and then quantified the time spent in each of 13 knee-straining positions out of the total time.[80] The most common technique by far for measuring occupational activities has been the use of self-report questionnaires.

Eleven high-quality studies from my literature review used this approach.[32, 80, 83, 86, 90-95, 98] Questionnaires are popular as they are convenient, relatively inexpensive, easy to use, and capture a large amount of data. Another advantage is that they permit greater heterogeneity in exposure calculation among people from the same occupation. Self-report measures allow data collection on less common occupations that may not always be included in ergonomist databases. However, a disadvantage of relying on self-report of historical occupational exposure is the risk of recall bias. Rogers et al. suggested that people with OA might over-report prior COPL if they perceived their prior activities had contributed to the disease.[117] However, it has been demonstrated that people can recall past physical activity with acceptable accuracy. Falkner et al. examined recall quality of occupational and leisure activity after 30 years in a prospective cohort of individuals and found that overall people tended to slightly underestimate past weekday activities.[118] The results correlated "remarkably" well between original interviews and recall interviews. The intra-class correlation coefficients ranging from 0.43 to 0.45 were close to those of other studies where recall times were less than 10 years.

The amount, type, and depth of information collected using questionnaires on occupational joint loading also varied among studies. Researchers have based their primary analysis on longest-held job,[92, 93] principal job,[86] current job,[95] or lifetime occupations,[94] yet often specific details, such as duration, frequency, and intensity of

exposure were not measured. Given the long induction time and asymptomatic latency period of OA, gathering a full, detailed history of cumulative lifetime occupational exposure is ideal when the goal is to investigate the development of this disease. Also, the definition of an occupation has been inconsistent across studies. More recently, the role of homemaker as an occupational exposure has been included in some papers.[83, 94] This will be discussed in further detail later in this chapter.

Some of the variation found when comparing my COPL measure to the expert ratings-based measure may be explained by the ability of my self-report measure to account for individual differences in occupational exposure between people with the same occupation. While this self-report measure of COPL requires further validation and testing in larger populations and ideally in longitudinal studies, the results from this agreement analysis suggest it may be a useful tool for measuring occupational loading in future research.

4.2 Occupational Exposure and Knee Osteoarthritis

The literature reports a variety of definitions of knee OA in research settings; however, to my knowledge no previous studies have examined risk factors using three different definitions. I applied the same COPL exposure to the following knee OA outcomes: SOA, MRI-OA, and ROA. Each OA classification had its own advantages. The comprehensive MRI-OA definition arguably captured earlier structural disease in either the tibiofemoral or patellofemoral joints. MRI can visualize cartilage defects invisible on x-ray that have been shown to predict future cartilage loss and joint space narrowing in people without radiographic knee OA.[119] With the ability to capture and quantify cartilage defects, researchers will be able to study factors that influence the initiation of pre-clinical OA in asymptomatic individuals. These individuals maybe the best suited for prevention strategies before clinical disease has developed. The Hunter criteria allowed for precise

identification of individuals with earlier visible structural changes in any knee compartment compared with the other definitions.

ROA, as the most traditionally used structural knee OA outcome in epidemiological research, allowed the current results to be easily compared with previous literature in this area. As per historical convention, this definition only included the tibiofemoral joint, and although it did not take symptom status into account, in the current study nearly all participants (over 95% of those in the ROA group) also had knee pain. The SOA subgroup combined radiographic changes in the tibiofemoral joint with the presence of knee pain. This focused definition slightly refined the ROA definition to capture individuals with the most advanced disease. This includes individuals with the most severe manifestation of OA who are most likely the ones using the health care system and resources. Without a cure for OA, this subgroup relies on a limited number of strategies for disease management and therefore must be an important, albeit challenging focus area for researchers to understand. The fact that all three variations of knee OA outcomes showed results in similar patterns across exposure levels with consistently high point estimates is highly supportive of a relationship between COPL and knee OA.

When randomized controlled trials are not feasible to expose individuals to a possibly harmful situation (e.g., occupational exposure), prospective longitudinal cohort studies are the next best methodology to minimize the uncertainty between cause and effect[120]. To my knowledge, there has been only one such study that examined occupational exposure as a risk factor for SOA,[1] and two older, lower-quality cohort studies classifying knee OA based on ROA.[75, 76] It is likely that many participants with ROA, especially those with severe disease, also have pain, and therefore SOA, as was seen in the current study. Consequently, synthesis of the literature in this area has made little distinction made between SOA and ROA.[69-71] As part of the Framingham study, Felson et

al. assessed occupational physical demands in relation to SOA and ROA in men and women.[1] He found no association with SOA in either sex, but he did find a relationship for ROA in men. In a large cohort study, Vingard et al. found a significant relationship with occupational exposure and ROA in men and women, despite selection bias and questionable exposure calculation.[75] Lastly, when investigating the lifting of heavy objects, Schouten et al.[76] failed to find a significant association with ROA as a risk factor, although this study had a low participation rate at follow-up, and a restrictive classification of ROA.[76] One additional recent prospective cohort study found significant results for occupational exposure and clinical knee OA via physician diagnosis.[121] Based on the nationwide Mini-Finland Health Survey, in this study a baseline sample of 8,000 individuals was re-examined 22 years later and adjusted OR for increased risk of knee OA for the physical stress at work was 18.3 (95% CI=4.2, 79.4).

The results from these above-mentioned cohort studies were inconsistent. While three studies support the relationship between occupational exposure and knee OA,[1, 75, 121] only two are of higher quality.[1, 121] Potential reasons for this inconsistency that have been suggested include variability in exposure measurement, different knee OA outcome definitions, diverse subject eligibility criteria, the use of covariates, or small sample sizes in higher-exposure categories.[70, 114] However, when these cohort studies are combined with more encouraging results from high-quality case-control and cross-sectional studies, such as the current study, evidence for the role of COPL as an important risk factor for knee OA is more apparent.

In the current study, the odds of ROA compared with the SOA were slightly lower and not monotonic, with the highest occupational exposure category having slightly lower odds of disease than the third exposure quarter. This being said, the point estimates for both ROA and SOA are large, suggesting a moderate to strong effect of COPL on both

outcomes. The large confidence intervals produced in both analyses show the amount of variability and the range of potential point estimates available based on probability. In the ROA analyses, QCOPL 2 had a moderate point estimate (OR=2.35) and confidence interval (0.86, 6.36) with the majority of spread above 1.0 suggesting a trend towards significance. Research journals such as *Epidemiology* have suggested a modern epidemiological approach to data analysis should be adopted by examining beyond only p-values in the interpretation of epidemiologic results from observational studies.[122]

Although ROA was purely a structural definition, as discussed above, there were only a few more participants in this subgroup than in the SOA group, which had the further criteria of knee pain. One plausible explanation for the small difference in results between subgroups is that those with knee pain (all of the SOA group and most of the ROA group) might have attributed their pain to previous occupational exposure and consequently over-reported COPL.[117] The few remaining participants without pain in the ROA subgroup had lower COPL scores, perhaps due to under-reporting COPL, which brought the average COPL for ROA to 242.1, whereas the mean COPL for SOA was 249.0. Upon analysis, this would have resulted in higher odds of disease for those with SOA than ROA, as was found in the current study.

The healthy worker survivor effect may have accounted for the slight decrease in risk between QCOPL 3 and QCOPL 4 in the ROA analysis. Shah et al. described this phenomenon as occurring when those with early development of disease modify their occupational exposure by changing careers to a less physical job or retiring early, leaving those without morbidity to work longer in more vigorous occupations.[123] This has been hypothesized to be a factor influencing results in other occupational exposure studies.[1, 124] In the current study, if those with early ROA modified their exposure, it would have

decreased their total score and thus they may be classified in the third instead of the fourth quartile.

The current study provided exciting results for occupational exposure as a risk factor for knee OA using a new MRI definition. The ability of MRI to visualize small cartilage defects prior to considerable joint damage occurring provides the opportunity to examine risk factors for OA over a larger spectrum of disease. In the past, most OA risk factor studies have focused on well-established moderate to severe disease as outcomes. MRI allows researchers a new perspective: to examine pre-clinical OA that may help us understand the trajectory of OA from its earliest stages. For example, recent studies have highlighted the importance of BML in knee pain, and how their presence is associated with increased knee pain in those with OA.[125, 126] However, these BML are only visible on MRI, which illustrates the value of using this form of imaging in research settings to learn more about the underlying complex relationship between articular damage and pain in OA. These authors suggested that future treatments could be developed to target specific patients with subchondral bone changes present in early disease stages. Other authors have suggested MRI could possibly reveal biomarkers linked to biochemical changes, which may precede the traditional OA diagnosis.[127] Therefore, using MRI may provide opportunities to discover new ideas and theories about the underlying mechanisms of OA, investigate the role of less traditional modifiable risk factors, such as dietary factors, and evaluate the effectiveness of both primary and secondary prevention strategies.[128]

This new MRI-OA outcome showed a monotonic relationship with comparable, yet even greater, odds of disease than the more traditional SOA outcome in the same population. Three possible explanations for the higher point estimates found with the MRI-OA definition involve the definition itself.

Firstly, as discussed above, MRI can detect earlier disease than SOA. Some individuals in the No SOA subgroup may actually have had MRI changes invisible on radiographs, such as BML, synovitis, joint effusion, and meniscal and ligamentous abnormalities and therefore could have been classified as MRI-OA. Consequently, compared with the SOA and No SOA subgroups, the MRI-OA and No MRI-OA division was a "cleaner" separation of individuals into two more distinctive subgroups, with those in the No MRI-OA subgroup having substantially fewer pathological joint changes. This was possibly due to the detailed and specific nature of the Hunter criteria compared with the K&L criteria, which relies largely on the presence of osteophytes and joint space narrowing. The creation of two more distinct subgroups would have facilitated the calculation of higher odds ratios. Secondly, MRI-OA was purely a structural definition and did not include pain. This means it would eliminate the influence of the healthy worker effect,[123] also discussed previously, compared with the SOA definition. Thirdly, and possibly most importantly, the MRI-OA definition included both tibiofemoral and patellofemoral disease, whereas the SOA definition only examined the tibiofemoral joint. It has been suggested that the biomechanics of the patellofemoral joint are unique than the tibiofemoral joint and this may have pathogenic implications.[129] For example, during squatting activities, shear forces on the patellar cartilage surfaces have been found to be higher than on the tibiofemoral joint.[111, 112] As the COPL exposure measurement in this study included quantification of both combined heavy lifting and kneeling tasks, these activities may have put additional strain on the patellofemoral joint rather than the tibiofemoral joint. This would not have been captured with the SOA definition, only the MRI-OA definition, which may have served to elevate the risks associated with this more comprehensive tri-compartmental definition.

MRI-imaged patellofemoral pathology was identified in the two recent studies that explored occupational-related squatting, kneeling, and heavy lifting.[32, 95] In a cross-

sectional study, Amin et al. evaluated 192 men (mean age 69 years) with SOA and found those men who reported performing occupational loading tasks had a modestly increased risk for worse cartilage morphology at the patellofemoral joint (OR=1.8, 95% CI=1.1, 3.2) when compared with men with no exposure.[32] It is noteworthy that a limitation of this study was that the entire sample already had SOA, yet a significant relationship was still detected between occupation and cartilage changes. In a similar study design, Teichtahl et al. analyzed 96 healthy, but overweight (mean BMI=34.1) women between the ages of 26 and 62 with no history of injury or knee pain and found the frequency of stair climbing (OR=2.9; 1.4, 6.0) and walking (OR=2.3; 95% CI=1.2, 4.4) was associated with increased patellar cartilage defects.[95] They also reported a trend towards heavy lifting, bending, and squatting having the same association (OR=1.8; 95% CI=1.0, 3.1). For both of these studies, possibly modifying the inclusion of individuals with and without disease would result in a better picture of the occupational risk associated with OA. Future work using MRI could possibly examine the impact of occupational exposure on each compartment of the knee.

The current study was among the first to use the new MRI-OA definition recently proposed by Hunter et al.,[16] and to reveal a substantial dose-response relationship between amount of occupational exposure and risk of disease using MRI as an outcome. Future use of the MRI-OA definition could facilitate in-depth learning about earlier stages of OA and the development of much-needed prevention strategies.

4.3 Sex Differences in Occupational Exposure and Knee Osteoarthritis

When divided by sex, the results for COPL as a risk factor for knee SOA in the current study are somewhat contrary to what has been found in the occupational literature. Significant odds of disease were found in women (OR from 8.24 to 9.69), but the results did not reach statistical significance in men. Despite this, point estimates for men were elevated

and showed a similar pattern to that of women, with increasing risk of SOA in response to increased exposure to COPL. One possible explanation is that COPL in this current study measured occupational exposure in a more comprehensive manner than has been done historically in women. Alternatively, there are a number of other plausible explanations including the possible role of true biological differences in women and other methodological issues involved in studying women.

The literature review performed before this study found 22 papers from 21 studies reporting results on occupational exposure in men,[1, 32, 52, 56, 68, 72, 73, 75, 77, 79, 80, 82-84, 86, 88, 89, 91-94, 101] with 20 of these having significant OR varying from 1.4 to 7.9 for increased risk of knee OA.[1, 32, 52, 56, 68, 73, 75, 77, 80, 82-84, 86, 88, 89, 91-94, 101] All 13 studies that received a high quality rating had statistically significant results,[1, 32, 56, 73, 80, 82-84, 86, 91-94] with one of those studies being a cohort design.[1] Conversely, for women, 15 studies examined the role of COPL and knee OA,[1, 56, 73, 75, 82-85, 87, 88, 92-96] 9 of which had a statistically significant increased risk of disease varying from 1.4 to 7.3.[1, 56, 73, 75, 83-85, 94, 95] Ten studies were rated as high quality,[1, 56, 73, 82-84, 92-95] of which seven showed a statistically significant relationship,[56, 73, 82-84, 94, 95] none of which had a cohort design. Out of a total of 32 papers in the review, 10 studies included results for both sexes separately. Of these, seven had significant results for both men and women examined separately, three had significant results for only men, and none had significant results for only women, as was found in the current study.

While the current results are not common in the occupational loading literature, they are consistent with the evidence that overall women have an increased risk of knee OA when compared with men.[13, 43] A number of biological hypotheses have been investigated in the literature in an attempt to explain this discrepancy. Firstly, studies have shown that compared with men, women have distinctive differences in their lower

extremity biomechanics and alignment, particularly in the coronal plane; that is, the relationship between the hip, knee, and ankle.[130, 131] One recent study found that women demonstrated a larger quadriceps angle (Q-angle), more genu recurvatum (knee hyperextension), greater anterior pelvic tilt, and increased femoral anteversion than men.[130] Both biomechanical studies[60] and animal studies[132] have confirmed that alignment influences load distribution across the knee joint. An early study by Schouten et al. examining tibiofemoral alignment found that previous malalignment of the tibiofemoral joint increased odds of knee OA by 5.1 (95% CI=1.1, 23.1) times.[76] A review by Tanamas et al. reported that malalignment of the tibiofemoral joint had only rarely been considered in epidemiological literature, despite being shown to be an independent risk factor for progression of knee SOA.[133] Two recent studies confirm the role of malalignment in knee OA for women.[94, 114] A previously discussed case-control study by Klussmann et al. performed multi-variable analysis and found that malalignment of the tibiofemoral joint was associated with SOA only in women with OR=11.5 (95% CI=4.7, 28.7).[94] In a comprehensive study of physical activity risk factors for knee OA, Ratzlaff et al. found that both varus and valgus malalignment caused a two-fold increased risk of knee OA in women, but not in men.[114] It is possible that alignment influenced the results of the current study with regards to women and SOA as an unexplored variable or potential interaction term with COPL exposure. A second biological reason for the higher risk of SOA found for women in the current results may be the role of hormonal factors.[42] Despite some conflicting observational studies, declining estrogen levels have been implicated in the increased risk of knee and hip OA in women around the time of menopause.[134, 135] This was not taken into consideration in the current study.

There are a number of potential methodological explanations for our results that revealed increased risk of knee SOA in women. As mentioned above, it is possible that the

comprehensive COPL definition used in the current study, which included homemaking as an occupation, was able to capture a part of physical activity that has often been overlooked in the past literature, therefore highlighting a true increased risk for women in heavy loading occupations.[114] Also, this exposure measurement allowed for multiple concurrent occupations to be reported, which has rarely been done. This may have meant that some women recorded both an occupation outside the home and also their status as homemaker. In these cases, both occupations were weighted at 50% for the overlapping time period; however, the physical nature of the homemaker occupation compared with that of a more typical sedentary job could still have had a large impact on women's overall COPL score. The long-standing societal beliefs surrounding gender stereotypes of men and women and occupational roles are another possible explanation. Of the 159 individuals who reported homemaker being their occupation, only one was a man. The use of the term "homemaker" may have introduced bias towards greater physical demands in women by prompting them to report it as an occupation. An equivalent prompt was not included for men.

The inclusion of the homemaker occupation in the COPL had a large influence on the results, as shown in the sensitivity analysis. When the homemaker occupation was removed, the overall SOA analysis was no longer significant, although point estimates were elevated and the same pattern of increased ORs for each level of QCOPL remained. While this revealed the results were not overly robust, it suggested that merely including paid occupations when studying occupational risk may obscure findings for women whose gender-specific role tends to involve homemaking activities. Omitting the homemaker occupation in the area of occupational loading may explain some of the differences previously seen between men and women. The results in the current study indicate that knee joint loading performed during household activities is an important source of overall

loading, and must be considered in some capacity, whether as an occupation or as a separate category of physical activity.

Previous researchers have suggested that measuring physical activity, including joint loading, in a way that accurately reflects the complex nature of women's lives is very challenging[136] and this may be responsible for the discrepancies found in risk of occupational joint loading tasks between men in women. Performing household tasks, as a full-time homemaker or otherwise, has been shown to account for a significant portion of overall activity level in women, greater than leisure or sport participation.[65] Studies using diaries to record daily physical activity have reported that women spend up to six hours per day on household chores or family care activities.[137] Homemaking involves many repetitive tasks, such as kneeling, lifting, and carrying, that have been considered strenuous on knee joints in occupational research.[68, 69] Avery and Begalla[107] examined tasks performed by homemakers in a group of 48 women and found that the physical demand was akin to that of a patrolman. Estimates from the United States Employment Census and Statistics Canada state that approximately 5 million American women[138] and 1.4 million Canadian women[139] are stay-at-home mothers. Hence, by discounting homemaking as an occupation, previous studies may have underestimated knee joint loading experienced by women and created a gender bias within the framework of occupational activity.(126)

A number of recent studies examining occupational exposure and knee OA have attempted to address this shortcoming by including homemaking as an occupation.[83, 94] Using a case-control design, Klussmann et al. analyzed data from 1,310 men and women about time spent in different positions and performance of physical tasks at their job, in which they included tasks performed in the home.[94] In women, occupational predictors of knee SOA included kneeling/squatting (OR: 1.36; 95% CI=0.78, 2.37 for 3,542 to 8,934 hours/life; OR: 2.52; 95% CI=1.4, 4.7; for greater than 8,934 hours/life) and daily lifting and

carrying of loads (OR: 0.69; 95% CI=0.38, 1.24 for less than 1,088 tons/life; OR: 2.13, 95% CI=1.1, 4.0 greater than 1,088 tons/life.) These authors claimed their study was the first to show a dose-response relationship between kneeling/squatting or lifting/carrying and SOA in women. Similarly, Sandmark et al. found that women performing physically demanding tasks in the home had 2.2 (95% CI=1.3, 2.6) times greater risk of knee OA than those not performing these tasks.[83] These two studies, in addition to the current results, indicate that the homemaker occupation should be accounted for when studying occupational exposure as a risk factor for knee OA.

A recent study by Ratzlaff at al. examined the physical activity in three domains (sports, occupations, and household tasks) and highlighted the importance of the role of performing homemaking activities in joint loading for women.[65] Performing these tasks made the greatest contribution to the lifetime physical loading of the knee, greater than sport participation or employment outside the home. They calculated a Cumulative Peak Force Index (CPFI), a time/joint force product involving years of force and the subject's body weight. Like the current COPL measure, it was a self-report lifetime joint loading measure, although it was Internet based and used skip logic technology that allowed subjects to follow an individualized path through the survey. The CPFI was more detailed and therefore more time-consuming to complete than the current measure. It asked respondents to recall time spent in many different positions, including standing, squatting, climbing, walking, kneeling, and lifting in each domain. Similarly to COPL, CPFI asked about the duration (years) of a job, but also asked about the average number of hours per week and if the job was full-time, part-time, or seasonal. The formula also took body weight into account when calculating joint force. Compared with COPL, CPFI included a greater variety of information for estimating knee joint loading. It should be noted that the current study was a secondary cross-sectional analysis of a cohort study and so the calculation of COPL

was limited to include only the information collected previously. Nonetheless, our findings concur with those reported by Ratzlaff et al. using CPFI, with both studies emphasizing the importance of including homemaking activities in studying the role of physical activities and knee OA in women.

By including homemakers as part of the occupational exposure, the current study provided further evidence on the importance of measuring the joint loading tasks associated with performing household activities in order to obtain a more sex-balanced approach to occupation as a risk factor for knee OA. It highlighted the fact that previous studies examining occupation in women have failed to measure this aspect of physical activity and that this may be a large contributing factor to the discrepancies in results found between sexes.

4.4 The Role of Age and Body Mass Index

While the main purpose of this thesis was to explore occupational exposure as a risk factor for knee OA, the results pertaining to the covariates age and BMI were worthy of discussion. OA is not an inevitable part of aging, although over time multiple local joint vulnerabilities can develop and interact with aspects of normal aging such as cartilage thinning and decreased muscle mass to make individuals more susceptible to OA.[2, 41, 42] It was important to include age as a covariate in this study as it is likely a confounder given that it is an established risk factor for OA and the logical assumption that as people age they will accumulate more occupational loading. Age was treated as a continuous variable. Therefore, there was a multiplicative effect of the odds of OA for every one year increase in age. The mean age per quarter was examined and the following distribution was seen in the data: QCOPL 1: 51.3 (SD=11.9) years old; QCOPL 2: 54.9 (SD=8.9) years old; QCOPL 3: 59.5 (SD=9.6); QCOPL 4: 58.2 (SD=7.6) years old. While the average age does increase for the

first three quarters, this distribution supports the fact that COPL scores were not overly influenced by age. The results for the SOA analysis were significant in both crude and adjusted analysis with OR 1.07 (95% CI=1.03, 1.12) and 1.05 (95% CI=1.01, 1.09), respectively. Similar findings were found in uni-variable and multi-variable analyzes for the outcomes MRI-OA and ROA, with only the adjusted OR for MRI-OA bordering on significance. While at first assessment these OR may seem small, when age was grouped as a categorical variable, there was a 1.26 times increased risk of SOA in those 5 years older, and 1.58 times increased risk of OA for those 10 years older. As age was not the primary variable of interest, it was felt that as a continuous variable it was sufficient to account for its small but significant effect on occupational exposure and knee OA.

With evidence linking it to both mechanical and inflammatory components of the disease, obesity is an undisputed risk factor for OA[41, 42] and therefore BMI was included as a covariate in the current study. A previous high-quality prospective cohort study by Reijman et al. found that those with a BMI greater than 27.5 had a three-fold increase in odds of knee OA.[48] As well, it has been found to interact multiplicatively with physical workload to increase risk of knee OA.[52] However, in the current study, BMI was found to be significant only in uni-variable analysis for SOA (OR=1.08; 95% CI=1.01, 1.17). On examination, the mean BMI of participants in the sample was 26.3 (SD=4.7), well below the national average of 27.7 in 40–59-year-olds and 28.2 in 60–79-year-olds.[140] It may be that there were not enough participants in the sample with a BMI that was high enough to be a significant risk factor for disease. This cohort was recruited from the Greater Vancouver region which has some of the lowest obesity rates in the country, with only 31.7% of the population considered overweight or obese, compared with 63.0% of Canadians nationwide.[141] Another difference between the current study and previous work is that this population-based cohort was specifically designed to include people across

the OA spectrum from early to late disease, whereas the majority of previous work has involved participants with more advanced disease, and who also tend to have a higher BMI (e.g., Teichtahl et al.[95]: mean (SD) BMI=34.1 (SD=9.8)). Although BMI did not reach significance in most of the models, it was important to account for it as a covariate as it has been established as a risk factor both independently and when interacting with occupational exposure.

4.5 Limitations and Strengths

This study had a number of limitations to consider when interpreting the results. The cross-sectional nature of the study design revealed an association between occupational physical loading and knee OA, but no cause and effect relationship could be inferred. However, being the first time a new MRI-OA definition has been utilized as an outcome, this study design was appropriate for a preliminary exploration to determine if greater time and resources should be invested.

This was an opportunistic secondary analysis of data that had been collected for another primary purpose, therefore certain shortcomings are present with regards to the information collected from participants on specific occupational details. Additional details such as the number of hours worked per week and if the occupation was part-time, full-time, or seasonal would have been interesting to include in the COPL exposure calculation. Also, the use of a self-report questionnaire to measure historical occupational exposure risks recall bias, although previous work has shown an acceptable level of accuracy for the use of self-report questionnaires to quantify previous physical activity.[118] The best way to avoid this bias altogether would be to investigate prospectively, but this demands a much greater investment of time and finances. The next best option would be to use a fully validated occupational questionnaire, such as the CPFI,[65] although with the limited scope

of this project and data available for secondary analysis this was not feasible. The agreement analysis that was conducted did illustrate that the COPL measure concurred with another expert-based ratings system.

While age, sex, and BMI were controlled for as covariates in the analysis, sports participation, another domain of physical activity, was not explored and could be an unknown confounder. However, recent research suggests both occupation and household duties are much greater sources of joint loading than sport activity,[65, 136, 142] and therefore its effect, if any, on the overall results should be small. As well, using the lowest quartile of participants as the reference category during analysis may have inadvertently affected the results, causing under-estimated ORs. Possibly, those with the most sedentary occupations were actually at increased risk of OA due to inactivity, which has been shown to cause cartilage thinning.[143] In this case, using COPL 2 as the reference category could have been an option.

Lastly, the size and composition of the sample was not ideal for investigating all hypotheses. The small sample size meant that power, especially when the sample was divided by sex, was low. A larger sample would have allowed for greater power to test the hypotheses on the associations between occupational joint loading and knee OA in men and women. Ensuring enough power is present to properly examine occupational exposure in men and women separately should be considered when designing future studies. Compared with those without disease, the proportion of those with knee OA in this sample was much greater than in the population (SOA sample: 31.2%; SOA population: 16%[26]). Thus, the results of those without knee OA were heavily weighted and so they had a large impact on the overall results. A sample with a disease distribution more similar to its prevalence in the population would be ideal and would require less weighting.

Despite its limitations, this study had several strengths. First, it had external validity as a population-based sample drawn from the Greater Vancouver community. Second, the use of three separate knee OA outcomes, one of which was a novel definition that included both tibiofemoral and patellofemoral disease, afforded the possibility to study OA beyond the narrow spectrum of radiographic disease. The power available for this innovative investigation of MRI-OA analysis was excellent. Third, this study involved detailed measurement of lifetime occupational exposure to lifting and kneeling in a manner that allowed the investigation of a dose-response relationship. Many previous studies have only examined this exposure using a dichotomous exposure variable.[73, 86, 92, 98] Revealing a dose-response relationship has greater clinical application and provides direction for future research. For example, an intervention aimed at OA prevention could be based on guidelines that would limit joint loading to a certain evidence-based threshold.

Additionally, the inclusion of homemaking allowed the exploration of this role as a valid occupation. It revealed the potential gender bias that may have been present in previous work examining occupation as a risk factor for OA and illustrated the relevance of homemaking as a source of joint loading in this population.

This study was also designed to include individuals with early OA, a disease subgroup that until recently has attracted less interest from researchers, compared with interest in those with later disease, who suffer severe radiographic changes or joint arthroplasty. It is unknown whether the relationship to occupational exposure is the same for early and advanced disease stages. Understanding modifiable risk factors for those with early disease is important if research is to develop viable prevention strategies. Lastly, the agreement analysis, and regression analyses for SOA, MRI-OA, and ROA outcomes had results that match my a priori hypotheses: strong agreement and a statistically significant relationship between knee OA and exposure to occupational physical loading.

4.5 Study Implications and Future Directions

As the leading cause of chronic pain and disability worldwide, OA is a major public health concern. In Canada, the daunting combination of an aging population and rising obesity rates has spurred new prevention efforts that are essential to curb the escalating incidence of this disabling musculoskeletal condition.[3] However, while substantial research has focused on generating best practice management and treatment approaches for knee OA,[10] there is a paucity of research examining prevention strategies. To develop a viable prevention plan, it is imperative to have a clear understanding of all major risk factors that contribute to the development of knee OA. This includes both systemic factors, which likely increase the vulnerability of the joint, and local factors, including mechanical loading, one source of which are the occupational tasks of lifting, kneeling, or knee bending.[69-71]

Workplace interventions and policies to prevent knee OA are difficult to implement and furthermore have seldom been evaluated.[144] Currently, minimal research has been conducted on the potential of these prevention strategies; Fransen et al., in a systematic review, found no randomized controlled trials investigating prevention of work-related knee injuries or SOA.[71] Ideas such as adoption of new work methods, use of better tools and equipment, implementing administrative controls, or better training and education of workers to minimize future harm have been proposed.[71] Issues with worker compliance and education must be addressed before any successful change can occur. There is potentially a role for clinicians in partnership with ergonomists to define and promote better principles of work design.[144] As well, clinicians may be able to influence occupational risks by educating workers on proper body mechanics, the importance of maintaining a healthy weight, and how to avoid high load positions. Given the worldwide trends of extended working life and later retirement, combined with the rising prevalence

of many chronic diseases, there is a pressing need to minimize the role of occupational exposure as a risk factor for knee OA.

The use of MRI in future studies to quantify early joint disease is essential as the development of OA takes decades to manifest and targeting an early OA population may prove most successful for secondary prevention strategies. Experts in this field call not only for the study of modifiable risk factors to continue, but also for the investigation and implementation of viable prevention programs for knee OA, at both the organizational and individual levels.[69, 71, 145]

Lastly, it is advisable that future studies planning to investigate occupational exposure should ensure sufficient sample size and power to be able to conduct separate analyses for men and women. Given the current knowledge base in this area and the difference in occupational definitions and roles between the sexes, it remains unclear whether occupational exposure affects men and women in the same way with regards to knee OA.

4.6 Conclusion

The overarching goal of this thesis was to obtain a greater understanding of the role of cumulative occupational physical loading (COPL) to the knee and the presence of OA in both men and women. COPL refers to an individual's history of lifetime work activity, which includes performing the potentially knee-straining tasks of heavy lifting, carrying, knee bending, or kneeling. Chapter 1 describes the state of knowledge on the role of heavy lifting and kneeling as risk factors for knee OA through a comprehensive systematic review. Based on the overall study design and methodological quality, the review concluded there was moderate-level evidence that occupations involving heavy lifting were associated with knee OA and limited-level evidence supporting the role of kneeling and knee bending in knee OA. In addition, moderate-level evidence was found for the combined occupational activities of

lifting and kneeling and knee OA. Finally, the review found that moderate-level evidence existed for men with regards to occupational exposure, but the evidence for women was considered limited, due to the lower quantity and poorer quality of studies.

This project was designed to address two main research questions: to examine the association between COPL and the presence of knee SOA or knee MRI-OA. Chapter 2 described the methodology used in this study, including design, participant recruitment, exposure and outcome variables, agreement analysis, and statistical analysis. The results were presented in Chapter 3. Finally, a detailed discussion, including study implications and future directions, was the focus of Chapter 4.

In conclusion, this thesis provided evidence that occupational exposure to physically demanding tasks of heavy lifting and kneeling or knee bending are risk factors for the presence of SOA, MRI-OA, and ROA of the knee in men and women, adjusted for the covariates of age, sex, and BMI. This cross-sectional study included an agreement analysis of a detailed self-reported COPL measure with an ergonomic expert-based ratings scale. This measure may be a useful tool for studying dose-response relationships between occupational exposure and knee OA in future research.

The use of multiple knee OA outcomes, including a novel MRI-OA definition of knee OA, facilitated examination of the disease across the spectrum of severity from pre-clinical to moderate pathology. The elevated odds of disease associated with high occupational exposure seen in this early OA subgroup highlighted the importance of aiming future research and prevention strategies at this subgroup by both employers and clinicians.

This thesis addressed a gap in the literature in the area of occupational exposure as a risk factor for knee OA in women and illustrated the importance of the homemaker occupation for calculating an unbiased overall COPL score in women. Future studies examining occupation in women should consider a broad definition of occupation to

facilitate gender equity. The differences in how occupational roles are defined between men and women means that future work must continue to clarify the evidence regarding occupational exposure as a risk factor for knee OA in women.

The results of this thesis provide further evidence supporting the role of occupational loading as a modifiable risk factor for knee OA. This evidence suggests that further longitudinal studies are justified in this area of joint disease and occupational health across the full continuum of OA.

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