LIFETIME PHYSICAL ACTIVITY AND OSTEOARTHRITIS

by

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ABSTRACT

Introduction: The overall goal of this thesis is to improve understanding of physical activity (PA), one of the most important, modifiable but controversial risk factors in osteoarthritis (OA). OA is the major public health problem in musculoskeletal medicine and leading cause of physical disability in older adults. The ultimate purpose is to provide evidence to inform OA prevention strategies, something not currently available.

Objectives: 1) To construct and describe lifetime trajectories of hip and knee joint force from physical activity in a large Canadian sample; 2) To validate self-report measures of medically-diagnosed OA and novel measures of joint vulnerability against clinical criteria; 3) To evaluate the relationship of lifetime joint force and hip and knee OA.

Methods: PA data were collected online from 4,269 subjects via a validated PA survey in a national population-based cohort from 2005 to 2007 and subjects ranked and lifetime trajectories plotted in terms of the 'cumulative peak force index', a novel joint force measure. Validation studies were conducted in a sub-sample. Population-based multivariable studies examining the relationship between joint force and incident hip and prevalent knee OA were conducted.

Results: 1) Overall women had slightly higher lifetime PA-related force then men. Six percent of subjects developed hip OA and seven percent knee OA during follow up. There was no risk from sport/recreational activity. Very high levels of total lifetime force (hip and knee), occupational force in men (knee) and household-related force in women (knee) were associated with an approximate 2-fold increase in risk of OA, as was

previous joint injury (5-fold increase hip, 3-fold knee). At the knee, lower limb malalignment but not joint hypermobility, was associated with knee OA. Higher coordination was protective.

Conclusions: Taken collectively, the results show that lifelong physical activity-related joint force is generally safe for the hip and knee, and the promotion of exercise as a major public health initiative should continue without concern for increased rates of OA. Very high levels of occupational force in men and household force in women were risk factors for knee OA. Joint injury, lower limb malalignment and lower coordination were associated with OA.

PREFACE

Sections of this thesis have been published and submitted as multi-authored papers in refereed journals. Details of co-authors contributions are provided.

The section in Chapter 2 on validation of the Lifetime Physical Activity Questionnaire (L-PAQ) has been published in the American Journal of Epidemiology. De Vera MA, Ratzlaff C, Doerfling P, Kopec J. Reliability and validity of an internet-based questionnaire measuring lifetime physical activity. Am J Epidemiol 2010; 172: 1190-1198. Dr. De Vera designed and led this study as part of her Master's thesis. It is summarized in Chapter 2, as validation of the L-PAQ is seminal to the work in this thesis. I contributed to the design and analysis as well as the writing and revisions of the journal manuscript. Dr. Kopec and Mr. Doerfling contributed to the design, analysis and revisions of the manuscript.

The section in Chapter 2 on joint injury is drawn in part from a published article in Arthritis Research and Therapy. Ratzlaff CR, Liang MH. New developments in osteoarthritis. Prevention of injury-related knee osteoarthritis: opportunities for the primary and secondary prevention of knee osteoarthritis. Arthritis Res Ther 2010; 12: 215. I conceptualized and designed this review with input from Dr. Liang. I performed the literature review and data abstraction. I wrote the manuscript with comments and feedback from Dr. Liang.

A version of Chapter 4 has been submitted for publication. Ratzlaff CR, Koehoorn M, Cibere J, Kopec J. Clinical validation of an internet-based questionnaire for ascertaining cases of hip and knee osteoarthritis. I conceptualized and designed the study with input from Drs. Kopec, Cibere and Koehoorn. I coordinated the study and clinical examinations. Dr. Cibere contributed to examination protocols and standardization of exam technique. I conducted the statistical analysis with support from Gavin Steininger. I wrote the manuscript with comments and feedback from all co-authors.

A version of Chapter 5 has been published in Arthritis Care and Research: Ratzlaff CR, Doerfling P, Steininger G, Koehoorn M, Cibere J, Liang M, Esdaile J, Kopec J. Lifetime trajectory of physical activity according to energy expenditure and joint force. Arthritis Care and Research 2010; 62: 1452-1459. I conceptualized and designed the study with the assistance of Drs. Liang, Esdaile, Kopec and Wilson. I contributed clinical and epidemiologic expertise to the joint force values used in key calculations along with expert opinion from Dr. Wilson (biomechanical engineering), Drs. Liang, Esdaile and Cibere (rheumatology), Drs. Kopec and Cibere (musculoskeletal epidemiology). I conducted the analysis with support from Gavin Steininger and Paul Doerfling. Drs. Koehoorn, Cibere and Kopec contributed to the interpretation and discussion of the statistical analyses. I prepared the manuscript and submitted for publication. All co-authors contributed feedback on drafts of the manuscript and I completed all revisions.

A version of Chapter 6 has been published in Osteoarthritis and Cartilage. Ratzlaff CR, Steininger G, Doerfling P, Koehoorn M, Cibere J, Liang MH, Wilson, DR, Esdaile J, Kopec J. Influence of lifetime hip joint force on the risk of self-reported hip osteoarthritis: a community-based cohort study. Osteoarthritis Cartilage 2011; 19: 389-398. I conceptualized and designed the study with the assistance of Drs. Liang, Esdaile, Kopec

and Wilson. I conducted the analysis with support from Gavin Steininger and Paul Doerfling. Drs. Koehoorn, Cibere and Kopec contributed to the interpretation and discussion of the statistical analyses. I prepared the manuscript and submitted for publication. All co-authors contributed feedback on drafts of the manuscript and I completed all revisions.

Ethics approval was obtained for the studies contained in this thesis from the University of British Columbia Behavioural Research Ethics Board (certificate number H06-04000) and the Clinical Research Ethics Board (certificate number H07-01062).

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GLOSSARY

PA	Physical Activity
PAQ	Physical Activity Questionnaire
L-PAQ	Lifetime Physical Activity Questionnaire
OA	Osteoarthritis
EE	Energy Expenditure
MET	Metabolic Equivalent
CPFI	Cumulative Peak Force Index
HPW	Hours per Week
BMI	Body Mass Index
MRI	Magnetic Resonance Imaging
ACL	Anterior Cruciate Ligament
ARC	Arthritis Research Centre of Canada
NM	Neuromuscular
JHS	Joint Hypermobility Syndrome
PPV	Positive Predictive Value
NPV	Negative Predictive Value
LR	Likelihood Ratio
PAJH	Physical Activity and Joint Health

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DEDICATION

This thesis is dedicated to my family.

To my younger, smarter brother and kindred spirit Greg – we explored doctoral work at the same time bro, but life had other plans for you. This project became a footnote in the face of your illness, and will forever be interwoven for me with your gentle kindness, laughter, and sweet brave spirit - and for trying to cram 40 years of conversation and brotherhood into a year and a half. The hole in my heart will be with me until I die. I miss you beyond words.

To my enduring personal cheerleading squad - Dad, Mom, Doug, Greg, Pete and Beth, for your unending support and belief. Dad you blazed the trail ahead of me, and I think even you're a little surprised by my various travels within the normal distribution. Your love, integrity and work ethic, your belief in the value of higher education have impacted me more than you know.

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Finally, to Jane for always saying when, not if; for being the rock of our family; for allowing me to live like I was single and childless in the last haul of this dissertation; for walking alongside me these many years no matter which mountains, deserts or oceans we crossed. For what you mean to me and the boys, words fail me.

1: INTRODUCTION

1.1 Thesis Organization

This thesis is on the subject of hip and knee osteoarthritis (OA) risk associated with lifelong physical activity (PA) and joint vulnerability. The overall goal of this thesis is to gain a better understanding of the role of PA, one of the most important, modifiable but controversial risk factors in OA. The ultimate purpose of this program of research is to provide evidence to inform OA prevention strategies, something not currently available.

The thesis is organized in a manuscript-based fashion and consists of eight chapters. Chapter 1 is introductory and gives an overview of the burden of OA, a summary of the key physical activity measures and their potential physiological link to hip and knee OA, and a description of the main study objectives. Chapter 2 covers key background material and rationale including the development and validation of the Lifetime Physical Activity Questionnaire (L-PAQ) the key measurement instrument in this thesis study. Chapter 3 describes the study methodology that is common to the population-based studies presented in Chapters 4 to 7. It provides details on recruitment and enrolment of subjects, data collection and derivation of primary exposures and outcomes. Chapters 4 to 7 are separate studies addressing the various objectives of the thesis on the relationship between PA and OA, and are versions of manuscripts that have been published or are submitted to peer-reviewed journals. Chapter 4 presents a validation study of the case definitions used in the population studies in Chapters 6 and 7. A second validation study assesses the validity of novel measures of self-reported

joint vulnerability. Chapter 5 is a population-based study demonstrating a novel method for estimating lifetime hip and knee cumulative joint force from physical activity, and the construction and description of lifetime trajectories of energy expenditure (EE) and joint force, stratified by age, gender and activity type. Chapter 6 is a population-based cohort study examining the relationship between lifetime hip force and incident hip OA. It also examines the lifetime trajectory for the impact of age-specific periods of cumulative hip force exposure on hip OA. Chapter 7 is a population-based prevalence study examining the effect of lifetime knee joint force and local joint vulnerabilities (alignment, decreased coordination and hypermobility) on the risk of knee OA. Chapter 8, the concluding chapter, synthesizes findings from each study and discusses strengths, limitations and potential implications of the collective work.

1.2 Overview

Burden

Osteoarthritis (OA) is the major public health problem in musculoskeletal medicine. It is the most common joint disorder worldwide, the most common form of arthritis, among the most frequent and symptomatic health problems for middle aged and older people (1, 2) and a leading cause of chronic disability, in large part due to hip and knee involvement. Disability due to knee OA is equal to that of cardiovascular disease and greater than any other medical condition in older adults (3). Since it can severely limit mobility and physical activity, it contributes to other health issues such as cardiovascular disease, obesity, diabetes and mental health challenges (4-9). Health Canada estimated the annual cost of musculoskeletal (MSK) diseases at $16 billion for medical care and lost wages, second only to cardiovascular disease (10). Despite this, little is known about the etiology and pathogenesis of this disease. Given that there is

currently no cure or specific treatment for OA, identification of risk factors to inform prevention strategies is paramount (11).

Theoretical Framework

OA is widely believed to be the result of local factors acting within the context of systemic susceptibility (12). The systemic factors (e.g., age, gender) contribute to cartilage, bone and joint properties, but it is the biomechanical loading factors (e.g., physical activity, previous joint injury, alignment, neuromuscular control) that are thought to have crucial significance on the final qualities of bone and cartilage, its wellbeing and breakdown, as well as the determination of site and severity of OA (13). However, apart from age, there are no unequivocal risk factors for OA that are consistent across all joints. The relative importance of risk factors varies not only by joint, but for different stages of the disease, for the development as opposed to the progression of disease, and for radiographic versus symptomatic disease (14). Recently, there has been a growing interest in the modifiable biomechanical and neuromuscular factors associated with the pathogenesis of OA (12, 15-18). The most important, modifiable risk factors for knee OA are physical activity (PA) and obesity.

Physical Activity and OA

The promotion of physical activity (PA) is a major public health initiative in western countries worldwide due to its protective effect on numerous major health problems, including cardiovascular disease, cancer, diabetes, obesity and mental illness (19), including Canada and the US where public health bodies recommend 30 to 60 minutes of moderate to vigorous activities per day. However, there has long been a concern that such promotion could lead to a rise in hip and knee OA. While there is broad agreement that PA is one of the most important determinants of joint health, it is unclear what amount and type of PA are beneficial or pose a risk. In short, despite

numerous studies, the association between PA and joint health is complex and poorly understood.

Moderate mechanical loading is necessary for homeostasis and to maintain healthy articular cartilage (20). Physical activity can elicit either anabolic or catabolic processes depending on the intensity or duration of activity, the age at exercise onset, and the type of activity (8, 12). Certain occupations (21), including farming (22) and those with prolonged kneeling and squatting (23) or regular knee bending and heavy lifting (22) have been associated with increased hip and knee OA. Sports played at high intensity or elite levels (18, 24, 25) and those involving pivoting and twisting loads (20) have also been shown to increase the risk of OA in some studies, however, there is controversy and large gaps in the literature regarding the impact of overall activity from sport, occupation and household activities in the general population (26). It is unclear which activities increase the risk, whether there is a dose-response relationship and whether and to what extent the association is modified by other risk factors such as age, sex, weight, previous injury and other local joint vulnerabilities (24, 27). There have been no studies to date designed to estimate hip and knee joint load over the long term, that assesses loads applied to the joint using joint loading units or that assess lifetime joint load as a potential risk for hip and knee OA.

Local Joint Environment

The importance of abnormal joint mechanics in the etiopathogenesis of OA cannot be overemphasized. OA is best defined as failed repair of joint damage that has been caused by excessive mechanical stress (28). Joint injury and leg alignment are two such mechanical factors. The risk of knee OA due to knee joint injury is large; approximately 50% of individuals with an ACL or meniscus tear develop knee OA (29-34). A long-term prospective study indicated an approximate five-fold relative risk for

knee OA for any previous injury of the knee (32). Given that these types of knee injuries are most common in the 2nd to 4th decade of life, that OA develops within 10-20 years (35, 36), and that there is a growing epidemic of these types of injuries in sport (37) , the number of younger people with knee OA is growing. There is much less data on the relationship between hip injury and hip OA, and the few reports published have not been consistent (38-42).

In recent years, local joint factors such as leg alignment which determine how load is distributed across articular cartilage, have been shown to be important determinants of OA (43). Onset of knee OA may be determined by a shift in load-bearing to concentrated and/or less frequently loaded regions of the cartilage and subsequent progression caused by increased loading of these regions (20). Leg alignment (knock-knee, neutral, bow-legged) plays a significant role in how load is distributed in the knee joint, and is gaining importance as a potential contributing factor in knee OA (18, 44-49). Malalignment confers high focal stress, a level of stress that probably transcends the ability of cartilage or bone within the joint to withstand it (50), and has been associated with *progression* of knee OA (51, 52). If malalignment is present, the amount of lifetime load may play an additional role in the development and progression of knee OA. Evidence of the affect of leg alignment on the risk of *developing* knee OA is limited (53, 54), and no studies investigating the association between PA and OA have considered or controlled for alignment.

Neuromuscular control is another factor that influences the local joint environment. Normally, joints are protected when loads are anticipated through a neuromuscular feedback system, with muscles and tendons assuming the correct tension to deflect these loads, distribute them across the whole joint surface, or lessen the rate with which the load is applied to the joint (18). Articular cartilage is only 3-6 mm

thick and depends on these systems to protect it from sudden impulse loads, shear forces and to distribute load across the joint surface (18). OA occurs when the physiologic system and structures protecting the joint fail. It often involves the failure of several local factors in combination, and is thought to be affected by the amount of load (physical activity) that the joint is subjected to (18). While neuromuscular control is difficult to measure directly, several physical attributes are associated with it, including proprioception (joint position sense), coordination and hypermobility. While proprioceptive impairments have been associated with existing knee OA in cross-sectional studies (55-58), the relative importance of proprioception for the development and progression of OA warrants further study since there is some evidence that diminished proprioception may be a centrally mediated phenomenon that precedes, and contributes to, the development of OA (58, 59). Coordination is closely related to proprioception, and its use as a proxy for proprioception is justified on clinical grounds (56, 60), but it has not been investigated as a risk factor for hip or knee OA. Joint hypermobility syndrome (JHS) is a recognized clinical condition characterized by joint and soft tissue laxity. It is associated with diminished proprioception (57), has been linked to the presence of OA (61-63), and is measurable clinically and by validated questionnaire (64). Hypermobile individuals have reduced neuromuscular control that may result in increased joint loading. However, JHS has not been investigated as a risk factor for the development of hip or knee OA.

Rationale

This thesis addresses several important gaps in the body of literature on PA, joint vulnerability and the risk of hip and knee OA. First, methods of measuring PA in past studies have not addressed PA by quantitatively accounting for joint load using joint loading units. Second, previous studies were not designed to test biological hypotheses

about the cumulative effect of different activities and the role of joint forces as a protective or risk factor for hip and knee OA. Third, previous studies have not examined trajectories of lifetime PA (energy expenditure or joint force) for periods of high force that may have etiologic relevance. Fourth, there are few, if any, studies investigating how the amount and type of PA is affected by joint vulnerability such as joint injury, leg alignment and neuromuscular control. Fifth, this thesis will improve upon the body of literature by identifying early cases of OA versus advanced OA cases or joint replacement as the main outcome. In summary, this thesis will investigate the effect of long-term PA-related joint force measures on hip and knee OA as part of multivariable models adjusted for confounding factors, including confounding by different types of activities.

1.3 Study Objectives

The objectives of this thesis project are: 1) to quantify lifetime physical activity and local joint vulnerabilities among a national sample of Canadian adults; 2) to develop and demonstrate the feasibility of a novel method for estimating lifetime hip and knee cumulative joint load in joint loading units; 3) to construct and describe lifetime trajectories of energy expenditure (EE) and cumulative hip and knee joint force in the sample; 4) to validate self-report measures of hip and knee OA, leg alignment, and joint hypermobility syndrome in a sub-sample of British Columbia residents; 5) to investigate the influence of lifetime cumulative hip force in a prospective analyses on the risk of incident hip OA; and 6) to investigate the association of cumulative knee joint force and local joint vulnerabilities with prevalent knee OA.

2: BACKGROUND[1,2]

2.1 Osteoarthritis

Definition and Nature of Disease

Osteoarthritis (OA) is the most prevalent joint disease worldwide and one of the most important health problems in modern industrial societies (65, 66). It is the leading cause of disability in older adults, as high as that for cardiovascular disease (3). It is a heterogeneous spectrum of disorders that are united by a number of common risk factors and pathogenesis, but differentiated by the site of disease, variable degrees of cartilage degradation, repair, and bone reaction; and wide variation in presentation and outcome (67, 68). It is a chronic disease that affects not only the articular cartilage but the entire joint, including the subchondral bone, capsule, synovial membrane, ligaments, menisci, and muscles; eventually leading to articular cartilage degeneration with fibrillation, fissures, ulceration, and full thickness loss of the joint surface (69). While an exact definition that includes the varied phenotypes is elusive, a recent definition by Brandt et al. suggest it may best be defined as failed repair of damage that has been caused by excessive mechanical load (i.e. force/unit area) on joint tissues (28). The mechanical stress triggers biologic events that destabilize the normal coupling of degradation and synthesis of articular cartilage of chondrocytes and extracellular matrix, and subchondral bone (69). Osteoarthritis affects certain joints while sparing others.

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[1] A section of Chapter 2 has been published in the American Journal of Epidemiology. De Vera MA, Ratzlaff C, Doerfling P, Kopec J. Reliability and validity of an internet-based questionnaire measuring lifetime physical activity. Am J Epidemiol 2010; 172: 1190-1198.

[2] A section of Chapter 2 has been published in Arthritis Research and Therapy. Ratzlaff CR, Liang MH. New developments in osteoarthritis. Prevention of injury-related knee osteoarthritis: opportunities for the primary and secondary prevention of knee osteoarthritis. Arthritis Res Ther 2010; 12: 215.

Frequently affected joints include the hip, knee, spine and hand joints, while the elbows, wrists and ankles are rarely involved (43). Hip and knee are the most prevalent OA sites and associated with the greatest disability. Clinically, the disease is characterized by joint pain, tenderness, limitation of movement, crepitus, occasional effusion (swelling), and variable degrees of local inflammation, but without systemic effects (70). Radiographically, it is characterized by the presence of osteophytes (bone spurs), joint space narrowing, subchondral sclerosis (bone thickening) and cysts.

Prevalence of Arthritis

The self-reported prevalence and population burden of arthritis, rheumatism, and chronic joint problems has been estimated in many national surveys in North America, Europe, and elsewhere (71). The Canadian Community Health Survey (CCHS) in Canada and the National Health Interview Survey (NHIS) in the United States (US) periodically collect data on self-reported arthritis diagnosed by a health professional. In a 2007-08 report using CCHS data, 4.2 million or 16% of Canadians older than 15 years self-reported health-professional diagnosed arthritis, a number that is projected to rise to 20% by 2031 (72). In the US, the number is even higher, with more than 21% of US adults (46.4 million persons) currently self-reporting doctor-diagnosed arthritis (73). Another US survey reported 33% of those aged 18 and older had arthritis or chronic joint symptoms – the higher estimate likely the result of a shift in case definition to include the presence of chronic joint symptoms (74). Since these large surveys generally only report on arthritic conditions in general, specific prevalence estimates of OA are not usually possible. However, since OA is overwhelmingly the most prevalent arthritic condition in Canada and elsewhere (75), these national data offer an indication of the probable burden of OA in general.

Prevalence of OA

The frequency of OA in the general population is large although precise estimates are not well established. While population-based studies consistently show high prevalence rates of OA in older adults, rates vary widely by geographic and racial characteristics, by the joint studied and by the method used to define OA. In epidemiologic research, there is no easy way to define the presence or absence of osteoarthritis or to distinguish between incident and progressive disease, unlike conditions with definitive diagnostic criteria for disease onset such as bone fracture, hypertension or myocardial infarction. Furthermore, determination of the prevalence of symptomatic or clinical disease is difficult due to the episodic nature of OA and the method of case ascertainment.

Most joint-specific studies of OA prevalence have taken place in cohorts such as the Framingham studies (76), and are based on case definitions involving radiographic OA or symptomatic OA (usually defined as a combination of x-ray changes and symptoms). Radiographic OA is based on a scoring system that evaluates the structural changes seen on x-ray. For over 50 years, epidemiological research on OA has relied largely on standard criteria for case definition based on radiographic features assessed according to the atlas developed by Kellgren and Lawrence (K/L) (77). It is a 5-point scale based largely on the size of osteophytes (bone spurs) seen at the joint margins (0-normal, 1-questionable, 2-mild, 3-moderate, 4-severe). Many studies continue to use this scale, often defining grade 2 or higher as radiographic OA, and classifying grade 3 and 4 as severe OA. The long-term use of this single scale may have contributed to consistency across studies. However, recent evidence suggests that osteophytes are not necessarily associated with pain or cartilage destruction and that they may be a part of normal ageing, and an adaptive and positive response to joint loads (19, 78). In addition, by the time a person has disease sufficient to produce the characteristic

changes of OA on conventional radiographs, marked structural damage is already present as assessed by methods capable of identifying early disease (79-82).

Prevalence of Knee and Hip OA

In the US, Sweden, Iceland, China and Japan, estimates of knee OA prevalence in large population-based studies range from 28-62% (76, 83-85) for radiographic knee OA in older adults (age varies by study) (Table 2.1) and from 10 to 26% for symptomatic knee OA (76, 83-85) (Table 2.2). No such studies have been carried out in Canada. While US studies report relatively consistent knee OA prevalence, studies from Japan and China report a much higher prevalence. The Beijing OA study compared Chinese data to that of the Framingham study (86) using identical methods and definitions to evaluate the prevalence of OA across the populations, and found that older Chinese women have a higher prevalence of knee OA than women in Framingham, Massachusetts. The prevalence in men was comparable. Possible explanations for these differences range from genetic differences to heavy physical activity among Chinese and the cultural tradition of squatting, which places high compressive forces on the knee joint (but not the hip). Based on the criteria developed by the American College of Rheumatology (87) (which were designed to separate OA from other inflammatory forms of arthritis in clinical populations), two other studies (88, 89) have estimated that over one third of adults greater than 65 years of age have clinical OA of the knee. Using outcomes from health records that defined OA based on ICD-9 diagnostic codes (all joints combined) Kopec et al. reported an overall population prevalence of 11% for doctor-diagnosed OA, and 29% for those 50 years of age and older among British Columbia residents covered by the provincial insurance plan (n>4 million) (71).

Table 2.1 Prevalence of Radiographic OA in Knees and Hips, by Age and Sex, from Large Population-Based Studies

Joint, age (years)	Study	% with mild, moderate or severe OA		
		Male	Female	Total
Knees				
≥63	Framingham OA study (US)(76)	31	34	33
≥45	Johnston County OA (US) (83)	24	31	28
≥60	NHANES III (US) (84)	31	42	37
≥60	ROAD study (Japan) (85)	47	70	62
≥60	Beijing OA study (China) (86)	22	43	34
Hips				
≥55	NHANES I (US) (38)	3	3	3
≥45	Johnston County OA (US) (90)	26	27	27
≥60	Beijing OA study (China) (91)	1	1	1
≥60	Copenhagen OA study (Sweden) (92)	5	3	4
≥35	Icelandic OA study (Iceland) (93)	12	10	11

Table 2.2 Prevalence of Symptomatic OA (Radiographic Changes Plus Symptoms) in Knees and Hips, by Age and Sex, from Large Population-Based Studies

Joint, age (years)	Study	% with mild, moderate or severe OA		
		Male	Female	Total
Knees				
≥63	Framingham OA study (US) (76)	7	11	10
≥45	Johnston County OA (US) (83)	14	19	16
≥60	NHANES III ((US) (84)	10	14	12
≥60	ROAD study (Japan) (85)	16	32	26
≥60	Beijing OA study (China) (86)	6	15	11
Hips				
≥45	Johnston County OA (US) (90)	8	11	10
≥60	Beijing OA study (China) (91)	1	1	1

There are fewer studies of hip OA prevalence, and estimates vary widely ranging from 1 to 27% for radiographic hip OA (90-92, 94, 95) (Table 2.1), and from 1 to 10% for symptomatic hip OA (Table 2.2). The Johnston County OA Project, a large study in North Carolina (US), reported radiographic hip OA in 27% of Caucasian and African-American adults over 45 years of age and symptomatic hip OA in 10%. By contrast, the Beijing osteoarthritis study reported a 1% prevalence of radiographic hip OA and 1% prevalence of symptomatic hip OA. The reported Chinese prevalence is over 90% less than most studies of white persons in the US. The Copenhagen Osteoarthritis Sub-study of Swedish adults over 60 reported radiographic hip OA prevalence of 4.4 to 5.3%, while an Icelandic study reported a prevalence of 11% in adults 35 years and up. When considering all ages in the Icelandic study, the prevalence was over five times higher than that found by using similar techniques in related populations in nearby southern Scandinavia.

As reported, hip and knee OA prevalence varies widely between countries, increases significantly with age, and is more common in women. As such, a discussion of age and sex specific prevalence in continental US North Americans is warranted, a group closer ethnically and geographically to Canadians than other studied populations. In adults aged 60 years and older, knee OA defined by K/L ≥ 2 affects 31-42% of women and 28-37% of men (76, 83, 84, 96), with current larger studies demonstrating a more consistent range than those from 10-20 years ago (38). Lawrence et al. (65) who recently used census data to age-standardize results from the Framingham, Johnston County and NHANES III OA studies reported prevalence of radiographic knee OA in adults 45 years and older, at 19.2% in Framingham and 27.8% in Johnston County, and the prevalence among adults age > 60 years at 37.4% in the NHANES III. Hip OA prevalence was high (27.0%) in Johnston County adults over 45, in contrast to another US community-based study of 4,855 women over 65, where prevalence was significantly less at 7.2% (97). While hip OA was defined differently using a broader case definition, the disparity between study results leaves uncertainty regarding the prevalence of hip OA (65).

While OA is often thought of as a disease of older adults, there is accumulating evidence that disease initiation occurs at younger ages, often with a lengthy induction and asymptomatic latency period, with clinical manifestation in the 40s and early 50s. In knees of those aged 26 and older, 14% had radiographic OA and 5% symptomatic OA in Framingham (65, 76), while of those 45 and older 19 to 28% had radiographic knee OA and 7 to17% symptomatic knee OA (65, 76, 83). Jordan et al. reported a prevalence of radiographic hip OA in 27% of adults 45 and older (83), with symptomatic OA in 10% (90). These and other data provide accumulating evidence that radiographic and symptomatic OA is very common and increasing among younger adults.

Incidence of OA

There is a dearth of evidence regarding the incidence of OA. Recently Kopec et al., using administrative data from British Columbia, Canada reported incidence rates for OA (any joint) of 11.7 per 1000 person-years in the total population (10.0 in men and 13.4 in women), and that rates increased linearly with age between 50 and 80 years (71). Two US-based studies, one in residents of Rochester, Minnesota and the other among members of the Fallon Community Health Plan, a health maintenance organization in Massachusetts, used symptoms and radiographic changes to define OA. The Fallon study reported hip OA incidence of 88 per 100,000 person-years, and knee OA incidence of 240 per 100,000 person-years. In Minnesota, incidence was lower, with knee OA at 205 per 100,000 person-years among men and 200 per 100,000 person-years among women, while hip incidence was 47 and 59 per 100,000 person-years for men and women respectively. Projecting this lower incidence to the US population, the authors estimate there are 500,000 new cases of knee and hip OA every year.

Outcome Measures in OA

An important question is whether hip and knee radiographic changes are associated with joint symptoms and result in disability or reduction in quality of life. Numerous studies report discordance between radiographic change, and symptoms and disability (98). As few as 35% of those with K/L scores of grade 2-4 on x-ray report knee pain (99). In the Baltimore Longitudinal Study of Aging, among subjects with moderately severe radiographic (grade 3) knee OA, only 54% reported knee pain within the previous year (96). Only advanced radiographic changes, a late feature in disease development, are consistently associated with knee pain (76, 96, 100).

Outcome measurement in epidemiologic research of symptomatic OA, whether including radiographic change or not, is a potentially important outcome in OA

epidemiology, as it is symptoms and disability, and not x-ray change that concern patients. For broader epidemiologic study apart from disease frequency, a single definition of hip and knee osteoarthritis may be neither feasible nor desirable (67). Evaluation of the tradeoffs between validity, reliability, and practicality will depend, in part, on the design and research question of a particular study (68). Nevitt has suggested that perhaps the most appropriate goal would be to strive for a high standard of clarity and simplicity, as well as detailed description of measurements and criteria within each study, so that definitions can be applied reproducibly across studies (67). For example in large epidemiological studies of disease etiology, questionnaire assessment of OA may be the only practical means for disease ascertainment since examination and/or radiologic assessment is prohibitively expensive and arguably unethical. Using questionnaire, the greatest accuracy and least misclassification is achieved by asking about physician-diagnosed arthritis (101).

Disability

Arthritis is the most frequent cause of physical disability in the older adult population in Canada (102, 103). The prevalence of long-term disability either attributed to or associated with arthritis in the general adult population is greater than 2.5% (104), and arthritis is also the leading cause of work-related disability in North America (105). Arthritis has a strong impact on daily function, ability to work, participation in social and recreational activities, and overall quality of life (106). The average impact of arthritis on a person's quality of life in the 1996/7 Ontario Health Survey was greater than that of cancer, heart disease, diabetes, or chronic bronchitis (107). In a 2003 Health Canada report, over half of people aged 45 to 75 year with arthritis and two-thirds of those 75 and over with arthritis reported activity limitations (108). It is projected that the number of

people with arthritis and arthritis-attributable disability in Canada will more than double by 2031 (102).

While there is less information on OA specific disability, OA is the most common form of arthritis, estimated to represent about 75% of all individuals with arthritis and rheumatism (75). Symptomatic osteoarthritis (OA) causes substantial physical and psychosocial disability (3). The World Health Organization estimates that OA is a cause of disability in at least 10% of the world population over age 60 years. Although OA rarely causes death, the Global Burden of Disease study ranked it ahead of such conditions as breast cancer or diabetes in terms of combined impact on mortality and quality of life (109). It has a formidable effect on the burden of disability and dependence and was second only to chronic heart disease as the primary diagnosis leading to adults' receiving Social Security Disability payments among older Americans (110). Disability due specifically to knee OA in the population is reported to be a significant cause of work disability, including both direct and indirect costs (111). In the well-known Framingham cohort in the US, the risk for disability (defined as needing help walking or climbing stairs) due to knee OA is equal to cardiovascular disease and greater than that caused by any other medical condition in the elderly (3). Estimates suggest that the public health consequences of the prevalence of knee OA is projected to double by the year 2020, due in part to increases in obesity and longevity (79).

Economic Burden

The economic costs due to OA are large. In 2002, Health Canada estimated the annual cost of musculoskeletal disease at more than $16 billion for medical care and lost wages, second only to cardiovascular disease (1). A 2003 study estimated the cost of arthritis to the United States economy to be over $116 billion in 1997 dollars (112). A 1997 analysis of the economic costs of musculoskeletal disorders in five industrialized

countries (Australia, Canada, France, United Kingdom, and United States) - in which OA was the most common disorder - found a rising trend of costs that had, by then, reached between 1% and 2.5% of the gross domestic product (GDP) of these countries (113). A more recent estimate placed costs related to arthritic and rheumatic conditions at 2.9% of GDP (114). Knee and hip OA are a main contributor to these costs. Apart from chronic cardiac disease, OA is the leading diagnosis requiring adults to receive Social Security disability payments (115). Since the majority of disability from OA occurs in older adults, the number affected will increase substantially as the "baby boom" generation ages, interacting with the obesity epidemic to place enormous demands on the healthcare system and society at large.

Given the tremendous and growing burden of hip and knee OA, the lack of a cure or specific treatment short of joint replacement, a thorough understanding of risk factors, particularly the modifiable ones, is warranted. A review of risk factors follows in the next section.

2.2 Systemic Risks Factors for Hip and Knee Osteoarthritis

Hip and knee joints become susceptible to OA when local joint factors (e.g., joint shape, previous injury, neuromuscular control) combine with systemic factors (e.g., age, gender, bodyweight) and joint use (physical activity) (43). The systemic factors help establish the basis for the physiologic, histologic and anatomic properties of the bone, cartilage and joint structures. However, systemic vulnerability, including older age, is not sufficient cause for disease development. Systemic vulnerabilities to OA probably act through local mechanisms and excess mechanical load for the most part (43). The most important established systemic risk factors are age, gender and bodyweight.

Age

While OA is not inevitable with older age, age is the strongest identified risk factor for the development of osteoarthritis (14, 65, 116), as is clear from prevalence and incidence data grouped on age (Tables 2.1 and 2.2 - previous section). Aging may bring together multiple local vulnerabilities (43). OA has a long induction and asymptomatic latency period suggesting that, while symptomatic OA usually occurs after age 40, the process that leads to OA likely begins earlier in life in the 3rd and 4th decades. This period corresponds to a time when early age-related cartilage changes have occurred (e.g., decreased glycosaminoglycan and water content, decreased growth factor, chondrocyte senescence (117, 118)) and where physical loads from occupation and household activity are at their highest lifetime values (119). It has been shown that abnormal mechanical forces in these periods can awaken the adult chondrocyte from a state of low metabolic activity and stimulate the cell to produce a host of inflammatory mediators, many that are normally produced by macrophages during responses to injury or infection (117). In addition, joint-protective neuromuscular and mechanical factors, such as proprioception (joint position sense), muscle strength and meniscal integrity, may become impaired with age (116). High cumulative joint force combined with less resilient cartilage and decreased repair capacity may also be particularly important for the initiation of the OA process, though this is not known. The increase in the prevalence and incidence of OA with age is probably the result of a multi-factorial process in combination with cumulative exposure to joint load. However, few prospective etiologic studies of OA have investigated OA as part of a multi-factor model that includes measures of PA across the life span, or investigated the role of cumulative joint force, adjusted for known risk factors such as age.

Gender

For reasons that are not clearly elucidated, the age-associated increase in OA is greater in women than men (116). Most studies report a higher prevalence of radiographic and symptomatic knee and hip OA in women (Table 2.1 and Table 2.1 – previous section). Women also tend to have more severe forms of knee OA than men (120, 121). Some studies have shown that before the age of 50 years, men have a higher prevalence of hip OA than do women, possibly owing to a reportedly higher rate of athletic, occupational and other joint injuries in young men (43). However, after age 50 years, there is consistent evidence that women have a higher prevalence and incidence of hip and knee OA (43, 76, 83, 85, 90, 122). The reasons for these differences are not clear. The definite increase in OA in women around the time of menopause has led investigations to hypothesize that hormonal factors may play a role in the development of OA (14). However, the effect of estrogen, either endogenous or exogenous, on OA has been conflicting in the observational studies conducted to date (123-125). The influence of PA in women has been under-investigated in previous studies of PA and OA. It has been demonstrated that women acquired the majority of their PA from household activities (119, 126, 127), yet this domain of activity is unmeasured in most previous PA-OA studies.

Bodyweight

Obesity (Body Mass Index (BMI) ≥ 30.0) and overweight (BMI ≥ 25.0) (128) are among the most significant risk factors for the development of certain subsets of osteoarthritis (14, 24, 40, 129-137) and obesity, whether defined by increased weight (kg) or BMI, is an unequivocal risk factor for the onset and symptoms of knee OA (138). In the Framingham cohort (129), the longest prospective follow-up study measuring bodyweight and OA, weight (in persons of median age 37 years) predicted the occurrence of knee OA 36 years later. The age-adjusted relative risk for knee

osteoarthritis in the highest quintile of baseline bodyweight versus the three lightest quintiles was 2.07 (95% CI 1.67–2.55) for women and 1.51 (95% CI 1.14–1.98) for men. Separate investigation on the same cohort showed that women who had lost about 5 kg had a 50% reduction in the risk of development of symptomatic knee OA and also showed weight loss was strongly associated with reduced risk of incident radiographic knee OA (139). In a recent meta-analysis of high quality studies, Blagojevic et al. (120) selected and evaluated 36 papers investigating BMI as a risk for knee OA, either as a primary exposure or a confounder. All studies assessing BMI showed overweight and obesity to be risk factors for future knee problems with effects ranging from a two-fold to three-fold increase for overweight and obesity respectively. .

The relationship between overweight (BMI ≥ 25.0) and hip OA is equivocal, and if it exists at all, is weaker than that for knee OA (14). The relationship with hip OA is stronger for obesity, and more robust for case definitions based on symptoms than on radiological findings (40, 131, 134-137, 140-143) including the relationship between obesity and a total hip replacement (a proxy for severe OA) (134, 135, 144, 145). In a 2002 systematic review of obesity and incident hip OA using a best-evidence synthesis, Lievense et al. (143) supported the finding that the association between obesity and hip OA was stronger in studies in which hip OA was based on clinical symptoms. Overall findings from the systematic review provided moderate evidence (OR~2) for a positive association between obesity and the occurrence of hip OA (all outcomes). However, a lack of well-designed prospective cohort studies with adequate follow-up time limit the veracity of the findings (143). Since then, in a large population cohort study using radiographic outcomes, Reijman et al. found no relationship between BMI and hip OA (137). More recently, Jiang et al. conducted a meta-analysis and meta-regression of fourteen epidemiological studies to quantitatively assess the strength of associations

between body mass index (BMI) and hip osteoarthritis risk (146) and showed that BMI had a weak but statistically significant positive association with hip OA. Across all studies and genders, a 5-unit increase in BMI was related to an increased risk of hip OA (RR: 1.11; 95%CI: 1.07, 1.16). The magnitude of associations were similar in women as compared with men (women, RR: 1.10; 95%CI: 1.05, 1.15; men, RR: 1.08; 95%CI: 1.04, 1.12; $p>0.05$), and summary measures were consistent across case-control studies (1.12; 95%CI: 1.02, 1.24) and cohort studies (1.11 95%CI: 1.06, 1.16). BMI was positively associated with hip OA outcomes defined by radiography and/or clinical symptom (RR: 1.04; 95%CI: 1.00, 1.07) and by surgery (usually THA) for OA (RR: 1.16; 95%CI: 1.11, 1.22).

Interestingly, while there is general agreement that biomechanics and increased dynamic loading of the joint are the reasons for the increased risk associated with obesity and overweight, other factors associated with obesity could contribute to the increased incidence of OA (140, 147). In part, this is based on the observation that there is an association between obesity and hand OA (a non-weight bearing joint). Some investigators have proposed that obesity may be a low-grade systemic inflammatory disease, suggesting that factors associated with obesity alter systemic levels of pro-inflammatory chemical mediators (e.g., cytokines) that contribute to the relationships between obesity and knee osteoarthritis. Several studies have examined measures of body composition (i.e., adipose, non-adipose) and their relationship with joint structure (e.g., cartilage volume, cartilage defects) (138, 148-150) and suggested that while increased body fat has a deleterious effect on joint health (e.g., more cartilage defects), non-adipose mass benefits tibiofemoral joint health in people without established knee OA (e.g., increased cartilage volume) (138). The evidence is based largely on healthy subjects and the mechanism by which overweight and obesity lead to symptomatic hip

and knee OA remains unclear. Two recent population-based studies investigating this question - one through direct measures of inflammatory mediators (147), and one through various measures of body mass (140) – have provided strong evidence that increased dynamic loading, and not metabolic issues, lie behind the elevated risk for hip and knee OA. This evidence, along with the unequivocal role of bodyweight in the genesis of knee OA underline the importance of incorporating measures of bodyweight into estimates of PA-related joint force when investigating its role in the development of hip and knee OA, something no studies have done.

2.3 Physical Activity and Osteoarthritis

It is widely accepted that participation in physical activity is associated with physical, psychological and social benefits (6, 151). Regular physical activity (PA) is also associated with lowered incidence of cardiovascular disease, diabetes, hypertension, osteoporosis and cancer (7, 152) and is essential for normal muscle and joint health. Many of the health benefits of PA accrue from the metabolic changes associated with energy expenditure (e.g., cardiovascular health, increased glucose tolerance). While energy expenditure may be similar across activities such as swimming, walking, cycling or jogging, hip and knee joint force varies considerably by sport (153-156). It is therefore important to distinguish between the different components of physical activity when investigating health outcomes such as osteoarthritis.

The hip and knee joints are used repeatedly over many decades. This use may have a positive effect on joint health leading to adaptive changes in bone and cartilage, or it may have harmful effects leading to osteoarthritis, depending on the activities undertaken and the vulnerability of the joint. Most day-to-day activities performed over months and years are not a sufficient cause for the development of hip or knee OA in a

healthy joint. However, if a joint is vulnerable it may become osteoarthritic even with normal day-to-day activity.

Biomechanical forces and dynamic loading of the hip and knee joint occur primarily through PA. In a normal young joint with limited or no vulnerability, normal daily activities would not likely result in joint damage. However, activities with very high loads or cumulative load over time may overwhelm the ability of a normal joint to adapt (43). In an older joint, activities once tolerated by a younger joint may lead to joint breakdown. There is some evidence that heavy PA encountered by older subjects leads to an increase in incident OA while the same level of activity has minimal impact on incident OA in the middle-aged (43, 157). Excessive amounts and/or specific types of loads (e.g., sustained squatting or kneeling) that cause static compression or shear have been shown to be detrimental to cartilage metabolism and structure (13, 158, 159), but their role in development of hip and knee OA from epidemiologic study is inconsistent (24). Knowledge of the effect of PA on the risk for developing hip and knee OA is controversial and its association with joint health complex and poorly understood.

Biological Considerations

Under normal physiological conditions, articular cartilage provides a nearly frictionless surface for the transmission and distribution of joint loads, exhibiting little or no wear over decades of use (160). This occurs due to the structure and composition of the extracellular matrix (ECM), which is composed of water (main constituent), a cross-linked network of collagen and proteoglycans (PG) – water-binding molecules. Cartilage cells (chondrocytes), determine the makeup of this matrix. Physical activity that produces moderate mechanical loading is necessary for homeostasis (20), facilitating chondrocyte function in the synthesis and rate of turnover of articular cartilage molecules, such as proteoglycans, which enhance cartilage stiffness (13, 161). A similar

process occurs in subchondral bone, with osteocytes regulating bone turnover, repair and overall health.

Studies in recent years have provided strong evidence that the most common forms of OA are initiated when normal joint physiologic mechanisms are overwhelmed via excessive local mechanical force. This in turn triggers biologic events that destabilize the normal coupling of degradation and synthesis of articular cartilage and subchondral bone (28). The failed attempt to compensate for this excess load and repair joint damage leads to the characteristic bone, synovial, cartilage and other changes seen in OA (28). These changes include irreversible matrix degradation, and the characteristic synovitis, osteophytosis, cartilage defects, subchondral bone sclerosis, cysts and bone marrow edema commonly seen in OA.

Animal studies of altered joint loading clearly illustrate that biomechanical loading factors affect cartilage metabolism and play a role in the development of OA (20). In rabbit and canine studies, varying physical activity levels have been shown to elicit anabolic or catabolic responses leading to enhanced or damaged cartilage depending on the intensity, frequency, duration, force of impact and age of exercise onset (13, 162, 163). A study using canine cartilage explants showed that damage to cartilage consistent with OA required repeated impacts with a peak stress above a certain level and suggested that impact damage is cumulative and stress-rate dependent (164). The amount of running has been related to OA development in rats (165). High-intensity exercise or a sudden increase in exercise at an older age produces catabolic changes in cartilage that eventually lead to OA (13). These degenerative changes include a decreased collagen network structure, site-specific proteoglycan loss, and reduced cartilage stiffness (20).

PA and OA in Humans

While it is accepted that the amount and type of joint load from PA has a bearing on joint health and bone, muscle and cartilage properties, epidemiologic studies of the relationship between physical activities and OA have been widely conflicting. High levels of particular types of PA in select sub-groups, such as athletes involved in certain competitive sports and heavy physical occupations increase the risk of OA, but there is controversy regarding the role of moderate and vigorous PA on the population risk. At the knee, a number of longitudinal studies have found an increased risk from PA (157, 166-170), others have reported no risk (171-175) and two reported a protective effect (172, 176). Results from case-control studies are similarly equivocal with a number reporting risk (23, 42, 177-183), and fewer reporting no risk (181, 183-185) or a protective effect (184, 186). At the hip there have been five longitudinal studies with three reporting risk (39, 41, 187) and two reporting no risk (167, 188). Among case-control studies at the hip all have found a risk for physical activity (40, 189-196). These studies will be reviewed in more detail in a subsequent section.

The lack of agreement is due in large part to methodological difference apparent in published studies of PA and OA, in particular different definitions and assessment methods of physical activity exposure. For example, many studies assess PA data from occupation, sport, or a combination of both, but rarely from household activity. Most studies measure current (e.g., past week) or recent (e.g., past month or year) activities and do not gather data on long-term PA patterns. In addition, physical activity has numerous attributes that may be important components of risk including time in activity, frequency of participation and type of activity. Many of the health benefits of PA accrue from metabolic changes associated with energy expenditure (e.g., cardiovascular health, increased glucose tolerance) from activities such as swimming, walking, cycling or jogging, despite the fact that the hip and knee joint force varies considerably by these

sports (153-156). These different aspects of PA may affect body systems differently, so that even though an activity is good for cardiovascular health, it may be at the expense of excessive joint force.

In summary, in epidemiological studies investigating the PA-OA relationship, key aspects to consider when evaluating PA exposure in the literature relate to PA domain (sport/recreation, occupation, household), PA period and joint force. The next section will consider epidemiologic studies focusing on some of these key aspects of PA exposure and their association with hip and knee OA.

PA Domain

Most epidemiologic studies have investigated one (occupation or sport) or two activity domains (mostly occupation and sport), while only a few have investigated all three primary activity domains (occupation, sport, household). A brief discussion of the relationship between domain-specific physical activity and hip / knee OA follows.

Occupational Activity

The role of occupational activity is better understood in men than in women, in part because previous studies were based historically on male-dominated workforce cohorts, and therefore excluded women and physical activity related to homemaking or child-rearing activities (116). Workers whose jobs involve physical labour have generally been found to have higher rates of both knee and hip OA (22, 39, 41, 157, 168, 178, 179, 189, 197), including in several high quality prospective cohort studies that show a moderate risk for heavy occupational activity (39, 41, 198). Two prospective cohort studies with 22 year follow up (longest in the literature) arising out of the population-based Mini-Finland Health Survey have recently been published (41, 198). Using physician-diagnosed OA, the adjusted OR for the heaviest category of physical demands at work compared with the lightest category was 18.3 for knee OA and 6.7 for hip OA.

Data from the Framingham Study suggest that job activities may cause as much as 15% to 30% of knee OA in men (170, 199). McAlindon et al. (157) using longitudinal Framingham data reported that the number of hours per day of heavy physical activity was associated with the risk of incident radiographic knee OA (OR=7.0 for 4+ hours heavy physical activity/day). No effects were observed from moderate and light PA. A study by Hannan et al. (175) in the same cohort found no increase in the risk of knee OA with increasing activity. In the highest quartile of habitual PA compared to the lowest, the OR was 1.3 for men and 1.1 for women (both non-significant).

A number of case-control studies have investigated PA and hip and knee OA. Coggon et al. (23) found increased risk of knee OA in subjects who reported prolonged kneeling or squatting (OR 1.9), walking >2 miles/day (OR 1.9), and regularly lifting weights of at least 25 kg (OR 1.7). In a study by Sandmark et al. (180), there was an association between knee OA and lifting at work (OR 3.0), squatting or knee bending (OR 2.9), kneeling (OR 2.1) and jumping (OR 2.7). Lau et al. (42) in Hong-Kong reported an OR of 2.5 in men and 5.1 in women for climbing stairs frequently, and 5.4 in men and 2.0 in women for frequently lifting heavy weights. In Japan, Yoshimura et al. reported a statistically significant association between regular lifting of 25 kg in the individual's first job (OR 3.6) or of 50 kg in their main job (OR 4.0) for hip OA (189). In contrast, those subjects who spent > 2 hours each day sitting during their first job were significantly less likely to have the disorder (OR 0.5).

Only a few studies that investigated heavy occupational exposure have shown no risk or a protective effect for knee or hip OA. Wang reported a composite sport and occupational exposure and found a risk for knee OA but not for hip OA (167), while Hart (200) found no risk from combined occupation, sport and walking, though very few details were provided on the PA exposure measurement.

Several reviews of occupational PA exposure and hip / knee OA have been reported. A review of 16 case-control and cross-sectional studies by Jensen et al. (201) found increased prevalence of knee OA for subjects who kneel or squat at work with prevalence ratios ranging from 1.4 and 4.0. Maetzel et al. (202) conducted a systematic review of 17 case-control and cross-sectional studies relating the presence or absence of radiographically diagnosed knee and hip OA to occupational factors and concluded that a strong positive relationship exists between work-related knee bending and knee OA in men (OR range 1.4-6.0) and a consistently positive relationship exists between work related exposure (farming in particular) and hip OA in men. Less information was available for women. A more recent systematic review by Lievense et al. (203) using the 'best evidence' method of synthesizing observational studies showed moderate evidence (OR ~ 3) for the role of heavy physical workload in general, and the subcategories of farming (>10 years) and lifting heavy weights (>25 kg) in particular. Vignon et al., in a 2006 international systematic review concluded there was a high level of scientific evidence for a relationship between occupational activity and OA of the knee and hip, and that while the precise nature of biomechanical stresses leading to OA required clarification, the role of high loads on the joint may be of particular importance.

Sports and Recreational Activities

The role of sport activity on knee and hip OA is less clear than that for occupation. While sport and recreational activity is widely advocated for its many health benefits, including muscle strength bone and joint structure, there has long been concern that OA may result from long-term participation in vigorous physical activities, or from sports that have high impact or torsional (twisting) loads. Long-term participation in sports with higher compression and torsional loads have been associated with an increased incidence of OA (204, 205) and the majority of case-control studies have

found an association between sport / recreation and OA (40, 191, 193, 206). Lievense et al. (207) in a 2003 systematic review using a best evidence synthesis concluded that there was moderate evidence for a positive association between hip OA and sporting activities. However, at the time no high quality cohort studies were available so analysis was based on retrospective studies only. Felson and Zhang (27) reviewed 10 studies examining the effects of running on hip and knee OA and concluded that elite runners, presumably with higher mileage, did appear to be at increased risk for OA. However, several long-term studies have reported that runners do not have a higher rate of OA than non-running controls (174, 208, 209), including recent evidence suggesting that running is safe for the hip and knee in the absence of a local factor such as joint injury (210, 211). A number of studies from other sport / recreational activities have also reported either no risk or a protective effect with sporting activities and knee and hip OA, particularly with low to moderate recreational activity (171-174, 176, 180, 181, 184-186, 212, 213). This is supported by two recent longitudinal cohort studies following over 800 population-based subjects for 22 years that found moderate regular recreational physical activity (measured as current activity at baseline) did not increase knee (198) or hip (41) OA risk and, at the knee, conferred a protective effect (198). Another longitudinal study with 12 year follow up estimated PA-related joint force from the previous 12 months of sport/recreational activities and did not find a risk for combined hip and knee OA (173).

Several studies using MRI outcomes have shown structural benefits within the joint in response to recreational PA. In a short-term trial, Roos and Dahlberg (161) reported that individuals without OA who were randomized to an exercise regimen had a healthier distribution of proteoglycans compared with sedentary individuals not participating in exercise, suggesting a protective effect on the development of OA over a longer period (171). Two recent high quality cohort studies have been published using

MRI outcomes of cartilage health, both reporting (172, 176) that vigorous physical activity or strenuous exercise is associated with fewer cartilage defects, while one (172) also found a positive association with tibial cartilage volume (improved joint health). A third (212) found no association between physical activity and knee joint cartilage, but the study had limited power to show an effect as it only included 28 subjects.

These findings have resulted in some confusion with regard to the role of sport/recreational activity and hip and knee OA. Some of the conflict may be due to recall bias, inherent to case-control studies in the measurement of PA exposure. Another reason may be the heterogeneity of study populations – some in athlete groups in competitive sport with relatively high amounts of exposure versus those in the community or general population-based studies with generally lower activity levels. The period of PA exposure varies widely in these studies as well. Some theories suggest that the increased risk of osteoarthritis among sport participants is related to joint injuries. Thelin et al. (2006) found that knee joint injuries (and not type of sport or other factors) accounted for all knee OA in a population-based case-control study of Swedish adults aged 51-70 (214). Another possibility is that while joint force from sport is likely the most important aspect of physical activity, only two studies have attempted to estimate it (173, 186). Moderate physical activities with lower joint forces, such as walking and bicycling, are associated with a lower risk of injury than are strenuous sports, especially among women (7, 215, 216). Further research is needed to clarify the relationship between these different components of sport-related activity and previous injury and the development of osteoarthritis.

Household Activity

Few studies of PA and OA have considered the role of household activity, despite previous research showing that household activity is a major contributor to

weekly energy expenditure (217-219), and is a much larger contributor to overall activity than leisure time sports/recreational activity in the population (119, 126). National data in Canada and the US report that only about 25% of the population perform regular sustained physical activity, and about 30% of the population is entirely inactive (127), but traditionally surveys have not inquired about detailed household physical activities. This may be an important oversight for PA-related energy expenditure and joint force in women. Many physical activity studies in the past have reported low female participation in regular physical activity with little or no engagement in vigorous activity (127, 220).

Women often spend forty-plus hours a week at a full-time job and anywhere from twenty-five to forty-five hours a week working in the home (221). Surveys used in many existing studies may fail to measure the frequency, duration and intensity of physical activities actually performed by women (127). The majority of women's exposure to physical activity, particularly in historic cohorts, is due to accumulation of regular household activities (127, 217, 218, 222). In a Canadian study of more than 6600 women in 1998, Weller et al. reported that non-leisure (household chores) energy expenditure represented on average, 82% of women's total activity (126). When the definition of regular PA measured in surveys is expanded to include household and other non-leisure activities, PA levels increase and associations with health outcomes are more apparent – including an inverse relationship with all-cause mortality (126, 127). The authors underscore the importance of including an adequate assessment of household activity and demonstrate how many commonly used past measures of PA have lead to gender bias (126). This bias is apparent in previous studies of OA as well where household-related PA has usually been overlooked, and/or not considered within the framework of occupational activity.

While household activity may generally not be considered vigorous from an energy expenditure perspective, there are many repetitive motions (e.g., stair climbing, squatting, kneeling) and activities (e.g., gardening, lifting, carrying) that are associated with high hip and knee joint forces (154, 155, 223, 224). Very few studies have investigated household activities, despite its potential role in joint health and the pathogenesis of OA, nor as a possible explanation of the higher prevalence of hip and knee OA in women. Sandmark et al. (180), in a study of 1173 Swedes measured exposure to physically demanding tasks at home and found it to be associated with knee OA among women (OR 2.2). Vingard et al. in another Swedish study investigated physical load from work and home in women and found that frequently climbing stairs (RR=2.1) and those who had physically demanding tasks outside occupational life (RR=2.3) had higher risks of hip OA (192). Both these studies inquired about lifelong exposure. Two prospective cohort studies investigating incident knee OA included aspects of household activity in overall activity scores using current or recent activity measures. McAlindon et al. summed activity from work, home and recreation into light, moderate or heavy activity groups in the Framingham cohort and reported that heavy physical activity, but not light or moderate was a risk for the development of knee OA (157). Verweij et al. found a risk for knee OA in those with a high total mechanical strain or low muscle strength score, while controlling for lifetime physical work and PA. No cohort studies have investigated the role of household activity in hip OA development.

PA Period

The time period over which PA is measured is a critical exposure component. Most epidemiologic studies (and all prospective population based cohort studies) investigating PA and OA measure current (past week or month) or recent (several months to past year) PA. While current and recent PA have higher validity and reliability

than periods in the distant past, a potential problem is that they are not representative of activity patterns during other life periods when joint forces may be higher, and do not assess cumulative load. This can be problematic even in the few prospective studies with longer follow-ups, which usually have measured recent PA at one (baseline) or two (baseline and follow up) time points. Another potential problem is that PA in the months and even years preceding the onset of clinical disease may be unrelated to pathogenesis, since hip and knee OA have a long induction and asymptomatic latency period with disease initiation usually occurring many years before the first symptom appears. A further problem is that recent activity may be affected by early sub-clinical or undiagnosed signs of OA (e.g., stiffness, occasional ache, clicking, catching, instability) which could affect participation in PA during the measurement period. Studies that have investigated long-term or life span PA exposure have been case-control or cross-sectional studies. Most of these studies asked subjects to report job titles or whether the activity involved specific motions (e.g. lift, kneel, walk), but did not take into account the duration, intensity and frequency of PA; and were not designed to test biological hypotheses about the cumulative effect of different activities and the role of joint forces. Sixteen case-control studies were identified that assessed long-term or lifelong exposure, with two including household activity (180, 192), while the others included occupation and/or sport. Most of these studies reported a risk of hip or knee OA associated with lifelong activity (23, 42, 177-180, 182, 183, 189, 191-194, 196). One study investigating lifelong occupational exposure found a risk for men but not for women (195), while another found a risk for hip OA from lifelong occupation but not sport (183). Further, one reported no risk from lifelong sport (185) while one found a protective effect from lifelong sport / recreational activity (184). The two studies that included lifelong measures of household activity both reported an increased risk of hip OA (180, 192).

Joint Force

Many of the studies cited in the preceding sections measured similar constructs (e.g., light vs heavy activity, activity causing sweating or shortness of breath, or specific activities such as climbing stairs, walking, standing, kneeling) at different life periods and from different domains. These measures of PA have not been linked to hip or knee OA risk in a consistent way. This may be in part because different activities have a cumulative effect, and this effect depends on the repetitive, compressive, high impact and torsional forces transmitted through the joint (164, 165, 225). The dose of joint force is influenced by the type, frequency and duration of physical activity, as well as by gender, age, body weight, and the presence of joint injury (173). The methods of measuring PA to date have not been designed to convert self-reported PA to joint loading units, nor to capture the cumulative effect of different activities. Two studies attempted to quantify sport-related joint force over the short term. One was a 2003 prospective cohort study (173), where PA-related joint stress was calculated using information on the frequency, intensity, and duration of individual types of PA over the past 12 months, and incorporated a quantification of joint stress. The authors did not find a relationship between joint stress from sport and the risk of combined hip/knee OA. The other was a nested case-control study that classified sport-related PA exposure by joint stress (moderate/high, low, or none) based on the intensity, frequency, and rate of joint injury, impact and torsional loading, and also did not find a relationship with hip/knee OA (186).

In summary, one of the most important modifiable risk factors for hip and knee health are joint forces associated with PA, yet the role of PA in joint health is still not well understood, in large part due to insufficient exposure measurement. While there are a number of case-control studies that estimate long-term exposure, only two consider all three major activity domains. Previous case-control and prospective studies have yet to

use physical activity data to develop a joint force measure, incorporating bodyweight, to test biological hypotheses about the cumulative effect of different activities. The next section will address the measurement of PA with a focus on an historical time frame, joint loading aspects and inclusion of all major activity domains.

Measurement of Historical Physical Activity – A Review of the Literature

Physical activity has been defined as "any bodily movement produced by skeletal muscles that result in energy expenditure" (226). In addition, PA is a multi-faceted construct with many properties and tremendous variability between individuals. Adequately measuring PA is important for determining patterns and trajectories of PA over time, and for assessing the effect of PA on health outcomes and its use as an intervention in treatment of disease. Poor measurement may hinder the detection of important associations or lead to spurious conclusions. In epidemiologic efforts to estimate PA, it is imperative to consider both the properties of PA that are of biological relevance and the instrument used to capture those properties. In the case of this thesis, detailed PA data from across the lifespan that can potentially be converted to a measure of joint load are of interest, and after an introduction to PA measurement, will be the focus of this literature review.

A number of methodological issues have made accurate measurement of PA a challenge. In part these problems arise from the diverse definitions of PA employed in studies; a lack of valid, reliable and standardized instruments used across studies; the large measurement error of the instruments; and the failure to utilize an instrument that reflects the health-related components of PA that are relevant to the disease or outcome being investigated (227). Where accurate and precise measures are available, they are usually impractical or expensive for use in population-based research. There are several objective measures of PA that include 1) *calorimetry* which measures energy

expenditure through heat production using both direct and indirect methods, and provides an objective and accurate assessment of physical activity; 2) *physiological markers of energy expenditure* (e.g., maximum oxygen consumption, doubly-labelled water technique); 3) *measures that estimate physical fitness* (e.g., heart rate monitor, treadmill testing); 4) *movement counters* (e.g., accelerometers and pedometers) which measure frequency of movement, and sometimes speed and change of direction; and 5) *direct observation* (monitoring individuals and rating observed activity). Most of these measures of PA are not practical in population-based epidemiology research due to their expense and respondent burden (leading to reduced compliance). They are also unfeasible as measures of historic or lifelong PA. Further, the relationship with outputs from these objective measures of PA and joint loading is questionable. For example, heart rates can be similar for periods of running, swimming, or carrying a heavy weight up stairs, yet hip and knee joint force vary considerably across these activities, and heart rates can be strongly influenced by a host of non-activity related phenomena. Likewise, an accelerometer or pedometer fails to register activity during sustained squatting, kneeling, standing, twisting, holding heavy items; or moving slowly while pushing or carrying heavy objects or tools – all examples of activities associated with high and potentially damaging compression and/or torsion forces at the knee and hip joint but with insufficient movement to trigger the motion monitoring device.

Job classification highlighted here as one of the most widely used methods for PA assessment due to its convenience and low cost, is based on ranking jobs by activity level, assuming that all individuals within each occupational category engage in similar levels of activity. While it is potentially useful in capturing the long-term effects of PA and has utility in ranking subjects by aspects of joint loading, it is problematic in that there is wide variability in PA volume, intensity and characteristics within the same job title and

seasonal and temporal variations in occupations. It also omits other key domains of activity (sports / recreational activities and household activities), and those not enrolled in the paid workforce (e.g., work in the home, the unemployed, retirees, volunteers).

Given the expense, impracticality and biases of the above methods for population-based research, survey and questionnaire methods have been the most widely used method in epidemiology when estimating PA. Reasons for their popularity include non-reactiveness (lack of alteration of the individual's behaviour as direct result of the assessment method), practicality (low cost and subject convenience) and accuracy (reliability and validity) (228-230). They also allow for the possibility of collecting data on PA in the distant past and can be tailored to capture the health-related aspects of PA under investigation. To date, they have been the only method utilized to collect historic or lifetime PA.

There are four common elements to PA questionnaires (PAQ) (229) including the *time frame* of PA measured, the *means of collecting* information and the *summary index* (a continuous score estimating energy expended or ordinal scale ranking subjects by level of activity). The fourth component is the *nature and detail of activity*. The assessment tool should elicit accurate information on the types of activity that encompass the greatest proportion of the aspect of PA (e.g., energy expenditure, strength, flexibility, bone loading, joint force) in the population of interest. If attempting to capture a summary or total score, than activity from all domains (occupation, sport/recreation, household) must be included. In many surveys, subjects are asked to self-rank their activities on some ordinal scale using simple questions that require less than 10 minutes to complete (e.g., light to heavy, caused sweating or not, caused shortness of breath or not). These surveys solicit little specific information about the nature and detail of the physical activities and are often referred to as general surveys,

regardless of the time frame of reference (229). Most past studies surveying PA for its risk/benefit for OA fall into this category. Surveys that inquire about detailed activity, such as the frequency, duration, and intensity of specific activities, performed over a longer period, are often called quantitative history procedures, are largely lacking in studies of PA and OA (none in prospective cohort studies), and are the type of survey of interest in this thesis. Primarily, they have been used in studies investigating the effect of historic PA on cardiovascular, diabetic, cancer and bone health outcomes.

The retrospective quantitative PA questionnaire is a rigorous form of survey procedure that requests detailed information on specific activities, tends to cover time periods of one year or greater and can require a subject to spend anywhere from 30 to 120 minutes to complete (227). It collects an enormous amount of data and accounts for seasonal and life period variations. Overall, the quantitative history surveys can be implemented on a population basis, yielding tremendous detail on the physical activity pattern (229). The measurement of historical exposure to physical activity in health research is prompted by the rationale that many diseases, including OA, have a long induction and asymptomatic latency period. Consequently, exposures in the distant past are often considered the most important for understanding disease etiology. Measuring current or recent (up to past year) levels of physical activity, though more practical, accurate and easier to validate, miss etiologically relevant associations between physical activity and disease, and may even be impacted by early symptoms and activity restrictions imposed by the undiagnosed disease under investigation, leading to specious conclusions. While the historic quantitative PA questionnaire has a number of issues that reduce its accuracy and precision, an accurate measure of a less important (or irrelevant) exposure such as recent or current PA, may be inferior to an imprecise measure of a more relevant exposure such as historic PA.

There are a number of problems contributing to the imprecision of quantitative historical surveys, and they involve subject burden, problems with recall, and the high study costs given survey administration and data processing (227, 229). The complexity of measurement of lifetime PA is rooted in the lengthy time frame during which exposure information is sought. One of the primary problems is the potential for recall bias (231, 232) as subjects are reporting on activities performed anywhere from 1 to 50 years in the past. Another is the amount and detail of information requested, contributing to subject burden and fatigue – questionnaires are lengthy and can become monotonous. Epidemiologists recognized and identified these problems a number of years ago (233). As a result they have worked with cognitive psychologists to improve and simplify survey methods to facilitate more accurate memory and reduce burden (232), to develop instruments based on measurement theory and to follow principles of construct validation in historical PAQ development (234-236). Understanding how information is recalled and what factors predict accurate and reliable recall, have led to methods that have improved question comprehension. This has included modifying question length, providing more instructions, using simpler wording, and changing the question order to be more compatible with autobiographical memory (for e.g., asking first why, then how, and, finally, when) (233, 237, 238). A critical step is to pilot test the questionnaire first in a laboratory setting and then in a field pre-test (239).

Despite widespread use and concerns regarding the accuracy of retrospective reporting, relatively few epidemiologic investigations have specifically examined the accuracy (validity) or reproducibility (reliability) of the historical quantitative PA questionnaire (229, 232, 240). Validity is the ability of the questionnaire to measure precisely what it has been designed to measure, while the reliability of a questionnaire refers to its ability to produce consistent results (236). There is no objective “gold

standard" available for measuring total lifetime PA. In theory, development of this gold standard would involve prospectively following a cohort of subjects for lifetime PA exposure using objective methods. The lack of such a gold standard for measuring lifetime PA necessitates the following steps: 1) application of sound methods of instrument development to ensure face and content validity; 2) thorough pilot testing; 3) evaluation of the instrument's reliability or ability to produce consistent results; and 4) most importantly, establishing construct validity or the ability of the instrument to measure what it has been designed to measure (241).

Review of Quantitative Physical History Questionnaires

A review of validated quantitative physical history questionnaires was conducted to identify and describe published questionnaires measuring lifetime physical activity as well as limitations in current measurement of this construct. This review was initiated under the direction of Dr. Mary De Vera as part of her masters thesis (241) in 2005, and was last updated to March 2011 as part of this thesis. A version of the following section is under preparation for submission to journal, with me as lead author and Dr. De Vera as second author.

The objective of this review was to identify, summarize and review the measurement properties of quantitative historical PAQs that have accompanying published validation studies. Medline (1966 – March 2011), Sportdiscus (1949 – March 2011) and PsychInfo (1987 – March 2011) were systematically searched using the following terms: questionnaire, health surveys, physical activity, exercise, activities of daily living, recreation, leisure activity, occupational activity, validation, reliability reproducibility of results, and psychometrics. To ensure that search results were inclusive, a term indicating the time span of measurement (e.g., lifetime or historical)

was not used. Bibliographies of selected references were also hand-searched for additional questionnaires or validation studies.

Questionnaires were included in the review if they measured lifetime or historical physical activity (>1 year), were used in adult populations and were in English. Descriptive information extracted included the time frame of PA measured, nature and detail of the activity including domains (occupation, sport/recreation/household) and time units or level of detail, method of collection and summary index of PA. Data extracted from reliability and validity studies include the type of study, sample size, study details (e.g., washout period for test-retest, method of validation), and main results (reported coefficients or measures of association), the authors' interpretation of results and whether the instrument was subsequently applied in analytic etiologic studies.

The search strategy resulted in 187 publications in which 61 physical activity questionnaires were identified. Abstracts of the 61 papers were reviewed for inclusion criteria. Questionnaires were excluded if the time frame of PA measurement was < 1 year or did not report on development or validation of the questionnaires. Overall, nine questionnaires met the inclusion criteria and were included in the review and are identified in Table 2.3, along with their abbreviated names. Table 2.4 summarizes each questionnaire according to the four elements of physical activity surveys described by Laporte (9).

Of the nine PAQ's, eight measured energy expenditure, with five reporting in metabolic equivalents (METs) by time unit (HLAQ, LT-PAQ, QUANTAP, CT-PAQ, H-PAQ, LPAQ), two reporting in kilocalories per week (RPAS, HPAQ) and one1 reporting in kilojoules per minute (HAPAQ). The BLHQ is a novel PAQ developed specifically for bone loading exposure and reports a spine and hip bone loading score (loading rate/magnitude * time).

Four of the PAQ's covered all three major activity domains of sport/recreation/leisure, occupation and household activity. Consistent with all PAQ's was the inclusion of sport/recreation/leisure activity. The focus on sport/recreation/leisure stems from a reduction in occupational PA and a concurrent increase in sport/leisure PA because of movement from the industrial to the information age in developed countries in the past several decades (8). However, it should be noted that in the historical cohorts used for these surveys (most have average ages ~ 60 years), together with the varied geographical settings and occupational diversity, it is probable that occupational physical activity remains highly important. The four questionnaires that cover the most comprehensive physical activity domains by including occupation, leisure, and household activity are the LT-PAQ, QUANTAP, H-PAQ, and HAPAQ.

All nine questionnaires asked details on duration and frequency of activities allowing for calculation of summary scores to quantify physical activity. Three of the questionnaires have a self-administered format and six are interview-administered. The LT-PAQ emphasized the incorporation of cognitive interview techniques to help improve respondent recall and the QUANTAP combined an interviewer-administered format with a structured, computer-assisted interview tool.

Table 2.5 summarizes information on reported reliability studies while Table 2.6 summarizes information on validity studies.

Table 2.3 Quantitative History Physical Activity Questionnaires Included in Review

Name of Questionnaire	Abbreviated Name	Primary Reference(s)
Retrospective Physical Activity Survey	**RPAS**	Kriska et al. 1988 (242)
Historical Leisure Activity Questionnaire	**HLAQ**	Kriska et al.1990 (243)
Historical Physical Activity Questionnaire	**HPAQ**	Winters-Hart et al. 2004 (244)
Lifetime Total Physical Activity Questionnaire	**LT-PAQ**	Friedenreich et al. 1998 (245, 246)
Quantification de l'Activite Physique	**QUANTAP**	Vuillemin et al. 2000 (247)
Chasan-Taber Lifetime Physical Activity Questionnaire	**CT-PAQ**	Chasan-Taber et al.2002 (248)
Bone Loading History Questionnaire	**BLHQ**	Dolan et al.2006 (234)
Historical Physical Activity Questionnaire	**H-PAQ**	DuBose et al.2007 (249)
Historical Adulthood Physical Activity Questionnaire	**HAPAQ**	Besson et al.2010 (250)

Table 2.4 Description of Reviewed Questionnaires

Questionnaire (Abbreviated)	Time frame	Nature and detail of activity	Time unit or level of detail	Method of Administration	Summary Index of Physical Activity
RPAS	Historical PA	Leisure	Duration and frequency of participation in 20 listed sports/recreational activities	Self-administered	**Energy Expenditure**: Kilocalories/week
HLAQ	Historical, Past-Year, Past-Week PA	Leisure, Occupational	Duration and frequency of participation in activity	Interviewer-administered	**Energy Expenditure**: MET*hours/week
HPAQ	Historical PA	Leisure	Duration and frequency of sports/recreational activities and specific questions about walking	Interviewer-administered	**Energy Expenditure:** Kilocalories/week
LT-PAQ	Lifetime PA	Occupation, Household, Exercise/Sports	Type of activity, duration, frequency, and intensity	Interviewer-administered	**Energy Expenditure**: MET*hours/week
QUANTAP	Lifetime PA	Sports at school, Leisure sport, Occupation, Daily Activities	Duration and frequency of participation in activity	Interviewer-administered	**Energy Expenditure**: MET*minutes/year
CT-PAQ	Lifetime PA (Past year PA)	Recreational, Household	Frequency and duration of participation in 27 listed recreational activities and 5 household activities	Self-administered	**Energy Expenditure**: MET*hours/week
BLHQ	Lifetime (5 life periods)	Primarily leisure, sport, and traditional exercise activities	Frequency and duration of participation in 36 listed (plus subject added) activities and urban/suburban/rural weighting	Self-administered	**Bone loading scores** for spine/hip: bone loading unit (rate and magnitude) *time in activity

Questionnaire (Abbreviated)	Time frame	Nature and detail of activity	Time unit or level of detail	Method of Administration	Summary Index of Physical Activity
H-PAQ	Up to 5 years previously	Sport / leisure, Occupation, Household, Transportation	Duration, frequency, time per occasion, with activities grouped as light, moderate or vigorous intensity	Interviewer-administered	**Energy Expenditure**: Min/week, MET-min/week
HAPAQ	several discrete time periods from the age of 20 years old to their current age	Sport / leisure, Occupation, Household, Transportation	Nature, duration, frequency of regular activities recalled by the participant for each time period	Interviewer-administered	**Energy Expenditure:** Kilojoules/minute

Table 2.5 Reliability of Reviewed Questionnaires

Instrument	Test-Retest Span	N	Age Range	Main Results	Authors Rating of Reliability
RPAS	2–3 mo	23	Post-menopausal women	Kappa statistics ranging from 0.39 to 0.47 **Authors did not provide further information about which statistic corresponded to which PA domain. However, authors stated that these values represented fair agreement beyond chance.*	Moderately Reliable
HLAQ	1–3 wk	69	10-59 yr	Historical Activity: $\rho = 0.94$ Past year Activity: $\rho = 0.89$	Reliable
HPAQ	*Not reported				*Not reported
LT-PAQ	6-8 wk	115	Not specified	Lifetime PA $\rho = 0.74$ Occupational PA $\rho = 0.87$ Household PA $\rho = 0.77$ Exercise/sports PA $\rho = 0.72$	Highly Reliable
QUANTAP	2 wk	30	13-90 yr	Sport at school $\rho = 0.64$ Leisure sport $\rho = 0.83$ Occupation $\rho = 0.85$ Daily activities $\rho = 0.81$ **Reported most relevant correlations*	Not commented

Instrument	Test-Retest Span	N	Age Range	Main Results	Authors Rating of Reliability
CT-PAQ	1 yr	131	39-65 yr	Total PA: ICC = 0.82 Recreational PA: ICC = 0.87 Household PA: ICC = 0.71	Highly Reliable
BLHQ				Elementary school ICC = 0.82 Junior high school ICC = 0.90 High school ICC = 0.94 Young adult ICC = 0.94 Adult* ICC = 0.95 Total ICC = 0.92	Good test-rest reliability
H-PAQ				*Not tested	*Not tested
HAPAQ				*Not tested	*Not tested

Table 2.6 Validity of Reviewed Questionnaires

Instrument	Description of Validity Study	Type of Validity Study	N	Age Range	Main Results
RPAS	Comparison of most recent time period of survey with Paffenbarger Survey	Not specified	223	Post-menopausal women	Sport Index ρ=0.09 Kcal/week ρ=0.38
HLAQ	Comparison with 7-day activity monitor (Caltrac accelerometer)	Not specified	69	21-36 yr	ρ = 0.62 **Validity for past-week PA component of the questionnaire*
HPAQ	Correlation with 4 administrations of the past year physical activity questionnaire over a 17-yr period	Construct validity	163	70–79 yr	1982 PAQ: ρ=0.39 1985 PAQ: ρ=0.45 1995 PAQ: ρ=0.57 1999 PAQ: ρ=0.62
LT-PAQ	Correlations with physical activity logs/ accelerometer data from 7 day periods 4 times over previous year	Construct validity	154	35–65	PA Logs: Total PA: ICC=0.42 Accelerometer: Total PA: ICC= 0.18 O2 Uptake: Vigorous PA ρ=0.37

Instrument	Description of Validity Study	Type of Validity Study	N	Age Range	Main Results
QUANTAP	Correlation with % body fat at time of survey administration	Construct validity	419	13-90 yr	Males: ρ=-0.17 Females: ρ=-0.30 **By years prior to assessment*
	Hypothesis testing of expected differences between gender in daily energy expenditure	Construct validity	419	13-90 yr	Male>Female sport Male>Female leisure Male>Female occupation Male<Female in ADL
CT-PAQ	Correlation with four 1-week Physical Activity Logs administered 4 times over 1-year study period	Construct validity	131	39-65 yr	Total PA : ρ=0.26 Moderate PA: ρ=0.15 Vigorous PA ρ = 0.52 **Validity for past-year PA component of the questionnaire*
BLHQ	4-step development using construct validity principles; Biological plausibility	Construct validity	80 women	13-40 yr (avg 31)	Higher bone loading exposure correlated with bone mineral density (BMD); r= 0.34 spine r= 0.32 hip; Adjusted OR 3.62 for low BMD (femur) among the lowest tertile of recent hip bone loading exposure

Instrument	Description of Validity Study	Type of Validity Study	N	Age Range	Main Results
H-PAQ	Correlation with 4-day activity monitor (Caltrac accelerometer) and PA logs taken 3-5 years previous to H-PAQ administration	Not specified	78 women	25-74 yr (avg 57)	PA Logs: Total PA: ρ= 0.20 Moderate PA: ρ= 0.22 Vigorous PA ρ = 0.02 Accelerometer: Total PA: ρ= 0.29 Moderate PA: ρ= 0.29 Vigorous PA ρ = 0.10
HAPAQ	Correlation with 4-day heart rate monitors and with O2 consumption measures during 2-time periods 5 and 10 years previous to HAPAQ admin	Convergent Validity	100 men/ women	Avg 64 years	Total PA: ρ= 0.44 Vigorous PA ρ = 0.40

Six of the nine PAQs were evaluated using test-retest studies, with washout periods ranging from one week (HLAQ) to one year (CT-PAQ). Three questionnaires (HPAQ, H-PAQ, HAPAQ) did not have a reported reliability study. The HPAQ was adapted from the Paffenbarger Questionnaire (251) which has been validated in a number of previous studies (251, 252). The test-retest study is a suitable method of establishing the reliability of the questionnaire with similar results from separate administrations indicating good reliability. Authors used various statistics to describe the reliability of their questionnaires. Pearson or Spearman correlation coefficients were reported for three studies, the kappa statistic for one study, and the intraclass correlation coefficient (ICC) for two studies. Good to excellent reliability were described by authors for most questionnaires, with most correlation coefficients falling between 0.70 and 0.95.

Assessing the validity of PAQs is more challenging. Shephard, in a 2003 editorial on the measurement limitations of PAQs, stated that a number of research groups developing PAQ's have limited the evaluation of measurement properties to reliability and often overlooked the more important issue of validity (2). However, all nine PAQ's reviewed reported on validity, though three of these validity studies were conducted for versions of the questionnaires that measure shorter time spans of physical activity. Specifically the validity study for the HLAQ was for the past-week version and the validity study for the LT-PAQ and CT-PAQ was for the past-year version of the questionnaire. The RPAS, which divided life into four time periods (14-21, 22-34, 35-50, and 50+ years), was validated by comparing subject response to the last age period (50+) against the Paffenbarger Questionnaire , an instrument measuring current physical activity. Two questionnaires (LT-PAQ, BLHQ) both had detailed descriptions of development, pre-testing and incorporation of construct validity and/or cognitive methods utilized to enhance subject recall. Various methods and statistics were used to assess validity,

including Pearson or Spearman correlation, ICCs, hypothesis testing using p-values, and in one case odds ratios. In the absence of a gold standard, construct validity was the primary methodology employed in the studies. Correlations between summary scores of historical PAQ's were derived from comparisons to other historical PAQ's measuring similar constructs (convergent validity), to short-term PA logs kept at distant points in the past, to motion monitoring devices (accelerometers) worn for a week or less in the past, and to physiologic measures (heart rate monitors, oxygen consumption) taken at points in the past which the historical PAQ covered. Hypothesis testing of expected differences between strata of the population (e.g., genders, domains, education level) was also used in several studies. For example, in some studies it was hypothesized that women would accrue more energy expenditure from PA in the home than men, and those with college education would accrue less energy expenditure from PA at work than those without post-secondary education. Validity coefficients varied widely and in general were lower than reliability, as might be expected. Correlations with other like surveys tended to be higher with coefficients in the 0.4 to 0.7 range. Correlations with objective measures (heart rate, O2 consumption, accelerometer data) tended to be lower, in the 0.2 to 0.5 range. Hypothesis testing of expected differences by strata of the population were confirmed in the studies that used them. In general, validity was reported by most authors to be acceptable and useful for rank-ordering individuals according to their past PA (but not for estimating actual dosage).

Validity and reliability, as well as the utility of PAQs are enhanced by their application in etiologic studies investigating the relationship of historical PA and health outcomes. Four of the nine PAQ's were utilized in at least one published epidemiologic study relating historic PA to health (RPAS, HLAQ, QUANTAP, BLHQ) (242, 253-257). One questionnaire (LT-PAQ) has been used in three etiologic epidemiologic studies of

cancer risk (255-257). In a study using the RPAS to investigate adult bone density in post-menopausal women, the authors report on a positive relationship between bone health and historical physical activity, in the expected direction, lending support to the utility of their instrument (242). Likewise, both the BLHQ and QUANTAP found a relationship with lifetime PA and bone mineral density of the spine and femur, confirming hypothesized relationships (253). The LT-PAQ was used in three separate case-control studies that confirmed a relationship with breast, prostate and endometrial cancers (255-257). In discussing the use of their respective historic PAQ's the studies generally found problems associated with recall and cite the possibility of non-differential misclassification bias of PA exposure, leading to a probable underestimation of the effect of PA on the health outcome investigated.

In summary, nine historical PAQ's were identified that had published validation studies. All estimated historic PA in terms of energy expenditure and one estimated lifetime bone loading. Reliability was generally reported as being very good to high, while validity was moderate. Four of the historic PAQ's have been used in analytic studies confirming expected relationships with a health outcome, lending support to their utility and validity.

This is the first review of validated instruments measuring lifetime or historical PA. While interpretation of lifetime physical activity data using self-report measures requires caution, and more high-quality validation studies are needed (258), it was determined that self-reports in questionnaires on physical activity are both practical and valid in epidemiological studies (259-261). Studies have demonstrated that people can recall past PA with an accepted level of accuracy. Falkner et al. conducted a study on the reliability of recall of PA in the distant past (30 years) and found acceptable levels of recall. Recall was best for weekday light and moderate activities and most participants

underestimated activity. They concluded that the correlations found were remarkable and close to those found in other studies where recall intervals were 10 years or less (262). Shephard (231) concluded that while detailed interpretation and attempts to estimate precise dosage are probably inadvisable, use of data to monitor change in population activity and provide categorical estimates are of value (231). They also allow all dimensions of PA to be assessed so that patterns of behaviour can be examined (263).

Physical Activity Questionnaires and OA

In the epidemiologic literature, PA is almost always investigated for its protective effect on a variety of health outcomes (e.g., cardiovascular disease, diabetes, cancer prevention). Since most of the benefit of PA is thought to be the result of energy expenditure, most questionnaires score physical activity exclusively by energy expenditure and metabolic equivalents (METs) and do not consider the mechanical joint loading aspect of activity (234). However, certain forms or amounts of PA can be a risk factor for the musculoskeletal system such as muscle, bone or joint injury or osteoarthritis. There are no historical or lifetime PAQ's that have been purposely designed to assess components of physical activity significant to joint force or joint health. Because hip and knee joints responds to activity that is different from typical measures used in studies of energy expenditure, a joint loading unit of measure is needed to reflect the strain on joint caused by PA. Further, the bone, cartilage, ligamentous and capsular changes associated with cumulative PA change very slowly over time and require many months or years of observation to detect. Therefore, questionnaires designed to assess PA associated with joint health should focus on variables other than those important to the cardiovascular system (i.e., long duration per activity occasion, with prolonged elevation of heart rate) and should reflect long-term

patterns of activity (234). For example, force, type and magnitude and the long-term pattern of participation in activities are important for understanding the bone and cartilage response to physical activity (234, 264, 265).

As mentioned previously, another major limitation of many PA and OA studies has been the focus on current or recent rather than historical or lifetime physical activity. Given the long induction and asymptomatic latency period for the development of OA, PA earlier in the life span is of potential importance and linked etiologically to hip and knee OA. Further, there is evidence that the effects of physical activity in childhood and adolescence on bone mass persist into adulthood (266), and that it is a unique period for musculoskeletal development. Bone mass attained in exercise during skeletal growth is thought to be more osteogenic than exercise after skeletal growth is complete (234, 267), though the effect on joints and cartilage is less well known. However, an MRI study of children aged 9 to18 years found younger children, males and those undertaking more vigorous sports have substantially higher articular cartilage accrual rates (268). While there are limitations to the available studies, the current evidence suggests that vigorous physical activity is important for optimum joint development in children (269). Thus, it is important to identify mechanical loads placed on the bone and cartilage throughout life rather than only during recent time periods. Finally, it is essential for a questionnaire, particularly one focusing on historical data, to be a reliable instrument and to produce consistent results when administered on separate occasions.

By building substantially on prior work, employing sound measurement theory and incorporating construct validity principles, our research group at the Arthritis Research Centre of Canada (ARC) developed a lifetime PA questionnaire based on two validated existing instruments (245, 247) that capitalized on several recent methodological innovations. These include a fully developed web-based data collection

system and a novel computerized questionnaire to measure total lifetime PA that used skip logic – a computer technology that allows subjects to follow individualized paths through a survey, moving forward based on responses to previous questions. It dramatically reduces the burden on individual respondents while maximizing efficiency, and is the first historical PAQ to both collect data over the Internet and use skip logic. Another important innovation was a method of converting self-reported PA to mechanical forces in the joint, incorporating data from in vivo measures (i.e., instrumented implants) of joint force. With the assistance of experts in biomechanical engineering, rheumatology, and musculoskeletal epidemiology and using the principles of construct validity, a team of researchers at ARC systematically developed the Lifetime Physical Activity Questionnaire (L-PAQ). This represents an historic PAQ that quantitatively and qualitatively captures PA data that can be converted both to energy expenditure and joint force. Cognitive methods were incorporated in the administration of the L-PAQ to improve respondent recall. The L-PAQ was extensively pre-tested and pilot-tested prior to its use. The methodology as it applies to this thesis will be described in the Chapter 3 (Methods) and in the methods sections of published articles that form the basis of Chapters 5, 6 and 7.

Reliability and Validity of Lifetime Physical Activity Questionnaire (L-PAQ)

The reliability and validity of the L-PAQ was undertaken by our research group at ARC under the direction of Dr. Mary De Vera, and recently published in the *American Journal of Epidemiology* (270), with myself as second author. As it is foundational to the subsequent analytic work presented in this thesis, a brief summary of the findings are presented here, and the reader is referred to the reference for a full description of the validation study.

The objective of the validation study was to evaluate the measurement properties of the Lifetime Physical Activity Questionnaire (L-PAQ), a novel Internet-based, self-administered instrument measuring lifetime physical activity, among Canadian men and women in 2005–2006.

Methods

A total of 88 subjects aged 45-85 were drawn from the baseline panel of the Physical Activity and Joint Health (PAJH) cohort, a population-based Canadian cohort. Sampling and recruitment for the larger cohort, as well as the measurement and scoring of lifetime PA exposure is described in detail in Chapter 3. The sub-cohort for the validation study were subjects who resided in the metropolitan Vancouver area of British Columbia were recruited for the face-to-face aspects of the validation studies. To determine reliability, a test-retest study was undertaken by providing subjects in the validation sub-cohort access to the online retest version of the L-PAQ, which consisted of questions identical to those in the baseline version of the L-PAQ. The average length of time between questionnaire administrations was 8 months.

Validity was examined in a 2-part study. The first part consisted of comparisons with previously validated instruments measuring similar constructs, the Lifetime Total Physical Activity Questionnaire (LT-PAQ) and the Chasan-Taber Physical Activity Questionnaire (CT-PAQ). The second part involved testing of hypotheses based on previously reported relationships between physical activity and sociodemographic variables (247, 271-273). The hypotheses were that:

1) males have higher participation in sports/recreational activity than females; 2) males have higher participation in occupational activity than females; 3) females have higher participation in household activity than males; and 4) subjects with lower levels of

education have lower participation in sports/recreational activity than those with higher levels of education.

Results

In general, the L-PAQ demonstrated good reliability, with intraclass correlation coefficients ranging from 0.67 for household activity to 0.89 sports / recreational activity (Table 2.7). Reliability tended to be higher for sports/recreational and occupational activity than for household activity.

Table 2.7 Reliability of the LPAQ Using a Test-Retest Method with 8 Month Washout

Lifetime Average Hrs/Week	Intraclass Correlation Coefficients (95% CI)
Sports/recreation	0.89 (0.84, 0.94)
Occupation	0.84 (0.75, 0.89)
Household	0.67 (0.49, 0.79)
Total PA	0.73 (0.57, 0.83)
Lifetime MET• Hrs/Week[a]	
Sports/recreation	0.88 (0.81, 0.92)
Occupation	0.77 (0.64, 0.86)
Household	0.67 (0.48, 0.79)
Total PA	0.72 (0.56, 0.82)

[a] One MET represents the metabolic rate of a resting individual and is set at 3.5 mL of oxygen consumed per kilogram of body mass per minute (274)

In the first part of the validity study, which was based on comparisons with two previously validated instruments, the L-PAQ showed good convergent validity for

household activity and moderate convergent validity for sports/recreational and occupational activity (Table 2.8).

Table 2.8 Convergent Validity of L-PAQ with LT-PAQ and CT-PAQ

LPAQ vs. LT-PAQ

Physical Activity Domain	Spearman Correlation Coefficient
Lifetime average hours/week	
Sports/recreation	0.52
Occupational	0.55
Household	0.71
Total	0.41
Lifetime MET-hours/week[a]	
Sports/recreation	0.60
Occupational	0.50
Household	0.71
Total	0.34

LPAQ vs. CT-PAQ

Physical Activity Domain	Spearman Correlation Coefficient
Lifetime average hours/week	
Sports/recreation	0.58
Household	0.56
Total	0.50
Lifetime MET-hours/week[a]	
Sports/recreation	0.61
Household	0.57
Total	0.49

[a] One MET represents the metabolic rate of a resting individual and is set at 3.5 mL of oxygen consumed per kilogram of body mass per minute (274)

In the second part of the validity studies, a priori hypotheses regarding sociodemographic factors and lifetime physical activity were confirmed - males had greater lifetime sports/recreational and occupational activity than females and females had greater lifetime household activity than males. There was also an increasing trend in amount (lifetime average hours/week) and intensity (lifetime average MET-hours/week) of sports/recreational activity with increasing level of education. There was a negative relationship between higher levels of education and intensity of occupational activity among males.

In summary, the L-PAQ is a useful instrument for assessing multiple domains of physical activity over a long time period with acceptable reliability and validity. It is comparable to other physical activity instruments that are used in large epidemiologic studies.

2.4 Local Joint Vulnerabilities

When load is well distributed across the articular surfaces, forces on the cartilage, bone and other joint structures are dispersed widely and concentrated focal effects of loading are minimized. Several local factors can influence load distribution at the hip and knee, including lower limb alignment, injury to structures within the joint and neuromuscular control of the joint. In recent years, evidence has emerged that local joint factors that determine how load is distributed are important determinants of OA (20, 43).

Alignment and Knee OA

Varus (bow-legged) and valgus (knock-kneed) alignment play a role in how load is distributed in the knee joint, and is gaining importance as a potential contributing factor in knee OA. While there has been increasing interest in its association with knee OA, the majority of studies have been cross-sectional or investigated its effect on

progression of established disease (18, 44-49, 51, 52). Very few studies have examined malalignment on the risk of incident knee osteoarthritis, and no studies have included physical activity as a covariate.

Biologic Considerations

In the literature, lower limb alignment refers to alignment in the coronal plane, that is, the distance between the knees in quiet standing, in relation to the hips and ankles. When the knees are aligned with the hips and ankles, alignment is neutral; when they come together medial to the hips and ankles it is termed valgus (knock kneed), and when they are apart from each other outside of the hips and ankles it is termed varus (bow-legged).

The knee is unique among weight bearing synovial joints in having two distinct compartments (medial and lateral) across which joint forces pass. When hip-knee-ankle alignment is neutral, load distribution across the joint surface is thought to be proportionately distributed between the medial and lateral compartments. When varus alignment is present, a disproportionate amount of force falls onto the medial compartment and the lateral compartment becomes relatively unloaded; in valgus, a disproportionate amount of force falls onto the lateral compartment and the medial compartment is unloaded. While alignment can be estimated for clinical and research purposes in a number of ways, true alignment is determined by the angle subtended by a line connecting the centre of the hip (femoral head) with the middle of the knee (tibial spines) and another line connecting the middle of the ankle joint (centre of talar surface) with the middle of the knee joint (44, 275). In neutrally aligned limbs, a line drawn from the middle of the femoral head to the middle of the ankle represents the load-bearing axis. In neutral alignment this axis falls slightly medial to the knee joint creating a slight

adduction (varus) moment, and thus the medial compartment bears 60% to 70% of the force across the knee during weight-bearing activity (276).

In theory, any shift from neutral alignment of the lower limb affects load distribution at the knee (275, 277) and biomechanical studies have confirmed that malalignment influences load distribution (275, 276, 278-281). Evidence of its role was derived first from animal studies (279, 282, 283) and fracture / surgical studies (275, 281) aimed at understanding and improving load bearing in injured or arthritic knees. These studies showed that in a varus knee, the load-bearing axis passes further medial to the knee and a moment arm is created, which further increases force across the medial compartment (275). In a valgus knee, the load-beading axis is lateral to the knee, and forces move towards the lateral compartment. Additionally, it has been shown that even small changes in leg alignment result in abnormal load distribution across the knee joint, with a 4–6% increase in varus alignment reported to increase loading in the medial compartment by up to 20% (275). It is these increases in compartment loading that are thought to increase stress on articular cartilage and other joint structures, subsequently leading to degenerative changes (11), Compartment-specific wear patterns and degenerative change have been demonstrated in cross-sectional studies (284, 285).

Alignment and Knee OA in Humans

Several studies (53, 54, 133, 284) have provided evidence of the role of alignment in development of knee OA. In the initial report in 1992, Schouten et al. (133) conducted a longitudinal risk factor study that included malalignment as a predictor variable (self-reported knock-knees or bow legs recalled from childhood), and reported a significant odds ratio of 5.1 for knee OA and in particular cartilage loss (scored as the change in joint space width). After the Schouten et al. study, there were no epidemiologic studies investigating alignment and knee OA for approximately 10 years.

At the time this thesis was first proposed, there were very few epidemiologic studies on alignment and knee OA. These were on the association (cross-sectional studies) or *progression* (longitudinal studies) of OA with malalignment; there were no studies on the role of alignment in the development (incidence) of OA. In the intervening years, there has been increasing interest in this topic. Therefore, a recent search of MEDLINE, EMBASE and CINAHL was conducted using the following search terms: knee, osteoarthritis, malalignment, varus, valgus and alignment. The focus of the review were epidemiologic risk factor studies investigating whether alignment (self-reported, clinically or radiographically measured) was associated with tibiofemoral knee OA (self-reported, clinical, radiological or MRI), or a factor in its development or progression. Studies that were not in English, focused only on the patellofemoral joint, involved conditions other than OA (e.g., fracture, rheumatoid arthritis), or did not focus on the role of alignment as a risk factor for knee OA were not included.

The search revealed eight cross-sectional studies (48, 285-291), one nested case-control study (292) and 10 longitudinal studies (44, 52-54, 293-298) (Table 2.9) investigating the relationship between knee OA and leg alignment. Of the 19 studies reviewed, only two (one case-control, one longitudinal) reported no relationship (292, 296), and both of these investigated the role of alignment on *incidence* of knee OA. Of the 10 longitudinal studies, a majority of the studies investigated *progression* of knee OA in subjects who had knee OA at baseline, and all 10 studies reported a positive relationship. All studies found an association between malalignment and risk of progression of OA in the anticipated overloaded compartment, with most studies showing a dose-response relationship, i.e., greater varus and valgus alignment and increasing risk of medial and lateral OA, respectively.

Of the eight cross sectional studies, four used radiographic outcomes and four used MRI outcomes. All reported the expected compartment-specific relationships with malalignment and the biomechanically stressed compartment – increased medial compartment OA in varus alignment and increased lateral compartment OA in valgus alignment. Cross-sectional MRI studies, which reveal a range of cartilage, bone, synovial and ligamentous pathology, have also generally demonstrated a dose-response relationship between the increasing presence of cartilage and other defects in the biomechanically overloaded compartment (288).

Four of the studies investigated incidence of knee OA. The first report of a relationship between malalignment and incident knee OA was in 2007 by Brouwer et al. (54) in Holland using a prospective longitudinal design and large sample (n=1501, average age 66, baseline BMI - 26.3; 6.6 year follow up). According to Sharma in an editorial in the same journal issue (277), it was also the first report of a relationship between a local mechanical factor and incident idiopathic knee OA. The study also confirmed that malalignment influences knee OA progression. Since that time, there has been one other high quality longitudinal study (n=3052, average age 61, baseline BMI - 31.7; 2.5 year follow up) that was conducted in the United States and investigated both progression and incidence (53), reporting that varus but not valgus alignment increased the risk of incident radiographic tibiofemoral osteoarthritis. Compared to Brouwer et al. (54) the study reported similar odds ratios (OR) for varus effect on medial compartment OA (OR 1.5 vs 2.1), but reported no relationship with valgus alignment and OA, while Brouwer et al. reported an OR of 1.5 (borderline significance) for lateral compartment OA. The studies were comparable in that similar categorical definitions of varus and valgus were used, neutral knees were defined as the referent, and both used radiographic definitions of OA only.

Hunter et al. (292), in a nested case–control study of 244 Framingham cohort members (average age: 55 cases, 53 controls; BMI: 30.5 cases, 27.1 controls) did not find a relationship with incident knee OA. However, apart from the weaker study design and smaller sample size, other significant differences may have contributed to the negative finding. In particular, the categorization of alignment was unlike other studies, using quartiles of alignment (5–10 valgus, 3–4 valgus, 0–2 valgus, 1–7 varus) which may have lacked biologic relevance. Additionally, neutral knees were not used as the referent - the most varus (1–7° varus) was compared with the most valgus quartile (5–10° valgus) as referent, in essence modelling a different relationship than the other incident studies, though allowing for examination of a potential dose-response effect (299). Likewise, Zhai et al. (296) in an Australian MRI longitudinal study (average age 45; baseline BMI – 27.2; 2.4 year follow up) did not find a relationship with incident disease. A possible contributing factor to the negative finding may have been the measurement of alignment – it was different from the other incident studies in that semi-flexed x-rays were used (i.e., knees were bent), which may have obscured the extent of malalignment. Further, subjects were significantly younger, which may have been more important when combined with the relatively short follow up period. Nevertheless, given the scarcity of studies examining malalignment and risk of incident OA, and the conflicting results to date, further study is required.

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Table 2.9 Malalignment and Knee OA

Type of Study	Malalignment associated with knee OA			Malalignment NOT associated with knee OA		
	Association	Progression	Incidence	Association	Progression	Incidence
Cross-sectional	Birmingham 2001(285)					
	van der Esch 2005(48)					
	Teichtahl 2006(290)					
	Khan 2008(289)					
	Issa 2007 (MRI)(287)					
	Janakir. 2008 (MRI)(288)					
	Friedrich 2009 (MRI)(286)					
Nested case-control						Hunter 2007(292)
Longitudinal		Sharma 2001(44)				Zhai 2007 (MRI)(296)
		Cerejo 2002(52)				
		Miyazaki 2002(293)				
		Felson 2005(295)				
		Cicuttini 2004 (MRI) (294)				
		Moisio 2011 (MRI) (298)				
		Sharma 2008 (MRI) (297)				
		Brouwer 2007(54)	Brouwer 2007(54)			
		Sharma 2010 (53)	Sharma 2010(53)			

While incident data are lacking, the results for progression of knee OA have been more numerous, consistent and with stronger effect sizes (44, 52-54, 293-295, 297, 298). The observed relationship between joint alignment and progression of OA have been consistent across study design, OA outcome assessment (clinical, radiographic, MRI), alignment measurement (self-report, clinical goniometric, radiographic anatomic and mechanical axis) and held across heterogeneous populations. Studies were also generally consistent in that varus and valgus alignment each increased the risk of osteoarthritis progression in the biomechanically stressed compartment and reduced the risk of progression in the unloaded compartment (53).

The evidence suggests that malalignment has a more harmful effect in knees with moderate OA than in knees with mild OA and a weaker effect on healthier (non-OA) knees (52, 277). This might be related to the greater vulnerability of more diseased knees to altered load distribution. In view of this, it seems likely that any alignment effect on the risk of incident knee osteoarthritis is smaller, and possibly more difficult to detect, than the effect on progression.

A contributing factor to the putative weaker signal between malalignment and incident knee OA, may be that radiographic measures of OA (most commonly used outcome) are notoriously insensitive to the onset or presence of early OA. In particular, as discussed in a previous section of this thesis, osteophytes, which are commonly used to identify and grade radiographic OA , have a low correlation with symptoms and may in fact be a healthy adaptation of bone to load (19). While MRI is more sensitive, there is no consensus to date regarding which MRI features represent OA, and the relationship between pain, symptoms and MRI finding require further delineation (53). Thus while MRI measures of OA should be used in future studies, patient reported symptoms (pain, aching, stiffness) are significant and should be included, as they are the most relevant

feature of disease to the patient and putatively related to the local joint loading factors and PA.

Alignment and Physical Activity

Any effect of malalignment-induced overload on knee joint structures would occur through physical loading of the joint, and bodyweight, the amount (number of loading cycles) and period (current versus historic) of physical activity is likely to be of importance. While there has been an increase in the interest in the role of malalignment in knee OA in the past several years, none of the reviewed studies assessed physical activity as a covariate. Urquhart et al. noted in a 2010 review that there is a paucity of data on the effect of joint malalignment on risk for developing OA in physically active individuals (151). Apart from one study in 1983 of 20 runners (300) which showed varus alignment to be a risk for knee OA, no other studies have directly investigated physical activity measures and alignment, or whether those who exercise in the presence of malalignment are at a higher risk for developing OA than individuals with neutral alignment (151). In a recent editorial on the role of PA and knee OA in *Arthritis and Rheumatism* (301), Minor commented that studies investigating the risk of PA would have been more informative had they considered the contribution of factors such as knee alignment and neuromuscular fitness. She also recommended that future research include more precise characterization of subjects in terms of biomechanics to give a more meaningful interpretation of the potential PA-related risk and translation of findings to clinical settings.

Evidence for the relationship between joint load and malalignment comes from preliminary data on the role of obesity in combination with malalignment. Brouwer et al. (54) stratified their data by categories of BMI and showed a stronger relationship between malalignment and the risk of development of OA in the overweight group than

in the non-overweight group. The authors propose that the relationship may even be absent in the non-overweight group, suggesting that an unfavourable load is less harmful in non-overweight persons. An earlier study by Felson et al. showed that the effect of BMI is limited to knees in which moderate malalignment exists, and suggested it was due to the combined focus of load from malalignment and the excess load from increased weight (51). The findings from both studies imply that increased load from elevated bodyweight and malalignment probably influence each other, though there is a need for further study. Hunter et al. (299) recently posited that malalignment and obesity may function in a synergistic fashion, and that if the effects of malalignment are magnified by obesity (effect-measure modification), then malalignment may only be of importance in those who have increased loading from obesity. Further evidence for the interaction of load and alignment is seen in a study that investigated quadriceps strength in malaligned knees, and found that increased quadriceps strength at baseline was associated with increased likelihood of knee OA progression (302). Local factors such as malalignment that alter load distribution, influence how well the joint disperses force and adapts to muscle forces and external load from physical activity.

To date, no PA-OA studies have considered the role of lower limb alignment. Such research could shed light on an important public health concern – namely the ability to identify high-risk individuals most likely to develop OA. This is a key step in the introduction of an effective and efficient prevention strategy. It may also have direct implications for clinicians offering exercise prescription and activity advice to patients with OA or those at high risk, since alignment may need to be considered to ensure that prescription of exercise is safe (151).

Joint Injury and OA

Introduction

Joint injury is another local factor that may affect joint loading. Injury may alter distribution of load through bony fracture, ligamentous disruption, cartilage injury, meniscal tear in the knee, labral tear in the hip or loose body interposed between joint surfaces (173). Injured cartilage, knee menisci or hip labral tears may fail in their stabilizing and shock absorption functions, increasing joint load. Muscle inhibition, weakness and imbalance subsequent to injury may similarly increase joint load. Individuals with these sorts of joint injuries and resulting changes in articular load bearing may form a segment of the population that differ from non-injured individuals in their response to physical activity. The following review offers a brief summary of the epidemiology on knee and hip joint injury, its relationship with subsequent OA development, as well as the studies that consider joint injury in the examination of the association between PA and OA. Portions of this section are drawn from my published article in *Arthritis Research and Therapy* (303), a review of injury-related knee osteoarthritis.

Knee

Injuries to the knee are common, though the true incidence and prevalence is not well known. The best-studied injuries of the knee are those to the anterior cruciate ligament (ACL) and menisci, which have been documented in both athletic and general populations. (29, 30, 35, 304-306). The ACL is the most commonly injured knee ligament. While the true incidence is unknown, the annual incidence of MRI verified ACL injuries has been reported at 81 per 100,000 inhabitants aged 10 to 64 years, based on well-designed registries in Scandinavia (307, 308). These estimates of annual population incidence suggest that the cumulative population risk of an MRI-verified acute ACL injury between the ages of 10 and 64 years is at least 5% (35). The true incidence is likely

considerably higher since ACL injuries can be unreported, undiagnosed or diagnosed without MRI. While ACL injury can occur throughout life, most occur before the age of 30. Over the past two decades, there has been an astounding increasing rate of ACL injuries in female athletes (309-311). Adolescent and mature females who participate in pivoting and jumping sports suffer anterior cruciate ligament (ACL) injuries at a 2 to 8-fold greater rate than male athletes participating in the same high-risk cutting and landing sports (309-311). This increased vulnerability along with a 10-fold increase in the female sports population since the inception of Title IX (equal opportunity law) in 1972 in the U.S and similar initiatives in other western countries, has resulted in a dramatic increase in the number of ACL injuries in females (310, 311).

Meniscal injuries are more common than ACL tears, in both athletes and the general population (35, 312-314). The incidence is not as well established as anterior cruciate ligament (ACL) injuries, since symptomatic meniscus tears are almost certainly under-reported and under-diagnosed (35). However, the rate is likely to be much higher than ACL injury. Lohmander reports that in Sweden there are 8 times more meniscal surgeries than ACL reconstructions. The cumulative risk of a meniscus injury leading to surgery in 10-64 year olds is at least 15%, to which should be added meniscus lesions not diagnosed or not treated by surgery (35). Additional injuries to the knee are less well documented but include injury to the other three major knee ligaments and the effect of less catastrophic but perhaps more common and potentially significant ‘minor’ cartilage injuries (e.g., osteochondral bruise) that require advanced imaging to detect.

Knee joint injury increases the risk of knee osteoarthritis. Multiple prospective studies demonstrate a significant increase in knee OA after a knee joint injury (29-34, 306). A prospective cohort study that followed 1321 medical students with a median follow up time of 36 years reported a relative risk of 5.17 for knee OA for any type of

knee injury at baseline or during follow-up (32). A study from England of 354 subjects followed for a mean of 5.1 years found a similar risk estimate (odds ratio 4.8) for any previous knee injury (34).

Individuals with ACL ruptures, whether known or unknown, comprise an estimated 20-35% of the overall knee osteoarthritis population (315, 316). In male and female soccer players sustaining ACL tears, approximately 80% of players had radiographic knee OA 12-14 years later, irrespective of whether they had had surgical intervention; approximately 70% had functional limitations and reduced quality of life due to their knee (29, 31). While short and mid-term results of ACL reconstruction are satisfactory, 10-20 years after injury approximately 50% of those with ACL or meniscus tear have OA with associated pain and functional impairment (35). There is also a strong association between meniscal damage and knee OA (35, 304, 306, 317, 318). Since the menisci play a critical protective role in the tibiofemoral compartment through shock absorbing and load-distributing properties (319), injury to the meniscus is an important risk factor for the development and progression of knee OA, with high quality longitudinal studies reporting relative risks of between 2 and 6 (306, 320, 321). The attributable risk of knee OA due to knee joint injury, while crude, point to a clinical problem of considerable importance given multiple reports that approximately 50% of individuals with an ACL or meniscus tear develop knee OA.

Hip

Unlike the knee joint, the hip joint is a deeply seated ball and socket joint with much higher congruity and inherent stability, and is surrounded by robust anatomical structures. Significant injuries leading to ligament tears and cartilage damage are thought to be rare, and hip injury has been less commonly reported in the literature. The nature of hip injury and articular structures involved are not well delineated with limited

data on the prevalence and incidence, and the role of hip injury as a risk factor for hip OA remains poorly understood (41). Most published epidemiological studies of hip osteoarthritis have been cross-sectional or case-control studies. Cross-sectional studies (40, 42, 322) have inferred that traumatic injuries might give rise to hip OA (41).

Joint Injury in Studies Investigating the PA-OA Relationship

At the knee, there is evidence that previous joint injury increases the risk for OA in physically active individuals, though risk estimates vary. Studies investigating PA and OA have reported an odds ratio from previous knee injury of between 1.82 and 8.0 (42, 173, 198). A recent large prospective population-based cohort investigating PA and OA with 22 years of follow up showed an OR of 5.1 for knee OA due to joint injury (198). Urquhart et al. in a recent systematic review (19) noted that while many PA-OA studies included subjects with injury (34, 42, 157, 170, 171, 175, 176, 181, 200, 204, 205, 208, 210, 323), only some have made adjustment for them in the analysis (42, 157, 170, 171, 175, 176, 181, 204, 205, 210). Several studies that do include injury have reported a very low incidence of injury, leading to imprecise estimates - true particularly of some of the studies reporting high OR's (42, 185). Some knee PA-OA studies have not measured injury at all, or provide little information (166-169, 174, 324).

At the hip, there is limited data on the relationship between physical activity, hip injury and subsequent development of OA. Most PA-hip OA studies have not measured previous hip injury. This may be in part due to under-reporting and/or relative rarity of hip injury. Where estimates do exist, OR's vary widely and are imprecise. One case-control study reported an OR for hip OA due to hip injury of 4.3 (95% CI 2.2-8.4) (40), while another reported an OR 15.6 (95% CI 3.4-70.5) for combined hip/knee OA (42). In the cross-sectional NHANES-I study, Tepper et al. reported an increased risk of hip OA associated with previous injury for men (OR 24.2, 95% CI 3.84-153.10), but not for

women (OR 4.17, 95% CI 0.50-34.71) (38). The widely dispersed confidence intervals reflect the low numbers of reported hip injuries in these studies. In a cross-sectional study of 7,217 subjects in Finland, Heliovaara et al. reported a prevalence of 8% for all self-reported *lower-limb* injuries, and an odds ratio of 2.1 (95% CI 1.4-3) for the association between low limb injury and hip OA. Two prospective cohort studies have investigated injury as a risk factor for hip OA (32, 41), though injury definitions varied substantially. In a 36-year follow-up study of 1321 medical students from the Johns Hopkins Precursors Study, hip joint injury was rare - 13 reported hip injuries at baseline and 17 reported hip injuries in follow-up. The cumulative hip injury by 65 years of age was 2.2% (32). The relation between a previous hip injury and incidence of hip osteoarthritis during follow-up was 3.50 (95% CI 0.84 to 14.69). In the first published population-based study, a 2009 study with a 22 year follow-up, Juhakoski et al. investigated risk factors for hip OA using the definition 'major musculoskeletal injuries' (not just hip region) and reported 47 such injuries in a cohort of 840 (approximately 5.5%). These injuries were associated with an OR of 5.0 (1.9-13.3) for hip OA.

In summary, one reason for conflicting results in PA and OA studies may be that subsets of joint-injured individuals have not consistently been accounted for in multivariable analysis. In order to obtain an accurate measure of effect of PA on OA, previous joint injury is an important covariate to consider. Consistent with previous studies on PA-OA, the measurement of previous joint injury will be via a validated measure of self-report, and is described in the methods section in Chapters 6 and 7.

Neuromuscular Control and OA

Introduction

Evidence is accumulating for the role of neuromuscular (NM) control in OA, potentially delineating another subset of individuals with a local joint vulnerability that

may be a factor in the relationship between PA and OA. As discussed, joint injury and malalignment may lead to altered loading patterns that place excessive stress on joint tissues. Alternatively joint damage can occur in a non-injured, neutrally aligned joint through minor, but repetitive microtrauma, when the NM system does not adequately anticipate and absorb load leaving the cartilage and bone to receive more force (325).

Biological Considerations

Normally, joints are protected when loads are anticipated through a neuromuscular feedback system, with muscles and tendons assuming the correct tension to deflect these loads, distribute them across the whole joint surface, or lessen the rate with which the load is applied to the joint (18). Ligaments and the joint capsule, in addition to protecting joints by passively restraining joint movement, provide sensory information to the neuromuscular system via embedded mechanoreceptors. While the properties of articular cartilage would make it an excellent shock absorber, it is too thin (3-6 mm in depth) to serve this purpose in the hip and knee joint; instead it depends on the neural feedback systems and the periarticular muscles they control to protect it from sudden impulse loads, shear forces and to distribute load across the joint surface (18).

The muscles are critical to joint protection (326-328). Most of the muscle activity generated during activity is not used to propel the body forward but rather to absorb energy to decelerate the body (329), as it stretches and lengthens eccentrically. The energy produced in normal walking is enough to tear the ligaments of the knee; that this does not occur attests to the importance and effectiveness of the active energy absorption by the muscles that surround the joints and cushion them from mechanical stress (28). When this shock absorbing system fails to function effectively, the result is cumulative micro damage, leading to remodelling of bone and cartilage (330). This illustrates that the manner in which physiologically reasonable loads are applied is

critical to the continued health of a joint (325). Loads that are applied too quickly damage joints and the supporting musculoskeletal structures, causing microinjury. Small, unexpected loads (e.g., misjudging the last step) are much more damaging to joints than large ones that have been anticipated (331). If the height of a step, stair, or curb is misjudged, the lower limb will be unprepared for landing, causing rapid and jarring loading of the joint, which may traumatize articular tissues (326). To prepare a neuromuscular reflex to handle an impact load for an unexpected fall of very brief duration requires approximately 75 milliseconds – not enough time to bring protective muscular reflexes into play (28, 332). Injurious loads need not be above physiologic thresholds in magnitude — they merely need to be delivered too quickly (325). Given the many thousands of hours and millions of gait cycles that occur over decades of activity, and the long subclinical latency period for OA, even subtle NM impairment is a potentially important factor in the relationship between physical activity and OA.

While potentially important, NM control is a broad construct that is challenging to measure. Part of the challenge arises because NM control encompasses a number of physical attributes including proprioception, coordination, balance, muscle weakness and postural control. The discussion here will focus on coordination and proprioception, the traits under study in this thesis. The reader is referred to recent comprehensive reviews of Roos (333) and Knoop et al. (334), and the book chapter by Brandt (331) for a fuller discussion.

Coordination

Coordinated joint movement and muscle activity control joint loading to ensure that even normal day to day loads applied across the joint are dissipated harmlessly (326). A normal, controlled heel strike requires a highly coordinated process that involves good visual awareness, accurate sensory input, rapid central processing, and

precise motor control of strong muscles (326) to protect the joint from rapid loading. Studies that have transiently blocked nerves to the quadriceps have shown the load rate at the knee in normal subjects during gait is substantially higher (327, 335). Even in normal individuals, minor incoordination in muscle recruitment, resulting in failure to decelerate the leg before heelstrike, may generate rapidly applied impulsive forces at the knee that are as high as 65 times body weight/second (327). Biomechanical gait analysis studies have shown that minor incoordination results in higher angular velocities and higher vertical ground reaction forces in the lower limb leading to the type of repetitive impulse loading at the knee that in animal experiments consistently causes osteoarthrosis (327, 336-338). In studies over the past several decades, Radin and co-workers (335, 339) examined coordination for its role in joint health and protection and reported that one in three adults have micro-incoordination, a phenomenon they termed as microklutziness, where neuromuscular protective mechanisms required to reduce the forces of joint loading are not fully coordinated. These individuals therefore subject their knees to impulsive loading during walking, resulting in overload and microinjury to the cartilage and subchondral bone (331). Since OA is thought to be the result of mechanical overload, characterized pathophysiologically by damage to the joint and attempted repair, minor incoordination is a potentially important factor in the etiology of OA (325). Whether minor incoordination in otherwise normal subjects, resulting in repetitive microtrauma with routine physical activities, is a risk factor for knee OA remains to be established by prospective longitudinal studies (28).

Proprioception

Closely related to coordination is proprioception, defined as awareness of limb and joint position and movement in space (56). It is a complex sensation derived from multiple inputs that also encompasses muscle force, stretching and overall body

position, as well as the unconscious regulation of postural response to positional perturbations (333). In providing this awareness and automatic adjustments, proprioception relies on afferent receptors in the muscles, ligaments, synovial capsule and skin (340, 341). Muscle and joint receptors are the major sources of joint proprioception and are critical to the maintenance of joint stability under dynamic conditions (56). Subtle dysfunction of this afferent system and the resulting change in muscular response may alter dynamic loading of joints and modify the ability to protect joint structures during movement (333).

NM Control and OA in Humans

A number of studies investigated impaired NM control as a mechanism that reduces protection of the knee joint in humans (56, 57, 327, 342-354). Results show that altered control results in increased joint forces. However, the link with OA is not well established. While the interest in the NM control of joints has spanned several decades, only recently has altered NM control been proposed and studied as a local risk factor in the onset of and progression of OA. Studies to date have largely focused on impaired proprioception in knee OA (56, 57, 342-349, 355), and an association between decreased proprioception and OA have been reported in a number of studies, although it is not clear whether it is primary or a consequence of intra-articular pathology (17). Several cross-sectional studies have shown that knee proprioception is worse in patients with knee OA than in age-matched, normal subjects (56, 58, 353, 354, 356, 357), though some studies have failed to find an association (344, 358). Interestingly, proprioceptive accuracy of the contralateral asymptomatic knee in unilateral knee OA patients has been shown to be reduced as well (58, 59). This has lent support to the theory that NM deficits are not solely the result of the OA process, but the result of a centrally mediated problem that may precede OA. Whether proprioception has a potential role in the development of

OA has not been clearly determined, in part because proprioceptive ability has been shown to decline with normal aging (353, 354). Several studies have investigated whether NM impairment precedes OA. Slemenda et al.(359) investigated muscle strength in a cohort of 342 elderly community dwelling subjects with no joint pain and reported that quadriceps weakness predicted radiographic progression and pain. Two recent prospective longitudinal studies both using subjects from the Multicenter Osteoarthritis Study (MOST) (345, 355) have also been conducted. While Felson et al. (345) reported a relationship between proprioceptive deficits and knee pain, they were unable to identify a significant association with incident knee OA in the course of the 3 year follow-up. Likewise, a study by Segal et al. (355) did not find a relationship between baseline proprioceptive testing and the subsequent onset of radiographic OA after 2.5 years of follow-up. Both studies used patients from the same cohort, had relatively short follow-up times, and used a joint angle-matching task (see next section) to measure proprioception. This last limitation may be particularly relevant given it 1) measures a very narrow aspect of a broad and multi-faceted construct, and 2) the sorts of deficits of interest may be undetectable since relatively high measurement errors require large minimal detectable differences (333).

Measurement of NM Control

A number of methodological issues make accurate measurement of NM control in epidemiologic research a challenge. In part this arises from the diverse and complex nature of the construct of NM control, the numerous sensory inputs that are involved and compensate for each other (e.g., visual, auditory, vestibular, cutaneous tension, pressure), and the number of physical attributes that it encompasses.

Where standardized and validated measures are available, they are often limited to joint-specific aspects of NM control and are expensive for use in population-based

research. The two most commonly used methods to measure proprioception include one that assesses joint position sense via a joint angle-matching task, and involves the knee being moved to a pre-determined angle, after which the knee is returned to the original position and the subject asked to reposition the lower limb at the perceived angle. The second is a threshold motion detection test and involves the slow passive movement of the knee joint, asking the subject to detect the start and/or stop of this movement. Other measures that have been used to capture aspects of NM control include standing balance (285), quadriceps weakness (360), postural orientation (361), medial-lateral knee motion during mini squats (362), vibratory perception threshold (363, 364) trunk displacement after a sudden force release on a force platform (365), and trunk (core) proprioception via an angle matching task (366). While all have been used in studies, important deficits may be undetectable by these methodologies, as the high measurement errors yield large minimal detectable differences among OA patients (367).

Regardless, these measures of NM control are not practical in population-based epidemiology research due to their expense, impracticality and respondent burden. Thus, no epidemiologic studies investigating PA and OA to date have been able to address the affect of NM control. Given the evidence that even with minor incoordination joint forces can be high, even from routine activities such as walking, it would be of value to acquire an indication, even if imprecise, of levels of NM control in a study investigating historic PA and OA.

To this end, a literature search using Medline, SPORTDiscus, PsychINFO, Ovid, EMBASE and CINAHL was conducted to determine if any existing validated self-report instruments were published that assessed NM control characteristics. Two validated questionnaires were found that were of interest. The first was the Physical Self-

Description Questionnaire (PDSQ) (60), an Australian developed validated and reliable instrument composed of 11 subscales, 9 of which are designed to tap perceptions of physical self-concept related to specific areas of physical fitness and competence. One of the subscales is a 6-item coordination instrument (Appendix A). The PSDQ instrument evolved from construct validity research related to both hierarchical model of self-concept and the Self Description Questionnaire (368, 369). While the PSDQ was designed for use with adolescents it has been subsequently validated among adults (369). The PDSQ has been extensively tested for its psychometric properties (60, 370, 371), used in numerous studies and is acknowledged as a leading multidimensional physical self-concept instrument (372). There is strong support for the psychometric properties and construct validity (369). Specifically it has demonstrated to have good reliability (median coefficient alpha = .92) across the 11 scales (60), and convergent and discriminant validity including with external criteria (370, 371). In summary, the PSDQ is a psychometrically strong instrument that is appropriate for a wide variety of sport and exercise research (369), including a measure of coordination for use in the current research.

The second instrument of interest was the Hypermobility Questionnaire (64), designed to detect joint hypermobility syndrome (JHS). JHS is a recognized clinical condition and has been associated with arthralgia, soft tissue injury, and joint instability (373). JHS has been associated with proprioceptive impairment (374-376), premature osteoarthritis (61-63) and laxity in joints and soft tissues (377). JHS is very common, occurring in 10-20% of populations of Western countries, and higher still in those in Indian, Chinese, and Middle Eastern groups (378-382). Hypermobile individuals lack good NM control, which may result in increased shear forces and joint loading. This may increase the risk for OA, particularly when interacting with high levels of physical activity.

While there is some evidence for a correlation between JHS and OA (383-386), there are also studies that show a protective effect (387-389), and the relationship remains unclear.

Of particular interest for this thesis project is the evidence that individuals with JHS have significantly diminished proprioception, compared with age- and sex-matched control groups (374-376). Further, there is a simple 5-item questionnaire (64) available to identify persons with JHS that has been validated against the clinically determined Beighton score (390). As a result, JHS was proposed here as a proxy for decreased proprioception. The hypermobility questionnaire has five items, each requiring a yes/no response (Appendix B). Subjects with a ‘yes’ response to at least 2 of 5 questions are categorized as having JHS. The questionnaire has a sensitivity and specificity of 84% and 89% respectively.

To assess the measurement properties of the instrument in the cohort of subjects in this thesis project, a validation study comparing questionnaire-defined JHS to JHS defined by clinical measures using the Beighton score (390) was conducted in a sub-sample of the overall study population, and results are reported on in Chapter 4.

In summary, the PDSQ and Hypermobility Questionnaire are validated instruments that may be useful for acquiring information on NM control at the population level, and will be used for the first time in the current study of historic physical activity and OA.

3: METHODS COMMON TO STUDIES

This thesis is organized in a manuscript-based format with Chapters 4 to 7 representing stand-alone studies. Methods common to these papers are presented here in this chapter to reduce redundancy in the dissertation collectively. Specifically, the data source, sampling, recruitment of subjects and measurement of the key exposure and outcome variables are presented. A diagram depicting study flow and thesis overview is presented at the end of this chapter in Figure 3.2.

3.1 Data Source and Study Population

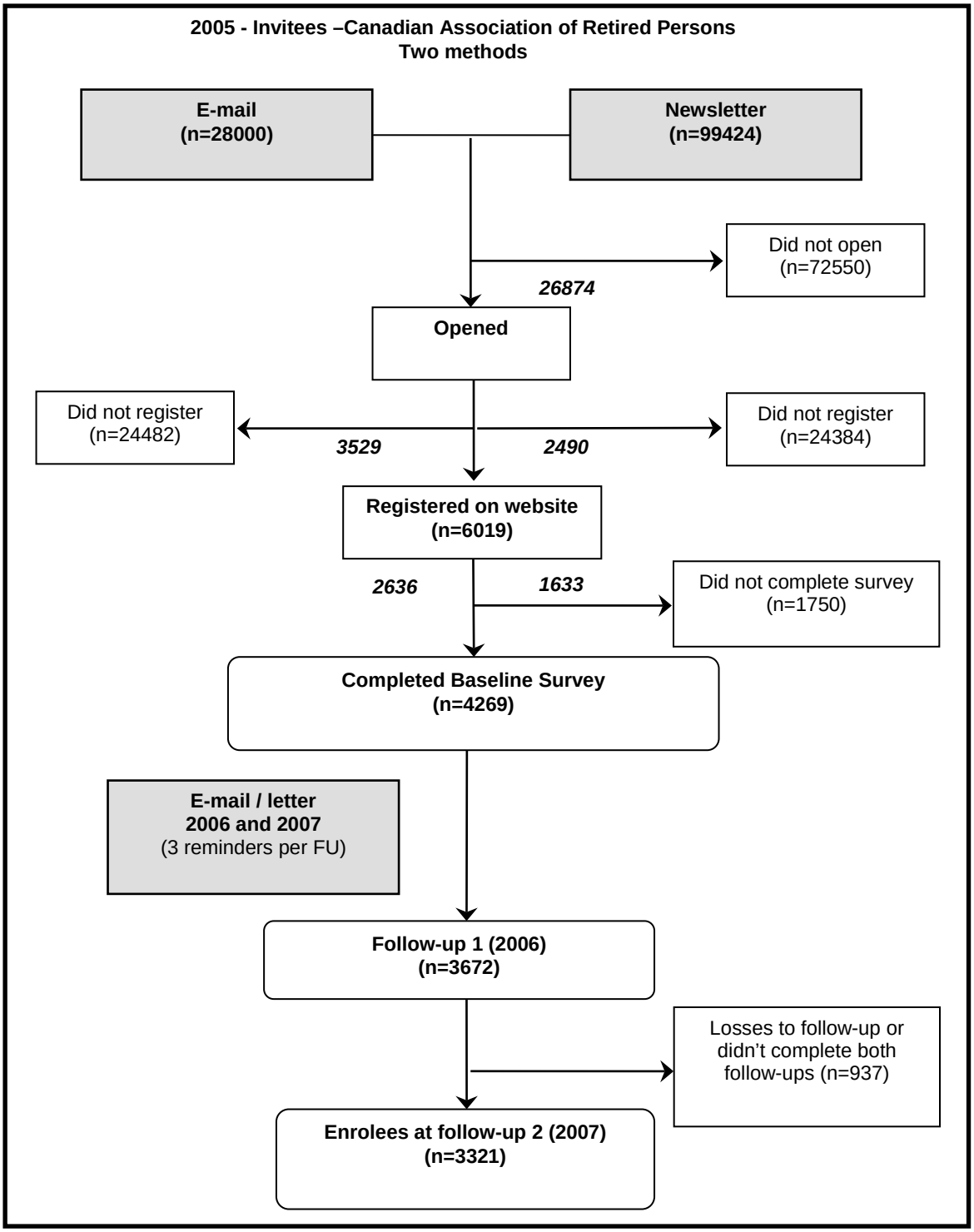
The source population was community-dwelling members of the Canadian Association of Retired Persons, Canada's largest 50-plus advocacy group with 350,000 members. Direct email was sent to 28,000 members with Internet access who had agreed to receive such e-mail, inviting their participation in a study of physical activity. Reminders were sent after 1 and 2 weeks. An advertisement in an online newsletter was also circulated to approximately 100,000 additional members, appearing in two consecutive newsletters. All e-mails and newsletters contained hyperlinks or banner advertisements directing subjects to the study website. Through these methods, subjects across Canada were recruited over the Internet. Incentives included $1,500 in lottery prizes. After completing an electronic consent form, subjects were given password access to the questionnaire.

All data collection was web-based and used skip logic technology that allowed subjects to follow individualized paths through the survey, moving forward based on responses to previous questions. Extensive pre and pilot-testing was carried out to

ascertain best recruitment methods (391), survey duration, navigation, and to ensure respondents could understand items, retrieve information and make appropriate estimations. A secure website for the study allowed subjects to save responses and return later. The baseline questionnaire, carried out from June to September 2005, took 60 to 90 minutes to complete.

Of the 28,000 individuals who received emails, 3,518 registered on the study website (12.7%) and 2,625 completed the baseline survey (9.4% of those contacted). Of the 99,424 mailed newsletters, 26,874 were opened (27%), 2,490 registered (2.5%) and 1,633 completed the survey (1.6% of those contacted, 66% of those registered) (Figure 3.1)

Figure 3.1 Lifetime Physical Activity and Joint Health Study – Recruitment and Enrolment



Individuals who completed the baseline survey were contacted by email and letter for follow-up surveys at approximately one (May 2006) and two years (June 2007). Up to three reminders were sent to non-responders, and efforts were made to locate individuals whose e-mail addresses had changed. Follow-up surveys inquired about hip and knee joint health using the same questions as the baseline survey (see below).

3.2 Exposure Assessment

Physical Activity Measurement

Lifetime physical activity was assessed using the Lifetime Physical Activity Questionnaire (L-PAQ) whose development and validation was described in detail in Chapter 2. In summary, the L-PAQ is a self-administered, web-based questionnaire that was based on existing instruments (245-247), adapted for self-administration over the Internet, incorporated skip logic technology, and expanded to capture more detailed information including bodily movements involving the hip and knee. In a validity study (see Chapter 2) using a sub-sample of the current study, intraclass coefficients for reliability ranged from 0.65 to 0.89; convergent validity testing against two validated lifetime questionnaires resulted in Spearman correlation coefficients ranged from 0.41 to 0.71 (270).

PA was measured across three domains – sport/recreation, occupation and household. Sample questions in each domain are shown in Appendix C. In the sports/recreational section, respondents were provided with a list of 64 possible sports and were permitted to add other sports. Respondent's who had performed an activity at least 100 times in their lifetime were prompted to provide detailed information. This included the *duration, frequency* and *average length of time per occasion.* In addition, for each type of sport respondents were required to report time spent per hour (none, 1-5,

5-15, 15-30, 30-45, 45-60 minutes per hour) in each of the following bodily movements: sitting, standing, walking, running/jogging, squatting or knee bending without lifting, squatting or knee bending with lifting or force.

The occupational section used an open format in which respondents indicated all jobs held over their lifetime. For each occupation, details were collected on job title or type, duration, average hours per week, and whether the job was full-time, part-time or seasonal. In addition, for each job, respondents were required to report time spent in an 8-hour period (none, 0-1, 2-4, 5-7, 8 hours) in each of the following bodily movements: sitting, standing, standing-holding or moving objects over 50 lb (23 kg), walking, walking-carrying objects greater than 50 lb (23 kg), moving-pushing objects over 75 lb (34 kg), using heavy tools, squatting continuously, kneeling continuously.

Household activity covered four areas 1) caring for children; 2) caring for elderly or disabled individuals; 3) gardening; and 4) housework. For each household area of activity, participants were prompted to provide detailed information on duration and average number of hours per week of participation. In addition, for each household area of activity subjects were required to report time spent in an 8-hour period for each of the bodily movements listed above for occupational activity with the exception of the use of heavy tools.

Primary Exposure Variables

Exposure variables were constructed to describe lifetime PA in terms of energy expenditure (MET-hours per week) and cumulative hip and knee joint force (bodyweight-hours).

Calculations of time in PA were common to both metrics. For the three activity domains, lifetime participation in each specific activity was calculated by taking the

product of duration (years), frequency (days/week), and length of each activity session (hours) (i.e., total lifetime hours =duration X frequency X length of activity session). Calculations were performed to obtain values for each activity, and then summed by activity domain (sport, occupation, household) and finally for total activity. Physical activity was also expressed as average weekly participation (*average hours per week)* calculated by dividing total lifetime hours by respondent age and 52 weeks (i.e., *average hours per week* = total lifetime hours / age / 52).

Energy Expenditure (MET-Hours per Week)

To obtain a measure of energy expenditure (EE) associated with PA, average hours per week in PA in each activity was multiplied by the specific metabolic equivalent (MET) associated with that activity, assigned using the Compendium of Physical Activities (392), [i.e., *MET-hours per week* = average hours per week * MET, per each activity]. A MET is defined as the ratio of the associated metabolic rate for a specific activity as compared with the resting metabolic rate.

Cumulative Peak Force Index (Bodyweight-Hours)

To obtain a measure of cumulative joint force at the hip and knee, a cumulative peak force index (CPFI) score was estimated for each joint (hip, knee-tibiofemoral) and activity separately, as the product of time spent in a specific activity (total lifetime hours), bodyweight (BW) and typical peak joint force for that activity (%BW), [i.e*., CPFI score (bodyweight-hours)* = total lifetime hours * bodyweight * typical peak joint force, per each activity).

The CPFI is a newly proposed measure and steps were taken to validate and/or ensure the greatest precision in the components that comprise it, as outlined in Chapter 2. In addition to validation of the lifetime PA survey (270), self-reported bodyweight and

height were utilized, measures with established validity properties (393) used in numerous epidemiologic studies. We improved on a single self-report of bodyweight by asking about it at three time points (baseline survey, age 20, maximum lifetime), and deriving a lifetime bodyweight trajectory, interpolated using a Lowess (non-parametric smooth) curve. The third component of the measure was the typical peak joint force assigned to each activity (Appendix D). These values were determined after an extensive literature (154-156, 223, 224, 394-417) (full bibliography available on request) that prioritized in vivo studies and incorporated judgments about data quality and study rigor. Data were synthesized and a consensus achieved by a panel of experts from biomechanical engineering, rheumatology, and musculoskeletal epidemiology.

Relative Joint Loading index

We also defined a "relative joint loading" index for each joint as the ratio of CPFI score to EE: [i.e. Joint Loading Index = CPFI (bodyweight-hours) / Energy expenditure (MET-hours)].

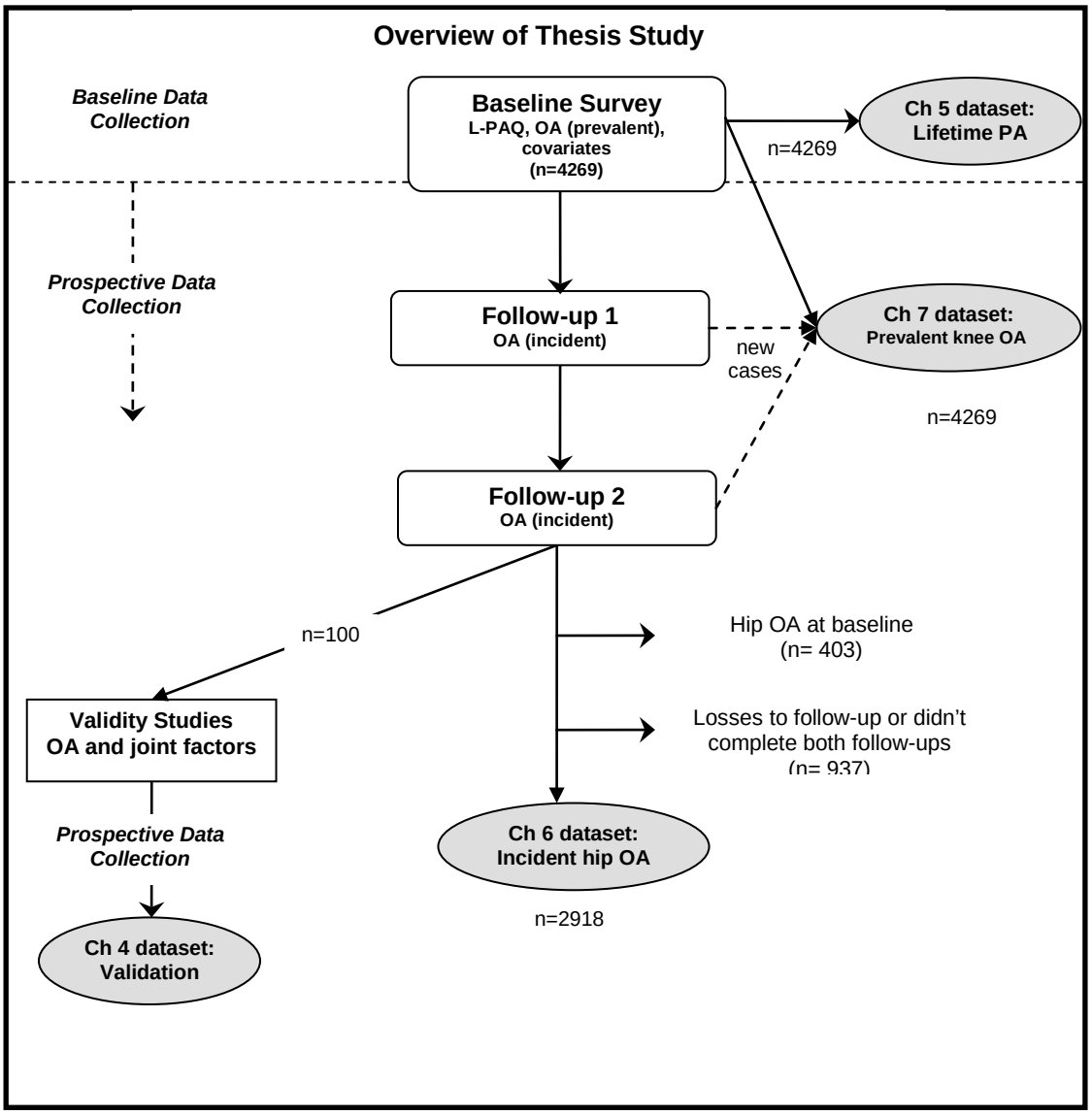
3.3 Outcome Assessment

Cases of hip and knee OA were determined by self-report. After an extensive review of the literature to determine previously validated self-report items on hip and knee joint health (166, 418, 419), questions were selected that were most likely to identify patients with knee or hip OA. These included questions on symptoms and on a medical diagnosis. Pre and pilot testing were carried out in an online computer format. The questionnaire used in this research project utilized skip logic technology which resulted in affirmative responses to items on medically-diagnosed OA and symptoms leading to further questions on side of involvement, age at diagnosis, onset of symptoms, and joint replacement surgery.

The question regarding knee symptoms was ‘On most days, do you have pain, aching or stiffness in either of your knees?’ and for the hip, ‘On most days, do you have pain, aching, or stiffness in your groin or upper thigh? (Appendix E and F contain the questionnaire items as they appeared on screen.) A diagram, to indicate the area of hip and groin pain common to hip OA, preceded the hip question. The questions regarding a diagnosis were separate for the hip and knee, and were: *'Have you ever been diagnosed by a health professional with OSTEOARTHRITIS of the knee/hip? (Please note that osteoarthritis, rheumatoid arthritis, and osteoporosis are different conditions).'* This question was repeated again on the next screen for response confirmation, with the additional highlighted phrase in green font “*This question is very important, please confirm your answer”* .For both the hip and knee, subjects were also asked whether joint replacement surgery had been performed, and if affirmative, further details were asked on side and time of surgery.

A validation sub-study was conducted in a sample of 100 members of the larger cohort and is reported on in Chapter 4.

Figure 3.2 Study Flow and Thesis Overview



4: VALIDATION STUDIES[3]

4.1 Introduction

This chapter describes validation studies carried out in a sub-sample drawn from the larger cohort, designed to assess the measurement properties of the hip and knee OA outcome variable, as well as novel joint vulnerability variables.

The background for these variables was presented previously. In summary, for hip and knee OA, several previously validated items drawn from the literature (166, 418, 419) were adopted and pilot-tested for inclusion in this study.

Self-report items for lower limb alignment were developed for use in this study (see section 4.2), but have not been previously validated. A previously validated measure for joint hypermobility syndrome has been used in other areas of research but not in OA epidemiology and is therefore validated in the current study population.

The purpose of this study was to estimate the measurement properties of 1) self-reported measures of medically-diagnosed hip and knee OA and pain compared to American College of Rheumatology (ACR) clinical classification criteria, 2) self-reported measures for lower limb alignment compared to clinical measurement using goniometry, and 3) the Hypermobility Questionnaire (as a measure of joint hypermobility syndrome) compared to the clinically measured Beighton score.

3 A version of this chapter has been submitted for publication. Ratzlaff CR, Koehoorn M, Cibere J, Kopec J. Clinical validation of an internet-based questionnaire for ascertaining cases of hip and knee osteoarthritis.

Section 4.1 will present the clinical validation of the hip/knee OA measures, and will be presented in in-depth fashion, with discussion, as it is central to the primary goals of this thesis.

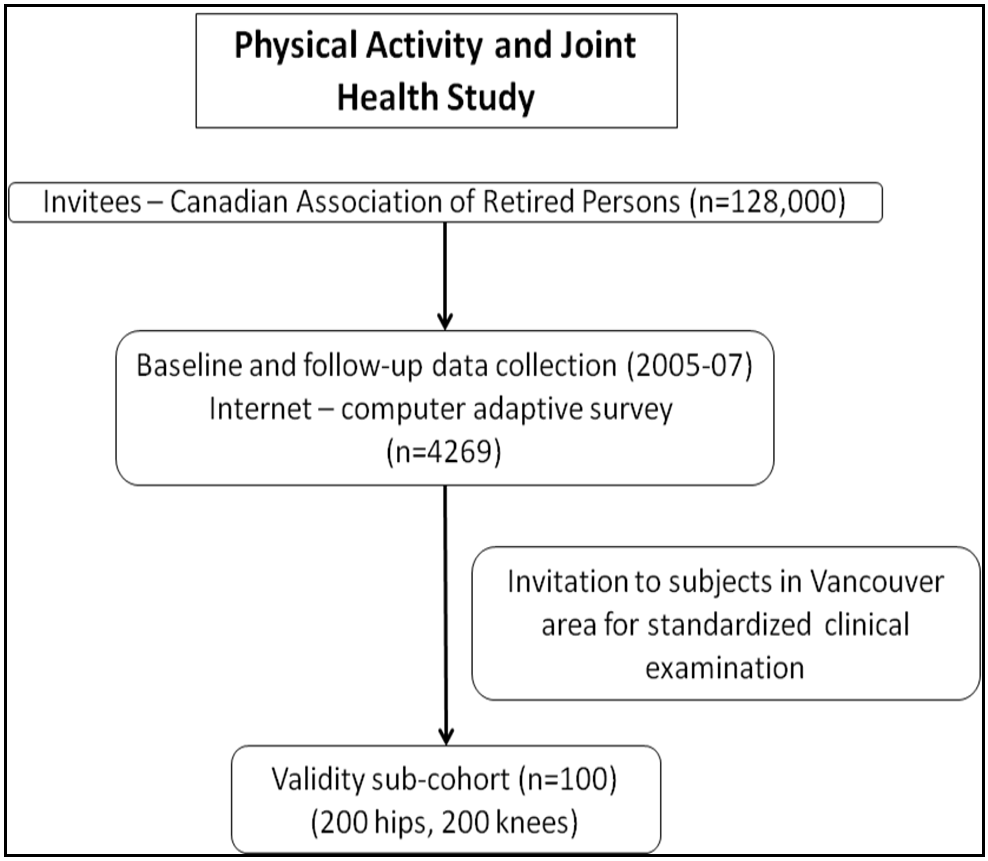
Section 4.2 will present clinical validation studies of the local joint factors (alignment and hypermobility). Results and a limited discussion are presented here. Findings will be utilized and discussed in Chapter 7, where these variables are applied in crude and adjusted models for knee OA.

4.2 Hip and Knee Osteoarthritis

Materials and Methods

Subjects for the validity study were recruited from the larger cohort study following three data collection cycles 2005-2007. The inclusion criteria were: 1) completion of at least the baseline survey; 2) subject permission for future contact and provision of contact information; and 3) residency in the Metro Vancouver region. After letters of invitation were sent, a sub-cohort of 100 subjects was assembled for face-to-face interviews and a clinical examination conducted at the Arthritis Research Centre of Canada (ARC) (Figures 3.2, 4.1).

Figure 4.1 Validation Study Flow Chart



Self-Reported Hip and Knee OA

Self-reported hip and knee OA was ascertained using questions and methods outlined in Chapter 3, section 3.3.

Clinical Measures

The 100 sub-cohort subjects underwent a standardized clinical interview and history. Interviews were conducted by a trained research assistant using a standardized clinical questionnaire (previously pilot tested and adopted by ARC). Items in the interview inquired about pain and symptoms, diagnostic history and previous surgery. Following the interview, a standardized knee and hip examination was conducted with the examiner blinded to subject history, interview and self-report status. The exam

followed a standardized format as outlined in Cibere et al.(420, 421), which demonstrated good reliability for physical exam tests that are part of the ACR clinical classification criteria. The examiner was an experienced orthopaedic physical therapist who underwent training sessions with a rheumatologist (lead author of the standardized exam studies (420, 421)) to confirm accurate examination technique. In a previous study at ARC, there was good reliability between a PT examiner and the same rheumatologist (JC) (422). Clinical data included all items comprising the ACR clinical classification criteria for OA of the hip and knee (423),and confirmation of a total joint arthroplasty (TJA) procedure, if present.

Analysis

Knees and hips were analyzed separately (200 knees, 200 hips). The ACR clinical classification criteria were used as the referent (424, 425) (Table 4.1). Since the ACR clinical criteria was not designed for epidemiological use (though often used as such) and have been linked with increased disease severity, it likely underestimates disease prevalence in epidemiological studies (426). Therefore, at the knee, two referents were examined, identical on all clinical examination criteria, but differing on the requirement for duration of pain. The first used the conventional ACR criteria pain definition requiring ‘knee pain on most days of the *prior* month’ (ACR clinical criteria 1). The second used a broader pain definition – ‘knee pain on most days of the month *at any time* in the past’ (ACR clinical criteria 2). All other clinical criteria were the same for both definitions. This second pain definition allows for a broader definition of joint health, reflecting the episodic, fluctuating course of OA, especially early in disease. In the hip analysis, we were only able to use a definition incorporating ‘pain on most days of the month *at any time* in the past’, as we did not have data on hip pain from the prior 30

days. To be consistent with the knee, this was designated ACR clinical criteria 2 of the hip.

Two self-report items for each joint from the on-line survey were examined. At the knee, 1) self-reported medically diagnosed knee OA, and 2) 'knee pain, aching or stiffness on most days' were compared to ACR clinical criteria 1 and 2 for the knee. At the hip, 1) self-reported medically diagnosed hip OA and, 2) 'pain, aching and stiffness in the groin or upper thigh on most days' was compared to ACR clinical classification criteria 2 for the hip.

Validity properties of hip and knee self-report status were compared to clinical status by calculating sensitivity, specificity, negative and positive predictive values (NPV, PPV). Kappa was used as a statistical measure of agreement as it is more robust than a simple percent agreement, accounting for agreement beyond chance. For interpretation of kappa coefficients, we adopted the standard kappa descriptive scale by Landis and Koch (427).To account for correlated joints of the same subject, a bootstrapping technique was performed to yield valid standard error used for 95% CI's.

Table 4.1 Clinical Criteria for Classification of Hip and Knee OA

HIP	**KNEE**
Hip pain on most days of the month and 1. Hip internal rotation ≥15° and 2. Pain on hip internal rotation and 3. Morning stiffness ≤60 min and 4. >50 years	Knee pain on most days of the month in addition to 3 of the following: 1. Crepitus 2. Morning stiffness <30 min duration 3. Age > 38 years 4. Bony enlargement of knee on examination 5. Bony tenderness of knee on examination 6. No palpable warmth

Results

Compared to the overall survey sample, the 100 sub-sample subjects were slightly older, less likely to be female, had slightly higher rates of self-reported medically-diagnosed knee and hip OA , were more likely to be university educated, and be in the highest income bracket (Table 4.2). Using the ACR clinical criteria 2, self-reported medically diagnosed hip and knee OA had moderate sensitivity and PPV and good specificity and NPV, and had better measurement properties than items on pain, aching and stiffness on most days (Table 4.3). Cohen's kappa was 0.76 and 0.65 for knee and hip respectively indicating substantial agreement (427). Using the ACR clinical criteria 1 at the knee resulted most notably in a lower prevalence of knee OA (17% versus 25%) and reduction of PPV and kappa. Self-reported pain, aching and stiffness on most days had poor agreement (kappa's < 0.30) with low sensitivity and PPV's. There were 11 self-reported total joint arthroplasty cases due to OA (4 knees, 7 hips) that were all confirmed by determination of arthroplasty status on physical examination.

Table 4.2 Subject Characteristics

Characteristics		Sub-Cohort (n=100)	PAJH Cohort (n=4,269)
Age, *yr*		**63.3 (7.2)**	**61.5 (7.6)**
Sex, (*%)*	*Male*	**46%**	**37%**
BMI		**27.4 (4.9)**	**27.3 (5.9)**
Knee OA prevalence			
	Self-reported medical diagnosis	**21%**	**20%**
	ACR† Clinical Criteria 1	**17%**	**-**
	ACR† Clinical Criteria 2	**25%**	**-**
Hip OA prevalence			
	Self-reported medical diagnosis	**14%**	**10%**
	ACR Clinical Criteria†	**11%**	**-**
Level of Education, *%*			
	College/University/Post Grad	**54%**	**47%**
Household Income, %			
	<20k	**5%**	**6%**
	20-40k	**20%**	**19%**
	40-60k	**18%**	**19%**
	60-80k	**10%**	**14%**
	80-99k	**6%**	**8%**
	100k+	**18%**	**9%**

† American College of Rheumatology;
Clinical Criteria 1 – conventional ACR Clinical Criteria
Clinical Criteria 2 – as per criteria 1 but pain defined as 'pain on most days of the month at any time in the past'
† At the hip, only ACR clinical criteria 2 used due to limitations with the available data

Table 4.3 Sensitivity, Specificity, Positive and Negative Predictive Values and Cohen's Kappa, with 95% CI, for Determining the Presence of Clinical Knee and Hip OA*

Question	Positive Predictive Value	Negative Predictive Value	Sensitivity	Specificity	Kappa
ACR Clinical Criteria 1 (Knee)†					
Self-reported medically-diagnosed knee OA	0.58 (0.43, 0.72)	0.94 (0.90, 0.98)	0.74 (0.58, 0.88)	0.89 (0.84, 0.93	0.57 (0.41, 0.73)
Pain, aching and stiffness on most days	0.33 (0.20,0.46)	0.89 (0.84, 0.93)	0.50 (0.33,0.67)	0.79 (0.72, 0.84)	0.24 (0.09, 0.39)
ACR Clinical Criteria 2 (Knee) ††					
Self-reported medically-diagnosed knee OA	0.86 (0.74, 0.95)	0.91 (0.86, 0.95)	0.73 (0.59, 0.89)	0.96 (0.92, 0.99)	0.73 (0.64, 0.89)
Pain, aching and stiffness on most days	0.46 (0.33, 0.59)	0.82 (0.76, 0.88)	0.47 (0.33, 0.60)	0.81 (0.75, 0.87)	0.28 (0.13, 0.43)
ACR Clinical Criteria 2 (Hip)†					
Self-reported medically-diagnosed hip OA†	0.61 (0.52, 0.70)	0.98 (0.97, 0.99)	0.81 (0.64, 0.97)	0.94 (0.91, 0.97)	0.65 (0.49, 0.81)
Pain, aching and stiffness on most days	0.18 (0.04, 0.33)	0.91 (0.86, 0.95)	0.24 (0.06, 0.44)	0.87 (0.82, 0.91)	0.10 (0.00, 0.26)

*Or clinical confirmation of total joint arthroplasty for OA

American College of Rheumatology:

†Clinical Criteria 1 – conventional ACR Clinical Classification Criteria for knee OA (knee pain most days *prior* mo.)

††Clinical Criteria 2 –ACR Clinical Classification Criteria for knee OA but pain defined as 'pain on most days of the month at any time in the past'

†At the hip, only ACR clinical criteria 2 used due to limitations with the available data

Clinical Criteria 2 – ACR Clinical Classification Criteria for hip OA but pain defined as 'pain on most days of the month at any time in the past'

Discussion

In this validity study, conducted in a sub-group of a large cohort study, it was shown that an Internet-based questionnaire has the potential to correctly identify most cases of self-reported hip and knee OA and TJA, as compared to clinical examination. Consistent with previous community-based postal questionnaires the greatest accuracy is achieved by asking about self-report of a medical diagnosis of OA.

Of note, specificity was very high for all OA definitions used. This is critical for studies of risk factors such as this thesis, since low specificity (inclusion of many false positives among cases) causes a greater attenuation of effect than low sensitivity. PPV was also high, another important measure indicating the vast majority of the cases identified in the survey were true cases.

At the knee, measurement properties were improved when we broadened the ACR criteria definition of pain from most days of the prior month to most days of the month at any time in the past – done to capture the episodic fluctuating course of early and moderate disease. As expected, prevalence of disease increased with this definition (17% to 25%), as some knees showed clinical OA changes without satisfying the definition of pain on most days of the prior month. The increase in prevalence was associated with a 3-fold decrease in the number of false positives (18 to 6), and a moderate increase in both accurately reported OA and false negatives resulting in a substantive improvement in PPV, specificity and kappa. The measurement properties are consistent with or better than other validity studies comparing self-report of medically-diagnosed OA to a clinical reference standard (166, 418), but require confirmation in other populations and must be compared cautiously with previous studies due to differences in study design, how subjects were assembled and subject

characteristics. In particular, no other studies recruited subjects and collected self-report data through the Internet, nor included validity of self-reported TJA due to OA. Including self-report (and clinical confirmation) of TJA increased accuracy of self-report, consistent with recent literature (428).

There are some limitations to this study. We did not use radiography as part of the classification criteria. Radiographic OA in the presence of symptoms is thought to represent the best definition of OA. However, x-ray change is associated largely with moderate to advanced disease (429) and there is only moderate agreement between pain and symptoms and x-ray changes (430). Not including x-rays probably resulted in a higher prevalence due to the capture of early OA cases prior to the development of radiographic change – cases that would have been classified as false positives had x-rays been used. Wu et al., in a study using a validated outcome instrument for knee OA based on arthroscopic visualization, suggest that the ACR clinical classification criteria can be used to identify patients with early articular cartilage loss, before any radiographic changes are evident (429). However, it is probable that the false positives include not only subjects with early OA not captured by the ACR criteria (429), but also other causes of hip and knee symptoms.

The other significant limitations relate largely to generalizability. It was performed among a relatively homogenous population – older well-educated Caucasians with a high level of literacy from a socio-economically advantaged, urban area with easy access to insured medical care – the latter is important because we asked for a medical diagnosis of OA. Subjects were Internet users, who typically are of higher SES status and demonstrate health-seeking behaviour (431). At the time of the baseline survey, about 50% of Canadians in this age group used the Internet (Statistics Canada). While not generalizable for all future uses, our findings are relevant to the broader cohort study

in which this study was nested, with a population generally similar to the sub-sample. Our method of case ascertainment by future researchers may not be as effective in low income and less educated populations or in countries without national health care – all would tend to decrease access to medical care. We did not have sufficient numbers to assess validity and agreement by co-morbidity status - some previous studies suggest that mood can effect case definition by lowering specificity (101).

The utility of criteria for OA depends on the purpose for which they are used. The ACR criteria were not designed or developed for use in population studies but to differentiate OA from other painful rheumatologic conditions (423). We broadened the definition of pain in the ACR clinical criteria, since using the criteria in epidemiological studies of OA has the potential to underestimate disease prevalence and increase false positives by capturing primarily more advanced disease. In the larger population survey in which this validity study was nested, we were interested in capturing early disease and pain and symptoms and its relation to a putative risk factor (lifetime physical activity). From a patient perspective whatever the cause, these symptoms and dysfunction are relevant, affect their quality of life and are potentially linked to the exposure in the larger study. Despite the limitations of our study, we propose that questionnaires of this nature are useful for identifying OA in population-based studies when the purpose is to link potential risk factors with knee and hip health.

Conclusion

In this sub-cohort from a large epidemiologic study, self-reported health professional diagnosed hip and knee OA had reasonable validity. Results can be used to interpret analytic results derived from this case definition.

4.3 Lower Limb Alignment and Hypermobility

Materials and Methods

Subjects were the same as those described in section 4.1 (Figure 4.1).

Self-report items for lower limb alignment. Based on clinical and research experience, and in consultation with experts in rheumatology, epidemiology, and physical medicine and with the services of a medical illustrator, novel line drawings were developed, adopted and pilot-tested for inclusion in this thesis study. The line diagrams depicted 3 pairs of lower limbs, 1 neutrally aligned, 1 showing varus (bow legs) and 1 showing valgus (knock knees) and were preceded by an introduction and a set of instructions communicating how the drawings should be used to determine lower limb alignment (Appendix G). The following screen presented an ordinal scale asking subjects to report their alignment ranging from strongly bow legged to straight (neutral) to strongly knock kneed at their current age and at age 20.

Self-report items for joint hypermobility syndrome. The Hypermobility Questionnaire (64), described in Chapter 2, is a validated 5-item survey for ascertaining individuals with joint hypermobility syndrome (JHS). Each or the five items requires a yes/no response (Appendix B). Subjects with a ‘yes’ response to at least 2 of 5 questions are categorized as having JHS. The questionnaire has a reported sensitivity and specificity of 84% and 89% respectively (64).

Clinical Measures

General examination procedures were described in section 4.1. Clinical measurement of alignment was conducted by long-arm goniometric measurement of standing knee alignment using a standardized technique described by Cibere et al. as part of the standardized knee exam (421). Subjects stood facing the examiner with feet

approximately shoulder-width apart, with weight born equally on both feet. The axis of the goniometer was positioned over the center of the patella, and the arms were aligned with the mid-thigh above the knee and with the patella tendon below the knee. Angles were recorded to the nearest degree, with 180° regarded as centre. Alignment was determined to be neutral if within ±2° of 180°, and subjects were categorized as varus or valgus if >2° away from 180° in the respective direction. In pilot-testing, this method was found to be reliable in our research centre (ICC 0.86).

Clinical measurement of joint hypermobility syndrome was by conducting a standardized clinical exam using the Beighton method and calculation of the Beighton score (390) (Appendix H). To summarize, passive range of motion at the fifth finger (≥90° extension of the MCP joint), thumb (touch to volar aspect forearm), elbows and knees (≥10° hyperextension) on each side of the body, as well as the ability to stand and place the hands flat on the floor without bending the knees were measured. Standard goniometry was used for measurement of the fifth finger, elbows and knees, and observation for the thumb and palms measurements. One point was awarded for each test where the hypermobility requirement was met. A score of ≥ 4/9 meets the criteria for JHS.

Analysis

Validity properties of self-report measures were compared to the referent (clinical status) in a similar method as described in section 4.1. For alignment, sensitivity, specificity, positive likelihood ratio, accuracy and kappa (with 95% CI) were calculated separately for varus and valgus. To calculate these outcomes, the self-report data were dichotomized as positive (e.g., varus knee) and negative (e.g. no varus knee).

The same measures of validity were calculated for self-reported JHS. Calculation of validity outcomes was straightforward as subjects were classified in dichotomous fashion (JHS positive or negative) on both self-report questionnaire and clinical criteria.

Results

Subject characteristics are presented in Table 4.1, and described in section 4.1. Measurement properties are summarized in Table 4.4. Compared to clinical goniometry, self-report of lower limb alignment using line diagrams had an overall sensitivity of 0.73, specificity of 0.91, a positive likelihood ratio of 9.23 and accuracy of 0.90. Compared to the clinically determined Beighton score, self-reported JHS using the hypermobility questionnaire had a sensitivity of 0.50, specificity 0.83, positive likelihood ratio of 2.86 an overall accuracy of 0.76.

Table 4.4 Sensitivity, Specificity, Positive Likelihood Ratio (LR) and Accuracy, with 95% CI, for Determining Lower Limb Alignment* and Joint Hypermobility Syndrome**

Question		Sensitivity	Specificity	LR (+)	Accuracy
Alignment (goniometry) †					
	Varus	0.75 (0.30, 0.95)	0.88 (0.79, 0.93)	6.00 (2.77, 13.02)	0.85 (0.77, 0.91)
	Valgus	0.70 (0.40, 0.89)	0.94 (0.88, 0.98)	12.60 (4.91, 32.37)	0.92 (0.85, 0.96)
	Overall	0.73 (0.54, 0.92)	0.91 (0.83, 0.98)	9.23 (3.12, 15.34)	0.90 (0.85, 0.96)
Joint Hypermobility Syndrome (Beighton score)					
	Self-reported JHS **	0.50 (0.30, 0.70)	0.83 (0.73. 0.89)	2.86 (1.45, 5.46)	0.76 (0.67 ,0.83)

* using line diagrams
** using the Hypermobility Questionnaire
† alignment neutral if within ±2° of 180°; as varus or valgus if >2° away from 180° in respective direction

Discussion

Briefly, in this validity study conducted in a sub-group of the larger cohort study, it was shown that Internet-based questionnaire items have the potential to correctly classify most lower limb alignment, as compared to clinical goniometry. Specificity was good (0.91) indicating those with neutral alignment can accurately report it a very high rate. Sensitivity (0.73) was lower than specificity (though still reasonably high), suggesting that some who report neutral alignment actually have some degree of malalignment. In 2010, the first study to report validation of self-reported lower limb alignment has been published, using similar line diagram methodology to the current study, but employing a gold standard of radiographically determined lower limb alignment (432). Measurement properties were extremely high, with sensitivity,

specificity, and accuracy all close to 100%. Given the similarity in self-report methods between the two studies, it is possible that some of the misclassification in the current study may be due to error in determination of the clinical gold standard (goniometry), and that self-report of malalignment may be more accurate than reported here.

Measurement properties for the self-reported Hypermobility Questionnaire here were lower than those reported in the original validation of the questionnaire (sensitivity 84%, specificity 89%) (64), particularly the sensitivity of 0.50. One reason may be that our cohort had mainly older adults, compared to the broad range of ages (16-80) of the original study. Older age is associated with a reduction in flexibility and joint range of motion. Even though all five items in the Hypermobility Questionnaire inquired about historical flexibility (e.g., ‘Can you now or could you ever...?’), some individuals may have problems recalling past flexibility or used current flexibility as a guide.

The findings of this validity study will be utilized and discussed in Chapter 7, where these variables are applied in crude and adjusted models.

5: LIFETIME TRAJECTORY OF PHYSICAL ACTIVITY ACCORDING TO ENERGY EXPENDITURE AND JOINT FORCE[4]

5.1 Introduction

The background and literature review for this chapter can be found in Chapter 2.

The purpose of this paper was twofold: 1) to develop and demonstrate the feasibility of a method for estimating cumulative hip and knee joint force using survey data on PA collected via a validated Internet survey, and 2) to construct and describe lifetime trajectories of EE and hip and knee joint load by gender and activity domain strata in a large Canadian sample.

5.2 Methods

Chapter 2 describes the development and validation of the Lifetime Physical Activity Questionnaire (L-PAQ) the key measurement instrument in this study.

Chapter 3 described the data source, recruitment and enrolment of subjects, data collection, variable derivation and calculations. In summary, validated survey data on lifetime PA was used to construct lifetime hip and knee cumulative joint force via the Cumulative Joint Force Index (CPFI), estimated as the product of time spent in specific activities (hours), bodyweight (BW) and typical peak hip or knee joint force for each

[4] A version of Chapter 5 has been published in Arthritis Care and Research: Ratzlaff CR, Doerfling P, Steininger G, Koehoorn M, Cibere J, Liang M, Esdaile J, Kopec J. Lifetime trajectory of physical activity according to energy expenditure and joint force. Arthritis Care and Research 2010; 62: 1452-1459.

activity (%BW). The CPFI is a newly proposed measure and steps were taken to validate and/or ensure the greatest precision in the components that comprise it.

Likewise, using validated methods widely used in PA epidemiology, a measure of energy expenditure (EE) associated with PA, was calculated. The average hours per week in PA in each activity was multiplied by the specific metabolic equivalent (MET) associated with that activity, assigned using the Compendium of Physical Activities (392), (i.e., MET-hours per week = average hours per week * MET, per each activity). A MET is defined as the ratio of the associated metabolic rate for a specific activity as compared with the resting metabolic rate.

Analysis

Descriptive statistics were performed to characterize the study sample. For each type and domain of activity, estimates were made for 5-year periods in a person's lifetime starting at age 10 for EE and age 20 for joint force. In order to calculate lifetime trajectories for both EE and CPFI scores, mean values for 5-year intervals over a person's lifetime, averaged over all subjects, were calculated and plotted. For each metric, trajectories over the lifetime were described for total EE and CPFI and across demographic strata of the sample including activity domains (occupational, sport/recreation, household) and gender. Comparisons for the CPFI measure were made to expectations based on the literature and known and/or rationalized relationships. All data were analyzed using SPSS 15.0.

5.3 Results

A total of 4,269 subjects completed the baseline measurements (Table 5.1). The sample was 63% female and 93% Caucasian. Sixty-six percent had post-secondary education. Lifetime trajectories for EE (Figure 5.1) in sport/recreational activity were

highest prior to the age of 20 and plateaued by age 25. For both EE and joint force (Figures 5.1, 5.2, 5.3), occupational and household measures were much higher than sport/recreation over the lifetime, increasing rapidly from age 20 to 35 (particularly male occupation and female household), before plateauing and then slowly declining.

Table 5.1 Subject Characteristics (n = 4269)*

	Overall	Males	Females
N	4269	1575 (37%)	2694 (63%)
Mean Age	61.5 (7.6)	63.0 (7.8)	60.6 (7.3)
Mean Current Weight (lb)	175 (41)	193 (41)	165 (38)
Mean Current BMI	27.3 (5.9)	27.0 (5.3)	27.5 (6.3)
Married (%)	65.9	79.2	58.1
Some post-secondary education (%)	66	68.8	64.8

* Values are the mean and SD unless otherwise indicated.

Figure 5.1 Energy Expenditure by Domain and Gender

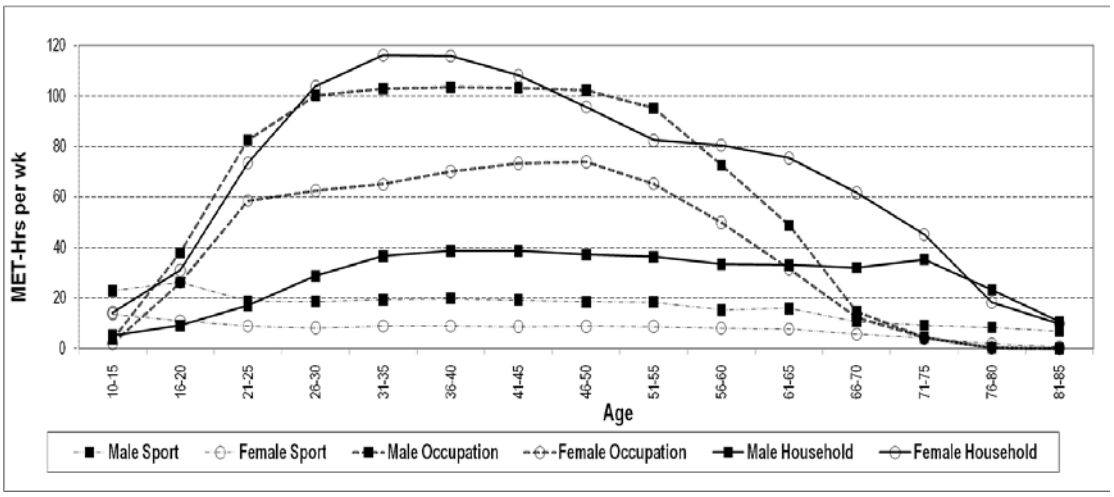


Figure 5.2 Knee (Tibio-Femoral) Force by Domain and Gender

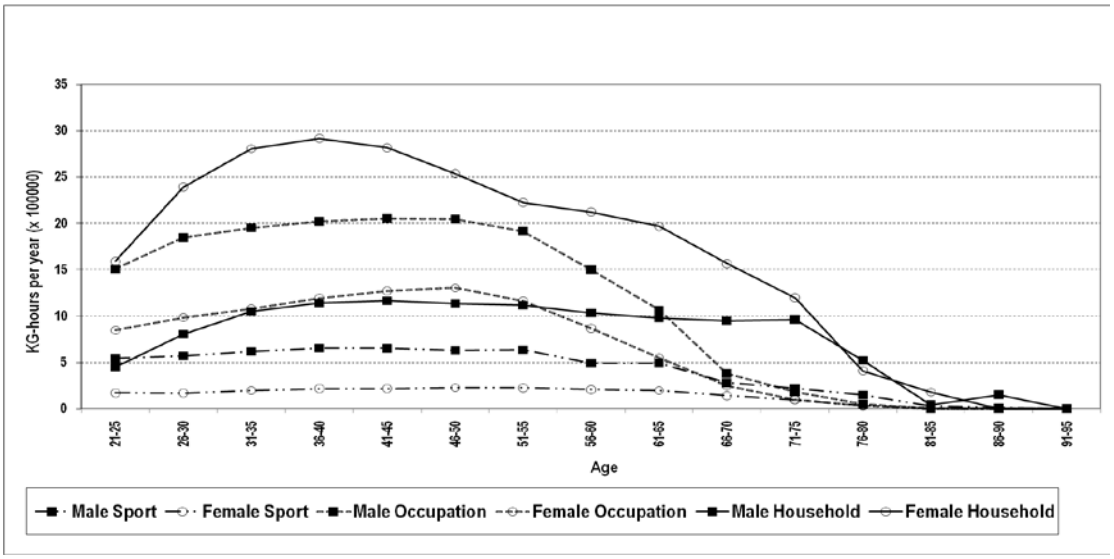


Figure 5.3 Hip Force by Domain and Gender

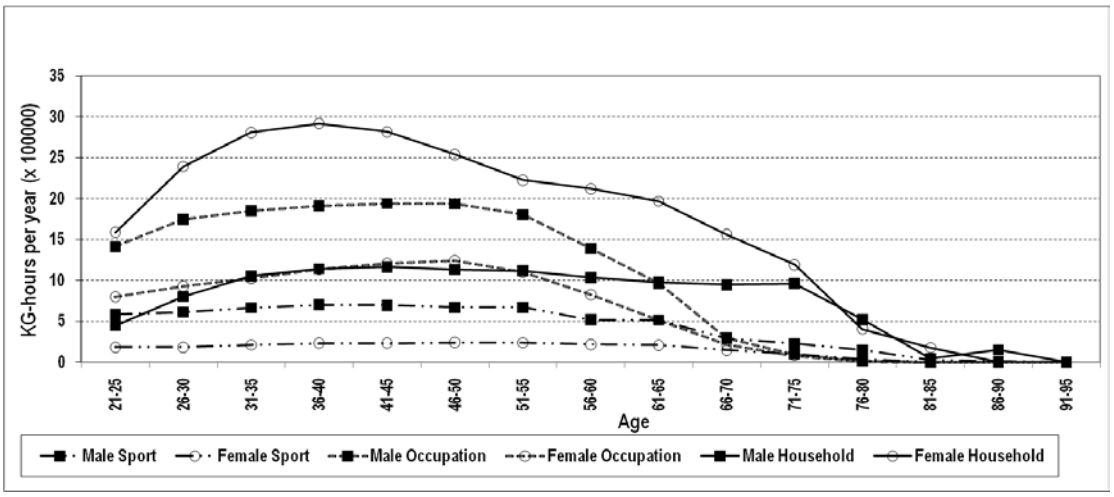
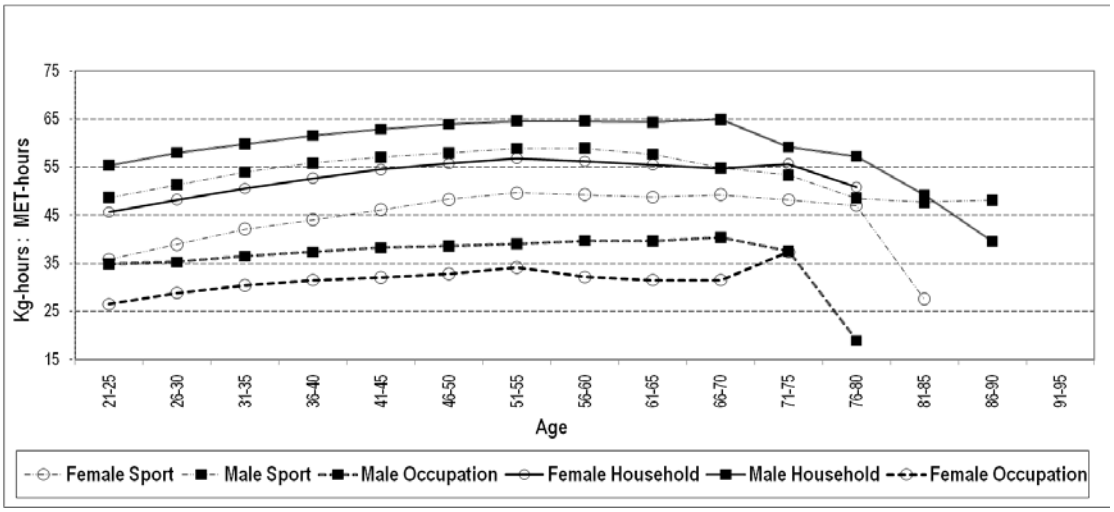


Figure 5.4 Knee Loading Index - by Domain and Gender



The mean EE from total PA in the study sample was 119.1 MET-hours/week. This level of activity is equivalent to 17 MET-hours per day or 12 hours of 1.42 MET of activity per day. Overall when accounting for total activity including household, women reported expending on average more energy than men over the lifetime (126 versus 107 MET-hours per week per year). Occupation EE for the overall sample was slightly higher than household (53.9 versus 49.8 MET-hours/week), while sport/recreational MET-hours/week was approximately 3 times less than either household or occupational activity (16.8 MET-hours/week).

Women reported approximately 1.74 times higher mean EE in household activity as compared to occupational activity (70.5 versus. 40.5 MET-hours/week respectively). Compared to sport/recreational activity, women spent approximately 7 times more energy on average in household activity (70.5 versus. 7.3 MET-hours/week). Men reported spending approximately 2.2 times more energy in occupational as compared to household activity (63.9 versus 28.6 MET-hours/week), and approximately 2 times more

energy in household as compared to sport/recreational activity (28.6 versus 16.9 MET-hours/week). Women's EE in household activity was approximately 2.5 times that of men, while men's EE in occupational activity was approximately 1.5 times that of women. For sport/recreation, men expended on average over the lifetime, approximately 2 times more energy than women (16.9 versus 7.3 MET-hours/week).

Hip and tibio-femoral joint CPFI scores were substantially higher than patello-femoral joint scores. Trajectories for the hip and knee CPFI scores by gender and activity domain are shown in Figures 5.2 and 5.3. We defined a 'relative joint loading' index as the ratio of cumulative joint load to metabolic equivalent to examine activities that produce high physical exertion without excessive joint force (low ratio) and vice versa (high ratio). For example, swimming would have a low ratio, while sustained squatting would have a high ratio. The lifetime trajectory for the knee (tibio-femoral) loading index is shown in Figure 5.4. Male household and sport activities had the highest relative joint load ratio. Occupational activity for females had the lowest ratio, approximately 50% of male household activity. Household ratios for both genders were higher than occupational. Hip and patella-femoral relative joint loading ratios showed similar trends to tibio-femoral by gender and activity strata (not shown).

5.4 Discussion

To our knowledge, this is the first attempt to quantify cumulative lifetime hip and knee joint force using joint loading units, an exposure that may prove to be an important measure to further understand the benefits and potential risks of PA at the population level. In particular, it may help to distinguish between energy expenditure and the biomechanical effects of different levels, types and combinations of PA that may be determinants of hip and knee joint health. Although additional work needs to be done in determining the reliability and validity of the lifetime joint force measure, the current

findings are encouraging. We were able to construct long-term trajectories for cumulative hip and knee joint force using data from an extensive online survey.

The reliability and validity of the lifetime survey on which the joint force measure is based was good (270). The joint force measure is new, however, and validation was limited here to comparing strata of the sample to expected or known differences from other PA measures. The lifetime EE (MET-hours per week) estimates were similar to several other studies reporting this metric (255, 256, 433). Sport/recreation and occupational activity accounted for more EE and joint force for men than women, while household EE and joint force were higher for women. In comparing the ratio of cumulative joint force to EE (joint loading index), male household and sport ratios were highest, while occupational ratios for both genders were much lower. These differences, as well as changes over the lifetime (by 5-year age period), were expected in this sample and provide face validity to the cumulative joint force and ratio metrics.

Of importance in introducing these new measures is that cumulative joint force has a biologically plausible relationship with hip and knee joint health. Moderate mechanical loading is necessary for homeostasis and to maintain healthy articular cartilage (20). Under normal physiological conditions, articular cartilage provides a nearly frictionless surface for the transmission and distribution of joint loads, exhibiting little or no wear over decades of use (160). However, physical activity and joint load can elicit either anabolic or catabolic processes depending on the intensity and duration, age at onset, amount and type of activity (20). Insufficient load through a joint compromises bone and cartilage health (13), while overloading the knee and hip joints could lead to cartilage breakdown and failure of ligamentous and other structural support (24). It is not known what level or type(s) of PA is optimal for joint protection and what may increase the risk of joint deterioration.

Some of the uncertainty may be the result of study designs that were not designed to test biological hypotheses about the cumulative effect or critical levels and combinations of different activities and the role of joint forces. Biologically, it seems likely that different activities have a cumulative effect, and that this effect depends on the mechanical forces transmitted through the joint (164). However, this theory has never been tested empirically. It is therefore important to attempt to quantify exposure to long term joint force.

There were two unexpected findings. First, overall lifetime EE and joint force estimates were slightly higher for women than men. Over the past several decades, women have increased both occupational and sport/recreational activity, while largely maintaining high levels of household activity. Women often spend forty-plus hours a week at a full-time job and anywhere from twenty-five to forty-five hours a week working in the home. We found that on average over the lifetime, women spend 4.23 hours per day in household activity. The only previous study to estimate *lifelong* joint load found that women differ in the quality and quantity of physical load and that a reduction of high physical load at home could probably lower the risk of knee OA later in life (180). It is possible that the high overall and household levels of joint force in women may contribute to the unexplained higher prevalence of knee and hip OA in women and is worthy of investigation in future studies.

A second unexpected finding was the relatively lower levels of sport-related EE and joint force. While early epidemiological studies based PA estimates primarily on occupation, PA has declined significantly in most occupations (243). Thus, since the 1990's there was a greater emphasis on investigating sports and leisure-time activity over the life course. However, we found that the occupation and household domains remain the most important in terms of accumulation of joint force and EE. This may in

part be due to the older average age of our cohort reflecting historical work patterns prior to the 1990's, and an age-related decline in sport related activity. Further we were able to measure sport-related activity relative to occupation and household activity – something few studies have compared. Previous studies investigating sport activity alone may not have concluded that sport levels were substantially lower than occupation and household - studies that considered sport activities alone may have been confounded by occupational and/or household physical activity-related joint force.

The EE estimates we found are consistent with previous literature (245, 255, 256, 433). In a study of the relationship between breast cancer and lifetime PA in 2,470 women (average age-56, BMI 27.5) (255), Friedenreich reported that women expended 127.8 MET-hours per week over the lifetime, while our study reported 126.0 MET-hours per week. Comparisons by type of activity were also similar by household (66.1 versus 70.5), occupational (48.1 versus 40. 5) and sport/recreational (13.6 versus 7.3). The differences may in part relate to the older age of women (average age 60.6 years versus 56 years) in our study, and are relatively small given that lifetime activity was measured. A similar study in men investigating lifetime PA and prostate cancer provided estimates that were also close to ours (256). In a criterion validity study assessing *past year* PA (using a questionnaire similar to the lifetime version our survey was based on), self-report data was correlated with data from accelerometers and activity logs (246). An acceptable level of reliability and validity was reported and the point estimates for EE for total and activity domain were similar to our estimates.

There are some limitations to this study. The interpretation of data using self-report PA measures requires caution and is limited to characterizing large groups of people rather than individuals because of large within-person variability and problems with recall (231, 242, 434). Despite these limitations, it has been repeatedly shown that

PA questionnaires are both practical and valid when used appropriately for large-scale epidemiologic studies (217, 231, 259, 261). Falkner studied the reliability of recall of PA in the distant past (30 years) and found acceptable levels of recall (262). Validity studies of PA questionnaires using accelerometers and/or physical activity logs have shown acceptable validity (259, 435). In a review focused on the limitations of PA questionnaires, Shephard concluded that while detailed interpretation and attempts to estimate precise dosage are inadvisable, use of data to monitor change in population activity and provide categorical estimates are of value (231). If the questionnaire is adequately designed for a particular population and has acceptable reliability and validity, the instrument should be able to rank-order adults by category of activity levels and by sociodemographic groups, providing a relative distribution of historical PA (242). Moreover, when used for etiologic analysis, a precise measure of an irrelevant variable (e.g., recent PA exposure) may be of little value, whereas an imprecise measure of a relevant variable may be useful.

We used a lifetime questionnaire that was based on existing validated instruments (245, 247), developed carefully using principles of construct validity, pilot-tested and validated in a separate study (270). Test-retest reliability with an 8-month interval was moderate to very good (ICC range 0.58 – 0.82). Construct validity was established in a series of sub-studies (using subjects drawn from the current study sample) with Spearman correlation coefficients ranging from 0.34 to 0.71.

The calculation of joint force was based in part on assigning typical peak forces for given activities or positions. The typical peak joint force is not the same for every individual and may not precisely represent the forces in our study subjects. Further, the biomechanical studies we reviewed to obtain typical force values presented *peak* joint force for that activity. The use of peak (as opposed to mean) force in the calculation may

result in overestimation of absolute lifetime joint load. However, as we are interested in relative and not absolute values, the biases introduced in the estimates would not significantly influence our findings.

The study had a number of strengths. A population-based study design and large sample size were employed. A novel feature of the questionnaire was its Internet-based administration that permitted the use of skip logic to maximize efficiency, minimize respondent burden, eliminate missing data and allow subject control of time management. This may have increased compliance, completion rates, accuracy and allowed capture of all relevant aspects of PA. We were also able to draw distinctions between time spent in different bodily positions that allowed for complete classification of the total volume of PA and loading aspects of joint force. The inclusion of household activities was critical because they account for most of the weekly EE in women. Lastly, we collected comprehensive data on PA that was that was quantitatively converted to joint loading units that will allow for the testing of biological hypotheses of the cumulative effect of joint force in hip and knee joint health.

In conclusion, lifetime joint force trajectories for the hip and knee were constructed from data using a validated survey, and followed expected trends by age, gender and PA domain, indicating the measure has face validity. The creation of a 'joint loading index' may be an important exposure that separates EE from joint force, and may reveal activity patterns that maximize health benefits while minimizing the risk of joint overload. Future research should examine the joint force-OA relationship and investigate the relationship of long-term joint force and local factors (e.g., alignment, injury, neuromuscular control). If the amount and type of PA associated with protective and more damaging loads can be identified, it could lead to relatively inexpensive and practical recommendations.

6: INFLUENCE OF LIFETIME HIP JOINT FORCE ON THE RISK OF SELF-REPORTED HIP OSTEOARTHRITIS: A COMMUNITY-BASED COHORT STUDY[5]

6.1 Introduction

The background and literature review for this chapter can be found in Chapter 2, and are briefly summarized below.

Hip osteoarthritis (OA) is among the most prevalent health problems for middle aged and older individuals and is a major cause of disability, health care utilization and diminished quality of life (3, 65). Although older age is a strong risk factor for hip OA (116), the role of other risk factors is less clear.

Studies of the relationship between physical activity (PA) and hip OA have been conflicting. Several studies have found a correlation between hip OA and occupational and/or sport demands (116, 166, 189), others have failed to find an association (171, 173) and one has shown a protective effect (186). The lack of agreement in part reflects variability in the parameters of PA measured - the domain (sport, occupation, household), period (e.g., current, past year), intensity, duration, type, measurement instruments used, and whether factors like injury and bodyweight were included. Few studies have attempted to estimate hip joint force (173, 186, 205), arguably the most important aspect of PA for joint health, and these studies have investigated primarily current or recent levels of sport-related activities.

[5] A version of Chapter 6 has been published in Osteoarthritis and Cartilage. Ratzlaff CR, Steininger G, Doerfling P, Koehoorn M, Cibere J, Liang MH, Wilson, DR, Esdaile J, Kopec J. Influence of lifetime hip joint force on the risk of self-reported hip osteoarthritis: a community-based cohort study. Osteoarthritis Cartilage 2011; 19: 389-398.

Measuring current or recent levels of PA are poor proxies for cumulative lifetime exposure (243), do not capture long-term joint forces and may miss etiologically important periods of exposure. Since both idiopathic and secondary hip OA have a long induction and asymptomatic latency period, historical exposure is of considerable interest and potentially allows for determination of etiologically important periods of disease development.

There are no studies of lifetime hip joint force from combined occupation, sport and household activity nor any that factor bodyweight into the joint force measure. Biologically, it seems likely that bodyweight, lifetime load and different types of activities have a cumulative effect on the mechanical forces transmitted through the joint (164, 165). We developed and validated a new lifetime PA survey measure to assess joint force (270) which has been used to study lifetime trajectories of hip and knee force in a Canadian sample (119). This study: 1) demonstrates the application of this measure of lifetime mechanical hip force on the risk of self-reported, medically-diagnosed hip OA and 2) examines the lifetime trajectory for the of age-specific periods of cumulative hip force exposure. Our primary hypothesis is that the risk of hip OA is associated with lifetime cumulative hip joint force.

6.2 Methods

Chapter 3 described the recruitment and enrolment of subjects (Figure 3.1).

For this prospective cohort study, participants reporting hip OA at baseline were excluded. Individuals who completed the baseline survey were contacted by email and letter for follow-up surveys at approximately one (May 2006) and two years (June 2007). Up to three reminders were sent to non-responders to initial contact, and efforts were made to locate individuals whose e-mail addresses had changed. Follow-up surveys

inquired about hip and knee joint health using the same questions as the baseline survey.

Case Ascertainment

Subjects were asked to report health-professional diagnosed hip OA on at least one of the two follow-up surveys. The method used and a validation sub-study were presented in Chapters 3 and 4.

Definition of Variables

Lifetime PA was estimated at baseline using the Lifetime Physical Activity Questionnaire (L-PAQ), whose development and validation was described in Chapter 2.Calculation of the Cumulative Peak Force Index (CPFI) in *bodyweight-hours*, a measure of lifetime hip joint force, was described in Chapter 3. In an article published in *Arthritis Care and Research* (119) a version of which is presented in Chapter 5, we demonstrated its feasibility, constructing lifetime force trajectories for hip and knee joint in a large Canadian sample. We were able to show a wide lifetime distribution of CPFI in the population that differed from PA measured by metabolic equivalent, and had expected differences in lifetime trajectory, gender and activity domains providing face validity to the measure.

Average Lifetime CPFI

Total hip CPFI for each 5-year age period was calculated to adjust for bodyweight over time. A lifetime average CPFI value was then calculated by determining the mean value of all 5-year age periods from age 20 to age at study entry.

Average CPFI for Each 5-Year Period (Age-Dependent Force)

To consider periods of hip force with potential etiologic relevance to development of hip OA, separate models were run for hip CPFI values for each 5-year age period separately, starting at age 20.

Domain – Specific Analysis

To assess the effect from each activity domain, the effect of hip force from sport/recreation, occupation and household activity was analyzed independently, and in models with adjustment for the other domains.

Body Mass Index (BMI) (kg/m^2)

Bodyweight was incorporated into the CPFI measure, as there is general agreement that weight affects OA via increased joint loading (147). In addition, BMI was investigated as an independent risk factor for hip OA, and adjusted for in models containing the CPFI measure. BMI was calculated for time of the baseline survey and for lifetime average, and categorized for analysis (<20.0, 20-24.9, 25.0-29.9, >30.0).

Covariates

The baseline questionnaire measured known hip health risk factors and included gender, age, weight, height, ethnicity (Asian, Black, Caucasian, First Nations, Hispanic, Other) and education (elementary, high school, post-secondary, trade/technical).

Injury

The following question from the baseline questionnaire was used to determine the presence of significant hip injury. *'Have you ever had a hip injury that required you to use a walking aid (e.g., cane or crutch) for at least one week?'* Follow-up questions included the side and age at injury (if more than one injury, the time of first injury was requested).

Statistical Methods

Hip OA status at the second follow-up was the endpoint. CPFI values for each activity were summed for sport, occupation, and household domains for each 5-year period of a person's lifetime to factor in changes in bodyweight over time, and these domain values were then summed to give a total CPFI value. Baseline variables and quintiles of the CPFI scores were assessed for crude relationship with hip OA at the time of the second follow-up. Reference categories were the lowest CPFI quintile, male sex, youngest age tertile (<58), normal BMI (20.0-24.9), and no previous injury.

Multivariate survival regression analyses were used to estimate the risk of hip OA according to the baseline risk factors and potential confounding factors. A Weibull model was chosen after examination of the baseline hazard showed a non-proportional, increasing hazard over time. Exponential models were run for comparison with Weibull models and showed similar results, however Weibull models, which allow scale and shape parameters to vary, had smaller residual deviance and are presented. The primary comparison was between the levels of lifetime average CPFI, with lowest quintile as the referent. Covariates were selected based on scientific knowledge and the conceptual framework of causal pathways to hip OA. Levels of gender, previous hip injury, and age were entered into the model as independent variables in regression to obtain adjusted effects. Analyses were carried out for the lifetime CPFI and by CPFI from each 5-year age period. Two additional adjusted analyses were carried out – one investigated the separate effect of occupational, sport and household CPFI (independently and adjusted for other domains); the other investigated the effect of BMI (independently and in models that included CPFI).

We conducted a sensitivity analysis to assess the potential effect of individual variability or reasonable error in choice of the peak force value assigned to each activity

(Appendix D) on the rank-ordering of subjects for the main outcome measure: lifetime average CPFI. A second sensitivity analysis assessed combinations of bodyweight (high/low) and total hours in PA (high/low) on hip OA, without use of the force multiplier. The effects of CPFI and covariates on the risk of hip OA were expressed as hazard ratios (HR), with 95% confidence intervals. Analyses were performed using SPSS version 17 (Chicago, Illinois) and R version 2.11.1 (Vienna, Austria).

6.3 Results

A total of 4,258 subjects registered and completed the baseline questionnaire. 1,750 registered but did not complete the survey; therefore, the completion rate was 71%. Participation rates (436) for those initially contacted were 9.7% for e-mail recipients and 2.5% for newsletter recipients. 76.8% of participants completed the survey in one sitting.

The study sample consisted of individuals aged 45-85 years of age, was predominantly Caucasian and more than two-thirds had some post-secondary education. BMI at baseline was 27.0 for males and 27.5 for females. Exclusions included 403 with diagnosed hip OA at baseline and 937 lost to follow-up or who did not complete both follow-up surveys, leaving 2,918 participants (Table 6.1).

Table 6.1 Subject Characteristics by Level of Lifetime Cumulative Peak Force Index (CPFI)

Lifetime Average Hip CPFI	N			Mean Age at Baseline†	Mean Weight at Baseline (kg)	Mean BMI at Baseline	Previous Hip Injury	Hip OA*
	Total	Men	Women					
Quintile 1	2918	1163 (40%)	1755 (60%)	62.0 (8.5)	74.9 (16.2)	26.9 (5.6)	14 (2.4%)	35 (6.0%)
Quintile 2				61.9 (7.3)	79.0 (17.4)	27.6 (5.4)	9 (1.5%)	26 (4.5%)
Quintile 3				62.0 (6.9)	81.9 (18.2)	28.5 (5.6)	21 (3.6%)	33 (5.7%)
Quintile 4				61.4 (6.8)	83.5 (17.6)	29.1 (5.7)	16 (2.7%)	32 (5.5%)
Quintile 5				60.6 (6.7)	85.1 (18.6)	29.7 (6.2)	29 (5.0%)	50 (8.6%)
Total				**61.6 (7.3)**	**80.9 (18.0)**	**27.3 (5.9)**	**89 (3.1%)**	**176 (6.0%)**

Values are the mean and SD unless otherwise indicated
†Baseline is time of baseline survey, 2005
*Hip Osteoarthritis at 1st (2006) or 2nd (2007) follow-up

The average time between the baseline survey and the first and second follow-ups were 36.01 weeks (SD 4.81) and 87.4 weeks (SD 5.88), respectively. Overall, there were 176 incident cases of hip OA – 43 in men and 133 in women.

Crude Analysis

Significant relationships were found between hip OA and previous hip injury, female sex, older age and the highest quintile of lifetime average CPFI. Crude analyses of hip OA and hip CPFI from each independent 5-year period over the lifetime revealed significant relationships for the highest quintile of CPFI for ages 30-34, 35-39, 40-44 and 45-49. Non-significant relationships were found between hip OA and BMI though there was a trend for increasing risk with increasing BMI. Our sample was predominantly Caucasian so we were unable to analyze ethnicity.

Adjusted Analysis

In the primary comparison, the risk of hip OA was significantly increased for the highest quintile of lifetime hip CPFI, compared to the lowest quintile (HR 2.32; 95% CI 1.31 to 4.12) (Table 6.2). Previous hip injury was associated with incident hip OA (HR 5.56; 95% CI 2.94 to 11.1). Oldest age tertile (>64) and female sex approximately doubled the risk of incident hip OA in all models.

Table 6.2 Adjusted Hazard Ratios for Hip OA from Lifetime Average CPFI*(quintiles) Adjusted for Sex, Previous Injury, Age and BMI† at Baseline

Variable	**Hazard Ratio**	Lower 95% CI	Upper 95% CI	**Hazard Ratio**	Lower 95% CI	Upper 95% CI
	No Adjustment for BMI			**Adjusted for BMI**		
Male	1.00			1.00		
Female	**2.65**	1.74	4.02	**2.34**	1.64	3.35
No Previous Injury	1.00			1.00		
Previous Injury	**5.56**	2.94	11.1	**4.42**	**2.49**	**7.85**
Age <58	1.00			1.00		
Age 58-64 (2nd tertile)	**1.80**	1.12	2.90	**1.66**	1.11	2.49
Age > 64 (3rd tertile)	**2.13**	1.33	3.42	**2.01**	1.34	3.00
BMI 20.0-24.9	-	-	-	1.00		
BMI< 19.9	-	-	-	0.78	0.23	2.58
BMI 25.0-29.9	-	-	-	1.13	0.74	1.73
BMI>30.0	-	-	-	1.40	0.91	2.17
Average CPFI.1	1.00			1.00		
Average CPFI.2	1.00	0.52	1.90	0.70	0.40	1.21
Average CPFI.3	1.29	0.69	2.40	0.88	0.51	1.52
Average CPFI.4	0.88	0.46	1.67	0.73	0.42	1.26
Average CPFI.5	**2.32**	1.31	4.12	1.53	0.94	2.51

*Referent categories are male sex, no previous hip injury, lowest tertile of age, normal BMI (20.0-24.9) and lowest quintile of CPFI in each activity domain

*CPFI = Cumulative Peak Force Index, a measure of lifetime exposure to cumulative hip force from all activity domains combined (sport, occupation, household)

†BMI at time of baseline survey 2005 (Similar trends were seen with lifetime average BMI, data now shown)

In the examination of the relationship between hip OA and age dependent force *(hip CPFI from each 5-year age period)*, the highest quintile of CPFI for three consecutive age periods had significant relationships with incident hip OA (Table 6.3) -

age 35-39 (HR 1.92; 95% CI 1.09 to 3.40), age 40-45 (HR 2.10; 95% CI 1.18 to 3.76) and age 45-50 (HR 1.85; 95% CI 1.03 to 3.36).

Table 6.3 Adjusted Hazard Ratios for Hip OA from Lifetime Average CPFI*(quintiles) by Age Category

Variable	**Hazard Ratio**	Lower 95% CI	Upper 95% CI	**Hazard Ratio**	Lower 95% CI	Upper 95% CI	**Hazard Ratio**	Lower 95% CI	Upper 95% CI
	Age 35-39			**Age 40-44**			**Age 45-49**		
Male	1.00			1.00			1.00		
Female	**2.60**	1.71	3.96	**2.61**	1.72	3.99	**2.63**	1.74	4.00
No Previous Injury	1.00			1.00			1.00		
Previous Injury	**5.56**	2.86	11.1	**5.56**	2.80	11.10	**5.89**	3.00	11.10
Age <58	1.00			1.00			1.00		
Age 58-64 (2nd tertile)	**1.82**	1.13	2.93	**1.81**	1.13	2.93	**1.74**	1.08	2.79
Age > 64 (3rd tertile)	**2.17**	1.35	3.48	**2.12**	1.32	3.41	**1.98**	1.24	3.17
Average CPFI.1	1.00			1.00			1.00		
Average CPFI.2	0.77	0.40	1.48	0.84	0.43	1.62	1.20	0.63	2.31
Average CPFI.3	0.92	0.49	1.73	1.02	0.54	1.95	0.77	0.40	1.49
Average CPFI.4	0.80	0.42	1.51	1.00	0.52	1.90	1.54	0.84	2.85
Average CPFI.5	**1.92**	1.09	3.40	**2.10**	1.18	3.76	**1.85**	1.03	3.36

*Referent categories are male sex, no previous hip injury, lowest age tertile and lowest activity quintile of lifetime average hip CPFI
*CPFI = Cumulative Peak Force Index, a measure of lifetime exposure to cumulative hip force from all activity domains combined (sport, occupation, household)
*In age-specific models, lifetime average hip CPFI from 5-year age periods was the key exposure variable (in quintiles). Separate models (adjusted) were run for each 5-year period of the lifetime.

In the domain-specific analysis, there was a trend for increasing risk with increasing levels of lifetime occupational force though none were significant in independent models or those adjusted for other domains (Tables 6.4 and 6.5). There was no evidence of trend with level of sport or household activity.

Table 6.4 Adjusted Hazard Ratios for Hip OA from Lifetime Average CPFI* (quintiles), by Independent Activity Domain

Variable	**Hazard Ratio**	Lower 95% CI	Upper 95% CI	**Hazard Ratio**	Lower 95% CI	Upper 95% CI	**Hazard Ratio**	Lower 95% CI	Upper 95% CI
	Occupation			**Domestic**			**Sport**		
Male	1.00			1.00			1.00		
Female	**2.75**	**1.90**	**3.98**	**2.34**	**1.58**	**3.47**	**2.41**	**1.65**	**3.52**
No Previous Injury	1.00			1.00			1.00		
Previous Injury	**4.98**	**2.78**	**8.91**	**5.10**	**2.84**	**9.14**	**5.01**	**2.80**	**8.97**
Age <58									
Age 58-64 (2nd tertile)	**1.65**	**1.09**	**2.50**	**1.64**	**1.08**	**2.50**	**1.63**	**1.08**	**2.48**
Age > 64 (3rd tertile)	**1.98**	**1.31**	**2.99**	**1.93**	**1.27**	**2.91**	**1.88**	**1.25**	**2.85**
Average CPFI.1	1.00			1.00			1.00		
Average CPFI.2	1.09	0.65	1.85	0.85	0.49	1.49	1.44	0.86	2.42
Average CPFI.3	1.26	0.74	2.13	1.01	0.58	1.75	0.96	0.56	1.65
Average CPFI.4	1.48	0.88	2.50	0.99	0.57	1.72	1.45	0.86	2.45
Average CPFI.5	1.67	0.98	2.85	1.07	0.62	1.85	1.07	0.61	1.89

*Referent categories are male sex, no previous hip injury, lowest age tertile and lowest activity quintile of lifetime average hip CPFI

*CPFI = Cumulative Peak Force Index, a measure of lifetime exposure to cumulative hip force from all activity domains combined (sport, occupation, household)

*In domain-specific models, lifetime average hip CPFI from 5-year age periods was the key exposure variable (in quintiles). Separate models (adjusted) were run for each domain separately

Table 6.5 Adjusted Hazard Ratios for Hip OA from Lifetime Average CPFI* (quintiles), Adjusted for Sex, Previous Injury, Age and Other Domains

Variable	Hazard Ratio	Lower 95% CI	Upper 95% CI
Male	1.00		
Female	**2.58**	1.73	4.02
No Previous Injury	1.00		
Previous Injury	**4.83**	2.69	8.64
Age <58	1.00		
Age 58-64 (2nd tertile)	**1.77**	1.12	2.92
Age > 64 (3rd tertile)	**2.15**	1.29	3.33
Sport CPFI.1	1.00		
Sport CPFI.2	1.44	0.82	2.33
Sport CPFI.3	0.91	0.53	1.60
Sport CPFI.4	1.44	0.81	2.35
Sport CPFI.5	1.00	0.56	1.79
Domestic CPFI.1	1.00		
Domestic CPFI.2	0.77	0.45	1.39
Domestic CPFI.3	0.94	0.54	1.65
Domestic CPFI.4	0.90	0.52	1.60
Domestic CPFI.5	0.98	0.56	1.71
Occupation CPFI.1	1.00		
Occupation CPFI.2	1.11	0.63	1.83
Occupation CPFI.3	1.30	0.72	2.11
Occupation CPFI.4	1.58	0.86	2.52
Occupation CPFI.5	1.80	0.95	2.82

*Referent categories are male sex, no previous hip injury, lowest tertile of age and lowest quintile of CPFI in each activity domain

*CPFI = Cumulative Peak Force Index, a measure of lifetime exposure to cumulative hip force

In domain specific analysis of age dependent force, only the highest levels of occupational force showed a tendency for relationship with hip OA, and this was significant for age 35-40 (data not shown).

In adjusted models investigating the independent effect of BMI, there was a trend for increasing baseline and lifetime average BMI to increase risk of hip OA, but these did not reach significance. Including BMI in the adjusted analysis, resulted in attenuation of the force effect, such that no levels of CPFI were significantly associated with hip OA (Table 6.2).

A sensitivity analysis was conducted to assess the impact of the force multiplier value for each activity (Appendix D) on rank-ordering of subjects in the CPFI. The multiplier for each activity was varied by ±20% to form an upper and lower estimate, while holding the other eight constant, and the percent of subjects moving from one category (quintile) of lifetime CPFI to another was tabulated for each scenario. In most cases, less than 3% of subjects were reclassified, with the common activities of walking (5% reclassified) and standing (3% reclassified) the highest. For each re-calculation of the CPFI, multivariate survival models assessed the impact on the HR for hip OA. HRs for the 5th quintile of lifetime average CFPI (compared to 1st quintile) varied by up to 10% but the significance did not change. A second sensitivity analysis assessed combinations of BW (high/low) and total lifetime hours in PA (high/low) on hip OA, without the force multiplier. The combination of high BW/high PA hours (compared to low BW/low hours) was significantly related to hip OA, but the effect was not as strong as in the CPFI models, and the model did not fit as well based on larger residual deviance.

6.4 Discussion

This prospective study on a large cohort of adults presents a newly proposed measure of lifetime mechanical hip joint force based on hours in PA, bodyweight and typical joint force for specific activities and relates it to medically diagnosed self-reported hip OA. We provide evidence that PA is generally safe for the hip joint, but that very high lifetime force, from all activity domains combined, is a risk for hip OA. These novel findings require confirmation in other populations.

We observed that previous hip injury is a risk for hip OA, providing prospective evidence on a relationship that has previously been unclear (38-42). The findings are consistent with previous studies that show older age (38, 437) and female gender (438) are risk factors for hip OA. The results of this study must be compared cautiously with previous studies due to differences in study design, how subjects were assembled, and how exposures and outcomes were measured. In particular, no other studies evaluating PA and hip OA have used the Internet for data collection, classified PA by a calculated lifetime joint force variable or reported total PA from all three activity domains (40, 166, 173, 186, 193, 194, 205).

The strengths of our study include its community-based, prospective design, large sample, and detailed measurement of PA that allowed calculation of total hip force over the lifetime. Despite a relatively short follow-up period, we had 176 incident cases of hip OA. We used a validated instrument to assess PA prior to OA diagnosis. Another strength of our study was the inclusion of household activity as in the general population, household activity is responsible for more PA than sport/recreation (119), the most well-studied form of PA. This study is the first to evaluate hip joint force from all three domains. Long-term PA and joint force data has not been collected in any of the prospective studies, and in only several case-control studies. Finally, this study is the

first quantification of the biomechanical effects and dose-response of physical activities on the hip joint.

A novel feature of the PA questionnaire was its web-based administration that permitted the use of skip logic to maximize efficiency, minimize respondent burden, eliminate missing data and allowed subjects to control time spent on answering questions. The prospective collection of outcome data reduced recall bias and allowed us to model the direction of causal associations.

Some caveats and limitations require comment. Self-reported diagnosis may result in misclassification. In a validation study conducted in a sub-sample of the cohort (Chapter 4), the sensitivity (0.81), specificity (0.94), positive predictive value (0.61), negative predictive value (0.98), and kappa (0.65) were consistent with other studies (101, 166, 418). It is probable that false positives include subjects with early OA not captured by the ACR criteria, and other causes of hip symptoms. From a patient perspective whatever the cause, these symptoms are relevant, affect quality of life and are potentially linked to the exposures in this study.

The decision to include inactive individuals and/or to use the lowest quintile of joint force (potential at-risk groups for OA) as the referent category may have resulted in attenuation of the force effect and masked a possible risk of hip OA from inactivity. Since moderate mechanical loading is necessary for homeostasis and to maintain healthy articular cartilage (20), low loading may elicit catabolic processes that affects cartilage health (439). Though there is scarce epidemiologic evidence, some animals studies and observations in humans subject to immobilization (e.g., after spinal cord injury or post-operatively) have provided evidence that reduced loading conditions can lead to reduced thickness and structural changes in cartilage (439-441).

Our findings may not be generalizable to other populations. The study sample was fairly well educated, largely Caucasian, Internet users and probably health seeking - this method may not be as effective in low income populations, with decreased access to medical care. Self-selection implies that the nature of the bias cannot be known with certainty (442). Studies of those who enrol in online research show they are more likely to be older, female and have higher socioeconomic status (431). Further, response rates for Internet surveys vary from traditional rates, depending on the denominator used, making external validity of results more challenging to interpret. In online surveys, there is no single response rate (436). Rather, multiple metrics for calculating a response rate have been defined such as the participation rate and completion rate (436). We did not do separate analyses by age or mood disorders - some data suggest that age (<65 years) and mood can effect case definition by lowering specificity (101, 443). The addition of radiographs might enhance sensitivity (slightly) and specificity, but are poorly correlated with symptoms and function (444, 445). The aim of this study was not to describe characteristics of, or estimate disease prevalence in, the general population but rather to assemble subjects to test hypotheses about PA and joint health in a large sample of subjects who met criteria for a disease and those who did not, sampled in the identical way (internal validity).

While our study measured lifetime PA using an instrument validated in a sub-sample of the current study (270), self-reported PA measures require cautious interpretation because of large within-person variability and problems with recall (231, 242, 434). The survey was not validated specific to age ranges and reduction in recall occurs over time. Though there is evidence recall of PA in the distant past (30 years) is reliable (262), it is important that the measure not be construed as an absolute measure of risk but as a way to rank order an exposure. Despite these limitations, PA

questionnaires are practical and valid when used for large-scale epidemiologic studies (217, 231, 248).

The CPFI, a time-force-bodyweight product, was a stronger predictor of incident hip OA than its component parts alone. Sensitivity analyses revealed that the CPFI measure was robust to ±20% variation in the force multiplier for each activity and that including the multiplier in the CPFI (versus considering only BW and total PA hours) increased the strength of the association and improved the model. Bodyweight was incorporated into the CPFI as there is general agreement that increased weight impacts OA via increased dynamic joint loading (147). However, since excess bodyweight may be part of a metabolic causal pathway to OA independent to force (446), BMI was adjusted for in models that contained the CPFI. This resulted in attenuation of the hip force effect on OA – point estimates for the 5th quintile of total force remained at HR of >1.5, but were non-significant. This is not surprising since weight was already part of the CPFI – adjusting for BMI likely reduces the effect of weight in the CPFI. However, relatively few of our subjects had BMI >30, and there was a trend (non-significant) for increasing risk with higher BMI, supporting continued investigation into its etiologic role.

Our finding of an increased risk of hip OA for the top quintile of joint force from all activity combined is generally consistent with systematic reviews (26, 203, 207). Sporting activity formed a small fraction of overall PA in our sample, with occupational and household contributing much more (119). There have been several prospective cohort studies investigating the role of PA on the risk of hip OA showing a moderate risk for heavy occupational activity (39, 41, 447) and no (41, 173, 188) or moderate (166) risk for sporting activities.

Our results indicate that the vast majority of PA is safe with regard to hip OA. However, very high levels of force, particularly from occupation, may be a risk. There

may be an upper limit to cumulative joint force that facilitates normal cartilage metabolism. While it must be interpreted cautiously because of the possibility of confounding due to reduction in recall of historic PA, we found ages 35-50 years may be a vulnerable period for hip OA. This period corresponds to a time when age-related cartilage changes have occurred (117, 118) and where force from occupation and household activity are at their highest lifetime values (119). High joint force during this period combined with less resilient cartilage and decreased repair capacity may be a sensitive period for initiation of OA. This finding is consistent with previous studies reporting certain sports and occupations that increase loading to the hip joint before the age of 50 years increase the risk of hip OA (448, 449).

In conclusion, a newly proposed measure of lifetime mechanical hip force was used to estimate the risk of self-reported, medically diagnosed hip OA. While there are limitations, this prospective study suggests that lifelong physical activity is generally safe. High levels of lifetime force from all domains combined, and in particular from occupational forces, may be important in the etiology of hip OA. Prevention efforts may best be directed at occupations requiring high physical demands. Future research should improve the estimation and validity of hip force measurement in new populations, and examine different activity types separately to identify high-risk activities.

7: THE ASSOCIATION BETWEEN LIFELONG JOINT FORCE FROM PHYSICAL ACTIVITY, LOCAL JOINT FACTORS AND KNEE OSTEOARTHRITIS[6]

7.1 Introduction

The background for this study was presented in Chapter 2 of this thesis. The large burden of knee OA on society, in terms of pain, disability and economic cost was described, as was the lack of a clear understanding of the role of modifiable risk factors that could lead to a primary or secondary prevention strategy. The gaps in the literature in terms of PA and its relationship with knee OA were also reviewed in Chapter 2. There are four main gaps:

- a lack of studies measuring historic PA , a key variable given the long latency and asymptomatic induction period of OA
- a lack of studies examining loads applied to the joint using joint loading units, that allows for assessment of cumulative force from PA, including dose-response
- a lack of studies investigating the effect of household PA on the risk of knee OA
- a lack of studies on the potential association of local joint factors with knee OA

[6] A version of this manuscript is in preparation for journal submission under the title above, with the candidate as first author.

To address these issues a prevalence study was conducted to 1) evaluate the association between levels of lifetime average knee joint force and knee OA in a large Canadian sample of community dwelling adults, and 2) investigate lower limb alignment and neuromuscular control (coordination and hypermobility) as risk factors for knee OA.

7.2 Methods

Design

A prevalence study using a cross-sectional design was conducted, as there were an insufficient number of incident knee OA cases to power the study to meet the objectives of this chapter. To compile the dataset, subjects reporting OA at any of the three time points (Figure 3.2) were identified as cases. Baseline exposure data was used. While the inclusion of prevalent cases could potentially limit the ability to delineate cause and effect, the approach was justified on several grounds and steps were taken to guard against reverse causality. First, increasing the number of cases allowed for greater study power to assess gender-specific relationships between PA and OA while including a number of covariates, dose-response relationship of PA with OA, and association of PA with joint vulnerability factors that had a skewed distribution in the population (i.e., a relatively small number of exposed). Second, since four putative risk factors were investigated for the first time (lifelong total joint force, malalignment, hypermobility and coordination), this study could be considered exploratory. Third, the relationship between the historic PA measured in this study (up to age 50, as discussed in Methods section below) and the time of diagnosis for the vast majority of cases is separated in time, providing some protection against reverse causality. Fourth, the highest levels of lifetime PA for most people occur prior to the age of 50 (119). Lastly, since OA is not a curable condition, prevalence is a relatively stable reflection of disease frequency.

Case Ascertainment

Subjects were asked to report on a medical diagnosis of knee OA and 'knee pain, aching and stiffness' as described in Chapter 4. An algorithm was used to ascertain knee OA cases, requiring that subjects report both 'health-professional diagnosed knee OA' and 'pain, aching or stiffness on most days' at any of the 3 time-points (baseline, 1st and 2nd follow-up). The questionnaire item on health-professional diagnosed OA informed subjects that OA was distinct from other MSK diseases (e.g., rheumatoid arthritis, osteoporosis), and a response confirmation to this question was required in a follow-up item.

The reliability and validity of self-reported knee OA was carried out in a sub-study and described in Chapter 4. Using the American College of Rheumatology (ACR) clinical classification criteria for knee OA (425) as a diagnostic referent, sensitivity was 0.76, specificity 0.98, positive predictive value 0.87 and negative predictive value 0.95. Kappa value was 0.76 indicating substantial agreement beyond chance (427). Our findings are consistent with other studies comparing self-report medically diagnosed OA and clinical OA (101, 166, 418).

Definitions of Variables

PA Exposure

Lifetime PA was estimated at baseline using the Lifetime Physical Activity Questionnaire (L-PAQ), as has been described in previous sections of this thesis. The development and validation of the lifetime PA questionnaire was described in Chapter 2. The methods for the assessment of PA and calculation of joint force have been described in Chapters 3, 5 and 6. The calculation of the joint force variable (CPFI) for the knee is briefly described below.

Cumulative Peak Force Index (bodyweight-hours)

To obtain a measure of cumulative joint force at the knee, a cumulative peak force index (CPFI) score was estimated for the knee as the product of time spent in a specific activity (total lifetime hours), bodyweight (BW) and typical peak knee joint force for that activity (%BW), [i.e., CPFI score (bodyweight-hours) = total lifetime hours * bodyweight * typical peak knee joint force, per each activity]. The approach was identical to the hip as described in Chapter 6, except that for the third component of the calculation, typical knee joint force assigned to each activity, replaced typical joint forces for the hip. As per the hip, this value was determined for the knee after an extensive literature review (409, 411, 412, 414, 415, 417, 450-452) that prioritized in vivo studies and incorporated judgments about data quality and study rigor (Appendix D). Data were synthesized and a consensus achieved by a panel of experts from the fields of biomechanical engineering, rheumatology, and musculoskeletal epidemiology.

The force exposure variable was operationalized as exposure prior to the age of 50. The main reason for this was to capture the primary PA exposure prior to the diagnosis of OA (and first symptoms) for the vast majority of cases, and to minimize the effects of sub-clinical, undiagnosed or early OA on PA patterns. Support for this approach was also drawn from the previous study on lifetime trajectories (Chapter 5) that revealed that peak exposure window for PA is prior to 50, being at its highest lifetime levels from ages 30-45.

Covariates

Age, gender, body mass index (BMI), previous, ethnicity and education level were measured as described in chapter 6 for the hip study.

Injury

The following question from the baseline questionnaire was used to determine the presence of significant knee injury. *'Have you ever had a knee injury that required you to use a walking aid (e.g., cane or crutch) for at least one week?'* Follow-up questions included the age at injury (if more than one injury, the time of first injury was requested). Only injuries that occurred before the diagnosis of OA were included in analysis.

Alignment

The baseline questionnaire included items on lower limb alignment, asking subjects to assess the standing presence of bow legs, knock-knees or straight leg, a measure described in chapter 4. A diagram was provided depicting levels of alignment (bow-legged, neutral, knock-kneed) with an ordinal scale for response (appendix G). A second ordinal scale using the same parameters was used to inquire about lower limb alignment at age 20. For the purpose of analysis, all bow legged and knock-kneed categories were combined to form varus and valgus groupings respectively. Alignment at age 20 was used in the primary analysis to protect against reverse causality, since there is evidence that OA may result in increasing malalignment.

Coordination

The coordination sub-scale of the Physical Self-Description Questionnaire (PSDQ), a self-administered validated, reliable instrument (60, 369), was used to measure coordination. The sub-scale was described in Chapter 2 and consists of six items (see Appendix A). Each item used a 6-point Likert scale (false, mostly false, more false than true, more true than false, mostly true and true) and were scored from one to six. The average of all six scores was calculated and entered into analysis as a continuous variable, as this was how the score was validated (60).

Hypermobility

The Hypermobility Questionnaire (64) was used to assess for the presence of joint hypermobility syndrome (JHS), a recognized clinical condition that has been associated with diminished proprioception (57) and with OA (61-63). The questionnaire has five items, requires a yes/no response to each item, and is described in more detail in Chapters 2 and 4 (Appendix B). Subjects with a 'yes' response to at least 2 of 5 questions are categorized as JHS positive.

Statistical Methods

The prevalence of knee OA and covariates for the study sample were calculated. As described in chapter 6, CPFI values for each activity were summed for sport, occupation, and household domains for each 5-year period of a person's lifetime to factor in changes in bodyweight over time, and these domain values were then summed to give a total CPFI value (see Chapter 5). For the total force (CPFI) variable, subjects were categorized into quintiles of exposure for the overall distribution, prior to stratification by gender. For the domain specific analysis, the quintiles were based on the relative distribution within each domain (occupation, household, sport), again prior to stratification by gender (for example, quintile 5 for occupation was at the same joint loading level for both sexes). Baseline variables and quintiles of the knee CPFI scores were assessed for crude relationship with knee OA. Crude odds ratios were calculated for the relationships between knee OA and joint force variables and other study covariates. Potential collinearity and interaction between covariates was examined on a bivariate basis.

Covariates were selected based on scientific knowledge and the conceptual framework of causal pathways to knee OA. Factors associated with an increased risk of knee OA, which also could be confounders, such as age, previous injury, BMI were

adjusted for in all the analyses, as were the novel measures of joint vulnerability. The potential effect of one domain on another (e.g., occupational activity when assessing the sport – OA relationship) was also potentially confounding and included. Men and women were examined separately because of known gender differences in disease prevalence, physical activity profiles, injury rates and BMI. Reference categories were the lowest CPFI, youngest age tertile (<58), normal BMI (20.0-24.9), no previous injury, neutral leg alignment and absence of hypermobility syndrome.

Multiple logistic regression was used to examine if levels of total knee CPFI were associated with a risk of knee OA, controlling for age, previous injury, BMI, leg alignment, coordination and presence of hypermobility syndrome. As with the hip study in Chapter 6, an additional adjusted analyses was carried out that investigated the separate effect of occupational, sport and household CPFI (adjusted for the other domains). Analyses were performed using SPSS version 18 (Chicago, Illinois).

7.3 Results

Subject characteristics for the sample have been previously described in Chapters 4 and 5 (Tables 4.1, 5.1), and frequencies of outcome, exposure and covariates for this study are provided in Tables 7.1 and 7.2. The prevalence of knee OA was 22.4 % for the sample overall - 17.8% for men and 25.1% for women (Table 7.1). Twenty-six percent of the sample were of normal BMI, with approximately 72% being either overweight (39.9%) or obese (31.5%). More men than women (47.7 to 36.1%) were overweight and more women than men were obese (33.4 to 29.5%). Twenty percent had a history of previous knee joint injury (24% in men, 18% in women). Neutral lower limb alignment was similar in both sexes (83% men, 86% women), but malalignment was predominantly in the varus direction for men (14%) versus women (6.5%). The average coordination score (1-low, 6-high) was 3.9 among those with knee

OA and 4.5 among those without. Twenty-two percent of the sample was classified as having hypermobility syndrome, but it was much more common in women (28.4%) than men (11.8%).

The prevalence of subjects in occupational and household quintiles varied substantially by gender (Table 7.2). For example, in the male household strata, the largest prevalence (36.3%) was in the lowest (referent) quintile of exposure, while the smallest prevalence (6.2%) was in the highest quintile of exposure. For women, the largest prevalence (27.5%) was in the highest quintile of exposure and the smallest prevalence in the referent quintile (11.1%). For occupational force, these relative proportions were reversed by gender, though the percentages were slightly different (Table 7.2).

Crude ORs provided evidence that older age, previous knee injury, malalignment in women, obesity in men and overweight and obesity in women were associated with knee OA (Table 7.1). Total knee force from all domains combined (Table 7.1) in men (4th and 5th quintiles) and women (3rd, 4th and 5th quintiles) were crudely related to knee OA, as was occupation and household activity in both men and women (Table 7.2). Having higher coordination was protective against knee OA (crude OR 0.62, 95% confidence interval 0.57–0.68). There was no association between hypermobility syndrome, malalignment in men and underweight with knee OA.

Table 7.1 Crude and Adjusted† Odds Ratios for Knee OA*, by Sex

		Males (n=1575)			Females (n=2694)		
		Prevalence (%)	Unadjusted OR (95% CI)	Adjusted OR† (95% CI)	Prevalence (%)	Unadjusted OR (95% CI)	Adjusted OR† (95% CI)
Knee OA*		17.8			25.1		
Age	<57	24.5	1.00	1.00	38.6	1.00	1.00
	58-64	34.6	1.13 (0.79, 1.63)	1.33 (0.82, 2.14)	32.6	1.11 (0.90, 1.37)	1.56 (1.14, 2.13)
	65+	40.9	1.49 (1.06, 2.10)	2.04 (1.28, 3.24)	28.0	1.28 (1.04, 1.59)	2.11 (1.54, 2.90)
Knee injury	No	76.1	1.00	1.00	81.7	1.00	1.00
	Yes	23.9	3.75 (2.85, 4.92)	3.76 (2.58, 5.46)	18.3	2.97 (2.42, 6.65)	3.67 (2.73, 4.94)
BMI+	Normal	22.0	1.00	1.00	28.9	1.00	1.00
	Underweight	0.8	1.37 (0.29, 6.47)	9.23 (0.90, 70.9)	1.6	1.21 (0.53, 2.80)	1.08 (0.31, 3.76)
	Overweight	47.7	1.19 (0.82, 1.74)	1.22 (0.74, 1.99)	36.1	1.79 (1.39, 2.31)	1.84 (1.31, 2.59)
	Obese	29.5	2.48 (1.70, 3.61)	2.55 (1.52, 4.28)	33.4	3.48 (2.72, 4.44)	2.71 (1.92, 3.82)
Alignment++	Neutral	82.7	1.00	1.0	85.9	1.00	1.0
	Varus	14.0	1.26 (0.80, 1.99)	1.18 (0.73, 1.91)	6.5	1.71 (1.11, 2.64)	2.16 (1.33, 3.52)
	Valgus	3.3	1.81 (0.81, 4.04)	1.26 (0.51, 3.11)	7.6	2.65 (1.79, 3.93)	2.33 (1.50, 3.63)
Coordination							
			0.76 (0.65, 0.88)	0.77 (0.65, 0.91)		0.59 (0.53, 0.65)	0.64 (0.56, 0.73)
Hypermobility	No	88.2	1.00	1.00	71.6	1.00	1.00
	Yes	11.8	1.34 (0.83, 2.16)	0.99 (0.65, 1.70)	28.4	0.91 (0.70, 1.18)	0.99 (0.71, 1.38)

		Males (n=1575)			Females (n=2694)		
		Prevalence (%)	Unadjusted OR (95% CI)	Adjusted OR† (95% CI)	Prevalence (%)	Unadjusted OR (95% CI)	Adjusted OR† (95% CI)
Total knee	CPFI.1	16.8	1.00	1.00	21.9	1.00	1.00
(TF) force	CPFI.2	21.4	1.08 (0.67, 1.76)	1.04 (0.57, 1.90)	19.2	1.14 (0.84, 1.55)	1.05 (0.69, 1.60)
	CPFI.3	23.7	1.16 (0.73, 1.85)	1.16 (0.63, 2.12)	17.8	1.44 (1.07, 1.94)	1.17 (0.78, 1.77)
	CPFI.4	22.0	1.76 (1.12, 2.76)	1.37 (0.76, 2.48)	18.8	1.38 (1.03, 1.86)	1.29 (0.85, 1.94)
	CPFI.5	16.2	2.48 (1.56, 3.95)	2.03 (1.08, 3.80)	22.3	1.96 (1.49, 2.59)	1.67 (1.11, 2.49)

*self-reported medical diagnosis of knee OA, plus pain, aching or stiffness most days
†Adjusted for all other covariates in table
+ BMI categories: normal (20-24.9), underweight (<20), overweight (25-29.9), obese (>30.0)
++Alignment at age 20

Table 7.2 Crude and Adjusted† Odds Ratios for Knee OA* by Activity Domain

		Males (n=1575)			Females (n=2694)		
		Prevalence (%)	Unadjusted OR (95% CI)	Adjusted OR† (95% CI)	Prevalence (%)	Unadjusted OR (95% CI)	Adjusted OR† (95% CI)
Knee OA*		17.8			25.1		
Sport knee	CPFI.1	12.3	1.00	1.00	25.1	1.00	1.00
(TF) force	CPFI.2	14.7	0.78 (0.44, 1.36)	0.72 (0.32, 1.62)	23.5	0.91 (0.69, 1.22)	0.93 (0.61, 1.43)
	CPFI.3	16.3	0.72 (0.41, 1.25)	0.85 (0.38, 1.89)	22.5	0.79 (0.59, 1.05)	0.80 (0.51, 1.24)
	CPFI.4	23.0	1.00 (0.61, 1.63)	1.01 (0.50, 2.03)	18.0	0.82 (0.60, 1.12)	0.84 (0.52, 1.35)
	CPFI.5	33.6	1.14 (0.72, 1.81)	0.95 (0.49, 1.87)	11.0	0.69 (0.47, 1.01)	0.60 (0.34, 1.07)
Occ knee	CPFI.1	7.5	1.00	1.00	27.6	1.00	1.00
(TF) force	CPFI.2	18.4	1.38 (0.68, 2.83)	1.80 (0.60, 5.40)	21.0	1.28 (0.97, 1.69)	1.11 (0.71, 1.75)
	CPFI.3	17.3	1.69 (0.83, 3.43)	1.49 (0.49, 4.55)	21.7	1.21 (0.92, 1.60)	1.01 (0.65, 1.56)
	CPFI.4	24.2	2.06 (1.04, 4.06)	3.33 (1.15, 9.65)	17.5	1.30 (0.97, 1.74)	0.97 (0.60, 1.57)
	CPFI.5	32.7	2.47 (1.27, 4.78)	2.60 (0.99, 7.44)	12.4	1.90 (1.39, 2.58)	1.23 (0.73, 2.06)
House knee	CPFI.1	36.3	1.00	1.00	11.1	1.00	1.00
(TF) force	CPFI.2	29.9	1.09 (0.76, 1.56)	0.93 (0.56, 1.55)	14.6	0.98 (0.65, 1.47)	1.29 (0.66, 2.53)
	CPFI.3	17.8	1.29 (0.80, 1.94)	1.26 (0.70, 2.27)	21.2	1.09 (0.75, 1.58)	1.59 (0.85, 2.98)
	CPFI.4	9.8	1.00 (0.59, 1.69)	0.52 (0.24, 1.16)	25.6	1.30 (0.91, 1.85)	1.66 (0.91, 3.06)
	CPFI.5	6.2	1.67 (0.95, 2.94)	0.94 (0.40, 2.23)	27.5	1.75 (1.23, 2.47)	2.24 (1.23, 4.10)

*self-reported medical diagnosis plus pain, aching or stiffness most days
†OR's adjusted for age, knee injury, BMI, lower limb alignment, coordination, hypermobility (as defined in table 7.1) and other activity domains

Adjusted ORs for risk factors on knee OA obtained from multiple logistic regression are presented in Tables 7.1 and 7.2. The strength of association for knee OA and total lifetime force remained significant only for the highest quintile in both men and women. In domain-adjusted models, only the highest quintile of household force in women and occupational force in men remained related to OA. In no models was sport / recreational force related to knee OA. After adjustment, older age, injury, high BMI, coordination and malalignment in women remained significantly related to knee OA. Being overweight doubled the risk of knee OA for women but was not related to knee OA in men. Obesity was a two to three fold risk for knee OA in both sexes.

7.4 Discussion

This prevalence study on a large sample of Canadian adults presents a newly proposed measure of lifetime mechanical knee joint force based on hours in PA, bodyweight and typical knee joint force for specific activities and relates it to self-reported knee OA (medical diagnosis and the presence of pain, aching or stiffness on most days). We provide evidence that lifelong PA is generally safe for the knee joint, but that very high force from lifelong total force, and from high levels of household activity in women and occupational activity in men, are a potential risk for knee OA. The results held after adjustment for known risk factors. These novel findings require confirmation in other populations and in longitudinal studies.

The results of this study must be compared cautiously with previous studies due to its cross-sectional design, how subjects were assembled, and how exposures and outcomes were measured. For example, no other studies evaluating PA and knee OA have used the Internet for data collection or have completely classified PA in terms of a joint loading variable over the long term, perhaps partly explaining inconsistent results

from these past studies (40, 166, 173, 186, 193, 194, 205). Of note, subjects with OA may have over-reported prior PA exposure because they perceive that PA caused their OA (recall bias), potentially increasing the risk estimates (186). Since this type of bias threatens most prevalence studies, (and will be discussed later in this section), emphasis should be placed on recent high-quality cohort studies evaluating the association between PA and OA. A recent prospective cohort study with 22 year follow up using physician-diagnosed OA, reported an adjusted OR for the heaviest category of physical demands at work compared with the lightest category of 18.3 for knee OA (198). Verweij et al. (168) during 12 years of follow-up, recently reported that 463 of 1678 respondents (28%) developed clinical knee OA, and that a high mechanical strain score (HR 1.43, 95% CI 1.15-1.77) was associated with an increased risk of knee OA after adjustment for a number of covariates. Several studies from the Framingham cohort suggest that job activities may cause as much as 15% to 30% of knee OA in men (170, 199). Felson et al. (170) reported that elderly persons (average age 70) in the highest quartile of PA at a baseline examination had over three times the risk of developing radiographic knee OA nine years later, when compared with those in the lowest quartile. McAlindon et al. (157) using longitudinal Framingham data reported that the number of hours per day of heavy physical activity was associated with the risk of incident radiographic knee OA (OR=7.0 for 4+ hours heavy physical activity/day). No effects were observed from moderate and light PA. In contrast, a study by Hannan et al. (175) in the same cohort found no increase in the risk of knee OA with increasing physical activity. In the highest quartile of PA compared to the least active, the OR was 1.3 for men and 1.1 for women (both non-significant). Hart et al. (200), using data from the Chingford study, followed 715 women (mean age, 54 years) for 4 years with no radiographic knee OA at baseline, and included the PA categories of walking, occupation and sport/recreation. They found no relationship between incident knee OA

and PA, while walking protected against joint space narrowing (OR=0.4, 95% CI 0.2–0.9).

It is evident from these often-cited reports that, despite the longitudinal cohort designs, large samples and lengthy follow-ups, estimates for the risk of PA on knee OA vary extensively. While differences in eligibility criteria, covariates included in multivariable models and small samples may account for some of the disparity, the most likely reason is the wide variation in PA exposure measurement, as discussed in Chapter 2. Of note, most studies have not considered joint-force aspects of PA nor attempted to completely classify PA (including historic PA) from all three major activity domains. Apart from the Verweij study (168), none of the above studies considered PA from all three major activity domains or attempted to estimate the effect of activities in terms of joint force. The main finding of Verweij et al. was an OR of 1.43 (95% CI 1.15-1.77) for a high knee mechanical strain score, lower but reasonably close to our reported OR's from the 5th quintiles of total knee force and occupational force in men and household activity in women. Results are not directly comparable since apart from differences in design, the mechanical strain score was a simple ranking (1 to 4) of certain physical activities over the past 2 weeks, did not fully classify activity in the in-depth way and over the lengthy time period of the current study and did not look at sex-specific differences in occupational and household activity. Consistent with the recent longitudinal cohort study of Toivanen et al. (198) and a number of longitudinal and case-control studies (171-175, 185, 186, 188, 200, 209, 210), we did not find a relationship between sport / recreational activity and knee OA. Studies that have shown a relationship between sport and knee OA have generally been in populations of athletes in specific sports with high knee forces (204, 214, 449, 453-456) and not from population-based studies, or the association has been explained by joint injury (214).

The prevalence of knee OA in our study was 22.4%, 17.8% in men and 25.1% in women. These gender differences in prevalence are consistent with previous large population-based North American studies (76, 83, 84). The prevalence falls below radiographically defined knee OA estimates in North America (28-37%) for this age group (76, 83, 84) (see Table 2.1), and above those defined symptomatically (radiograph and symptoms) (10-16%) (76, 83, 84) (Table 2.2). Radiographic definition alone captures cases that have no pain and estimates are often higher than definitions that include symptoms. Symptomatic OA captures those with symptoms and radiographic change. Since radiographic change in painful knees is usually associated with moderate to late disease, this definition may miss early cases. It is probable our estimate is somewhat higher than the reported symptomatic (radiograph and symptoms) prevalence since our definition probably captures some early cases that would not likely have radiographic change yet and because some subjects with other knee conditions (e.g., rheumatoid arthritis) mistakenly self reported OA. Conversely, our definition may have missed those with knee OA but who have not yet received a medical diagnosis. Even though there is probably some misclassification, our definition, which required a medical diagnosis *and* the presence of pain on most days, is important since pain is usually the most important aspect of disease to patients and putatively tied to the key exposure variable in this study. We also reported the results of a validity study (chapter 4) in a sub-sample of the current study comparing self-reported OA to clinical OA.

As noted in Chapter 6, it was important to measure and simultaneously adjust for PA-related force from all three major activity domains. Most previous PA-OA studies have investigated one or two domains (usually sport and/or occupation). Given the high levels of household and occupational PA reported in Chapter 5, omitting one or both of

these domains leaves these studies vulnerable to confounding from the unmeasured domain(s).

In studying all three domains separately by sex, we also observed relationships of PA with very high occupational force in men and household force in women. Questionnaires used in many previous studies did not assess the frequency, duration and intensity of PA actually performed by women (127). The majority of women's exposure to PA, particularly in older cohorts such as the current one, is due to accumulation of regular household activities (127, 217, 218, 222). While household activity may generally not be considered vigorous from an energy expenditure perspective and is often ignored in epidemiologic study of OA, there are many repetitive motions (e.g., stair climbing, squatting, kneeling) and activities (e.g., gardening, lifting, carrying) that are associated with high hip and knee joint forces (154, 155, 223, 224) but have low energy expenditure.

This is only the second study to measure lifelong household load at the knee joint and relate it to knee OA, and the first to quantify household knee joint force from historic activity for the assessment of dose-response. In the previous study by Sandmark et al. (180), exposure to physically demanding tasks at home was significantly associated with knee OA among women (but not men), and was the strongest risk factor for women among the physical load variables that were investigated in that study. Given that women have been shown to have higher PA than men when including household together with occupational and sporting activities (119), and that reasons for the higher prevalence of knee OA in women are not clearly elucidated (116), our findings provide preliminary evidence that the role of historic household PA requires further investigation. The role of occupational activity has received much more study, and is better understood in men than in women, in part because previous studies were based historically on male-

dominated workforce cohorts, and therefore excluded women and physical activity related to homemaking or child-rearing activities (116). Our finding of an increased risk of knee OA for the top quintile of occupational joint force is generally consistent with previous studies (167, 198) and several systematic reviews (26, 203, 207).

Despite the lack of a significant risk from the highest quintiles of adjusted household force in males and occupational force in females, it should not be concluded that the risk does not exist. The relative distribution of subjects within the quintiles was substantially different by gender, with relatively few subjects in the 5th quintile of male household and female occupation, potentially limiting the ability to detect a difference. Crude analysis did reveal a putative risk in the 5th quintile of household force in men (1.67, 95% CI 0.95, 2.94) and occupational force in women (1.90, 95% CI 1.39, 2.58), which disappeared after adjustment.

The CPFI, a quantitative joint force measure, together with a large sample allowed for evaluation of a dose-response relationship between lifelong force and knee OA. In most of the models where a significant relationship with knee OA was found at the highest quintile of force, there was an increasing, though non-significant, trend in the OR's from lower to higher levels of CPFI. While this requires confirmation and further delineation in future studies, the presence of dose-response strengthens evidence for a causal relationship (457).

Our results are consistent with previous studies that show overweight/obesity, age, female sex and previous injury are significant risk factors for knee OA (14, 24, 42, 116, 129, 130, 181, 185, 204). This study also reports that malalignment in women, is an approximate 2-fold risk for knee OA in fully adjusted models. Alignment has been shown to be important in knee OA previously (11, 53, 54, 298) (see chapter 2), but has not before been included in multivariable models investigating PA and OA.

Two exposures that were used as potential measures of neuromuscular control - coordination and hypermobility syndrome – were entered into models for knee OA. In crude and adjusted models, a higher coordination score was protective against knee OA, the first report of an aspect of neuromuscular control protecting against knee OA. The importance of the neuromuscular feedback system, whereby joint loads are controlled through quick and highly coordinated adjustments in muscle and tendon length have been shown to lessen the rate with which the load is applied to the joint (18), and are important in providing limits to joint movement. The coordination score used in this analysis may reflect this. Conversely, the joint hypermobility syndrome (JHS) was not associated with knee OA. While there is a theorized link and some evidence for a correlation between JHS and OA (383-386), there are also studies that show a protective effect (387-389), and the relationship remains unclear. JHS was used here as a proxy for decreased proprioception, an aspect of NM control, as individuals with JHS are known to have diminished proprioception (374). Our study did not reveal a relationship and the use of a surrogate measure of control may have missed an underlying relationship. In addition, measurement errors in the self-report measure of JHS (Chapter 4) may have attenuated the effect on knee OA.

This study had several strengths, including a large sample drawn from the community and a sufficient number of cases to adjust for a number of covariates, the separate analyses of men and women (equivalent to including interactions with gender for all variables), and assessment of dose-response. Another strength was the use of detailed information on the duration, frequency and joint loading aspects of historic activities, from all three main physical activity domains, allowing for relatively complete classification of the total volume of PA. Historic PA is important in OA given the lengthy induction and asymptotic latency period, and because current or recent levels of activity

can be affected by early symptoms of OA and are poor proxies for cumulative lifetime exposure (243). Lastly, many studies have used advanced disease markers, such as total joint arthroplasty or marked radiographic change as the outcome in assessing the role of PA. It is not clear whether the relationship with PA for early, symptomatic cases is the same as that observed for advanced or radiographically defined OA. Our case definition allowed us to capture information on earlier stages of disease. This may be important in understanding modifiable risk factors that could play a role in a prevention strategy for OA, something not currently available.

There are a number of limitations that are important in interpreting the results of this study. The potential limitation due to self-report of diagnosis has been discussed in chapters 4 and 6, and to self-report of PA measures and construction of the CPFI variable in chapters 5 and 6. Although this study provides evidence of an association between high levels of joint force, overweight/obesity, previous injury, malalignment and BMI, the cross-sectional design makes the determination of a cause and effect more challenging. However, the time window used for the main PA exposure (prior to age 50) captures the ages (30-45) with the highest level of lifetime force and is separated in time from knee OA diagnosis for the vast majority of cases. Supporting this, most of the risk estimates for covariates reported in this study were in the expected direction and effect sizes consistent with the literature (14, 24, 42, 116, 129, 130, 181, 185, 204). Further, since this study is the first attempt to examine four putative risk factors with knee OA (lifelong total joint force, malalignment, hypermobility and coordination), it is exploring new models of causation (458) for which a cross-sectional design is reasonable.

As discussed in Chapter 6, it is possible the decision to include inactive individuals and/or use the lowest quintile of joint force as the referent category may have resulted in attenuation of the force effect and masked a possible risk of knee OA from

inactivity, since low loading is a possible risk for cartilage thinning (439-441), and may potentially be a risk for knee OA.

Another potential limitation was the self-reported measurement of early adult life malalignment of the lower limbs using novel line diagrams. We conducted a validation study of this variable against clinical measures, and reported good reliability and validity (see chapter 4). Two recent studies have also reported the use of self-report of alignment using diagrams similar to those in the current study (432, 459). One of these conducted a validation study using a radiographic gold standard and reported extremely high sensitivity and specificity (432). The other conducted an analytic study and found that self-reported varus or valgus malalignment during young adulthood was a reliable measure and associated with the subsequent development of knee OA in later life (459).

The finding that most PA-related force is not related to knee OA, but that the highest levels of joint force are, is biologically plausible and fits within the conceptual framework of causation. Under normal physiological conditions the transmission and distribution of joint loads can occur for decades with little or no wear (160). Physical activity that produces moderate mechanical loading is necessary for homeostasis (20), facilitating chondrocyte function in the synthesis and rate of turnover of articular cartilage molecules, such as proteoglycans, which enhance cartilage stiffness (13, 161). However, when normal joint physiologic mechanisms are overwhelmed via excessive local mechanical force, biologic events are triggered which destabilize the normal coupling of degradation and synthesis of articular cartilage and subchondral bone (28). The failed attempt to compensate for this excess load and repair joint damage leads to the characteristic bone, synovial, cartilage and other changes seen in OA (28). Animal studies clearly illustrate that high joint force from PA affects cartilage metabolism and play a role in the development of OA (20, 164, 165).

In summary, a newly proposed measure of lifetime mechanical knee force was used to estimate the risk of self-reported knee OA (medical diagnosis plus symptoms). While it must be interpreted cautiously because of the cross-sectional design and the possibility of recall bias, this study suggests that lifelong physical activity is generally safe. The observed relationship with other known and suspected covariates was in the anticipated direction, lending face validity to the model. High levels of lifetime knee force from occupational activity in men and household activity in women were associated with knee OA. Obesity and previous injury were also a significant risk, consistent with previous studies. Prevention efforts may best be directed at occupations and household activity requiring high physical demands, at weight-control programs and injury prevention. Future research should improve the estimation and validity of knee force measurement in new populations, and apply these measures in longitudinal studies.

8: CONCLUSIONS

The manuscripts comprising this thesis are unified by the common goal of gaining a better understanding of the role of physical activity (PA) in hip and knee joint osteoarthritis (OA), one of the most important, modifiable but controversial risk factors. It represents a comprehensive epidemiologic program of research encompassing a) the development and validation of a historical physical activity questionnaire that assesses loads applied to the joint using joint loading units, b) the validation of self-reported measures of hip and knee OA, c) an epidemiological, multivariable analysis of the effect of lifetime hip and knee joint force on the risk of OA, and d) the assessment of local joint factors of importance in the PA-OA relationship. The results of this population-based research provide evidence that the majority of lifelong physical activity is safe for the hip and knee, but that very high levels of total lifetime force (hip and knee), occupational force in men (knee) and household force in women (knee) may be associated with OA. In addition, local joint factors including previous joint injury (hip and knee), malalignment (knee), and reduced coordination (knee) were found to be related to the risk of OA. Methodologically, this study provides evidence of the validity of self-reported PA and local joint measures, as well as the validity of self-reported hip and knee OA. The ultimate goal of this program of research is to provide evidence to inform OA prevention strategies – something not currently available.

8.1 Key Findings

To address the overall goal of investigating the effect of PA measures on the risk of OA required the development of an instrument that covered existing gaps and

captured the two most important aspects of PA for joint health – PA-related joint force and historic PA from all three major activity domains (sport, occupation and household). **Chapter 5's** population-based study in a large Canadian sample, published in *Arthritis Care and Research* (119), addressed these issues. It outlined the development and feasibility of a method for estimating lifetime hip and knee joint force in a biologically meaningful way that allowed for assessment of the cumulative effect of activity-related force. This work was accomplished by gathering data using the comprehensive Lifetime Physical Activity Questionnaire (LPAQ), a self-administered Internet instrument whose development and validation was described in **Chapter 2** and published in the *American Journal of Epidemiology* (270). The data, together with subject body weight and typical peak forces from common bodily movements, was then used to construct and describe lifetime trajectories of hip and knee joint force using the cumulative peak force index (CPFI) – a novel time-force-bodyweight product whose development, derivation and construct validity was described in **Chapters 5 and 6**. The results revealed a wide lifetime distribution of CPFI in the population that differed from PA measured by energy expenditure (EE), and had hypothesized differences over the lifetime trajectory by age, gender and activity domain, giving face validity to the measure. This provided an exposure method that could, for the first time, allow for the evaluation of a dose-response relationship between lifelong PA-related joint force and OA.

A second objective of **Chapter 5** was to describe the lifetime trajectories of physical activity by energy expenditure (EE) and joint force across gender and activity domain, as well as the ratio between joint force and EE ("relative joint loading" index) to distinguish between the energy costs and biomechanical effects of PA. There were two novel findings: that women had slightly higher lifetime physical activity levels (EE and joint force) than men, and the relatively low levels of sport/recreation activity in

comparison to occupation and household activity. Most PA-OA studies to date have focused on sports/recreation and/or occupational activity (historically dominated by male cohorts).

The second requirement to meeting the overall goal was the validation of self-reported measures of hip and knee OA and local joint vulnerability that may be risk factors for OA. **Chapter 4** comprised validation studies evaluating the measurement properties of the survey instruments measuring these variables – items that were largely drawn from the literature. The first validation study, submitted for publication, evaluated the outcome measurement. Using the American College of Rheumatology (ACR) clinical classification criteria for hip and knee OA (425) as a diagnostic referent, self-reported medical diagnosis of OA was very good for the hip and knee, as measured by sensitivity, specificity and predictive values. Kappa values indicated substantial agreement beyond chance (427). The measurement properties were consistent with or slightly better than other studies comparing self-report medically-diagnosed OA and clinical OA (101, 166, 418) and provide evidence that these items have utility for identifying hip and knee OA in population-based studies when the purpose is to link potential risk factors with knee and hip health. Self-report of two local factors, lower limb alignment and neuromuscular control (as measured by coordination and hypermobility), were also validated in Chapter 4.

The final step towards the overall goal was the multivariable analysis of lifetime joint force and hip and knee OA. **Chapter 6**, published in *Osteoarthritis and Cartilage* (460), is a longitudinal population-based cohort study evaluating the impact of levels of the hip CPFI on the incidence of hip OA. The key findings from this study provide evidence that lifelong physical activity is generally safe for the hip, but that very high levels of lifetime force from all domains combined, but not from any one domain alone,

are associated with an approximate 2-fold risk for hip OA. Specifically, there was no trend for sport/recreational activity to be related to hip OA. Very high levels of joint force from occupational activity, though non-significant statistically, may be important in the etiology of hip OA, suggesting that prevention efforts may best be directed at occupations requiring high physical demands. The prospective cohort design mitigated the impact of recall bias and differential misclassification, allowing for the evaluation of temporality and directionality of the causal effects of PA. We also observed that previous hip injury is a risk factor for hip OA, providing prospective evidence on a relationship that has previously been unclear.

Chapter 7 is a population-based prevalence study evaluating the impact of the CPFI in multivariable analysis on the risk of knee OA. High levels of lifetime occupational force in men and household force in women were associated with a 2- to 3-fold increase in knee OA. It is the first study of lifelong PA-related knee joint force that includes household activity, and while the results require confirmation in other populations, it sheds potential light on the consistently reported, but unexplained, higher prevalence of knee OA in women. It is also the first epidemiologic study of PA and OA that included simultaneous evaluation of lower limb malalignment and neuromuscular control. The novel self-report measures of these variables, while validated in a sub-study, are not gold standards for measurement, and are therefore exploratory. Nevertheless, malalignment in women and a lower coordination score were associated with knee OA. The coordination score, extensively validated and widely used in other literature, was applied in an OA study for the first time and may be of value as a marker of neuromuscular fitness in studies of joint health, and is worthy of further study.

Taken together**, Chapter 5, 6 and 7** represent a comprehensive evaluation of PA patterns in a large sample of Canadians, describing joint force over the lifetime by gender and domain, and how these forces relate to hip and knee joint health.

8.2 Integration and Implications of the Research

Addressing the overall goal of this thesis called for synthesis of a wide range of literature, development and validation of novel measurement instruments, implementation of several study designs ranging from clinical validation studies to population-based cohort study, application of several analytic solutions, and interpretation of findings for clinical, research and patient populations. In turn, as stand-alone studies or as a collective work, this thesis offers potential contributions across several clinical disciplines (rheumatology, physical medicine and rehabilitation, general practice, orthopaedics) and research areas (physical activity and risk factor epidemiology, measurement, biomechanics, public health).

The systematic review in **Chapter 2** revealed that all validated lifetime PA questionnaire's to date have measured PA by energy expenditure units (kilocalories or MET-hours) except for one that measured lifetime bone loading. Thus, the introduction of a validated lifetime PA questionnaire that captures joint force is an advance on previous exposure measures in OA epidemiology, which to date, have been largely based on current or recent PA, classified by simple ordinal category or specific activities, did not include data from all major sources of PA (household, occupational, sport/recreation) and have not been able to completely classify the total volume of PA.

As the first study to estimate and plot population-based lifetime hip and knee joint force trajectories across the lifespan using joint force units, **Chapter 5** represents a contribution to PA epidemiology, biomechanical and public health literature on joint

loading across the lifespan. Specifically, the high lifetime level of joint force in women provides potentially useful information for understanding their unexplained but consistently reported higher prevalence of OA. It also sheds light on sport/recreational activity - the most widely investigated PA exposure in OA epidemiology – suggesting that at the population level it is not a risk for OA, and that the sport - OA relationship is probably most applicable to athlete groups in certain sports.

As the first study to evaluate the measurement properties of an Internet-based self-administered survey in ascertaining cases of hip and knee osteoarthritis, **Chapter 4** represents a novel contribution to the questionnaire identification of OA cases in large population or community-based studies. Specifically, this study, using previously validated items, extends the literature from community-based postal questionnaires (101, 418) to the Internet, reporting similar or slightly better results, and confirming that the greatest accuracy is achieved by asking about self-report of a medical diagnosis of OA. While Internet samples have been shown to have slightly higher SES and more female respondents in initial studies (431), online methodologies may have broad applications in epidemiology, given its widespread availability, ability to target non-urban, remote and shut-in populations and the extremely low cost of prospective data collection. Beyond this contribution, Chapter 4 also contributes to the exploratory evaluation of measurement properties of newly proposed self-report items on lower limb alignment and neuromuscular control. At conceptualization stages of the thesis, no self-report items of lower limb alignment were available in the literature. Therefore, based on clinical and research experience, and in consultation with experts in rheumatology, epidemiology, physical medicine, orthopaedics, and with the services of a medical illustrator, novel line drawings were developed, adopted and pilot-tested for inclusion in the current thesis study. These measures had good validity in comparison to clinical

goniometric measurement. Likewise a previously validated questionnaire on joint hypermobility syndrome (the Hypermobility Questionnaire), which was used as a proxy for decreased proprioception and used for the first time in a PA-OA study, was shown to have moderate validity and good reliability, contributing an exploratory avenue of exposure measurement in OA epidemiology.

Chapters 6 and 7 are the culmination of this thesis research and represent a contribution to the rheumatologic, epidemiologic and public health literature as the first multivariable reports of the effects of lifelong PA-related joint force on hip and knee health. When taken together, the studies provide evidence that sport/recreational activity is unrelated to hip and knee joint health - conclusions that have implications for public health bodies, researchers and clinicians. The promotion of exercise is a major public health initiative in western countries worldwide due to its protective effect on numerous major health problems, including cardiovascular disease, cancer, diabetes, obesity and mental illness (19), including Canada and the US where public health bodies recommend 30-60 minutes of moderate to vigorous activities per day. Exercise is also widely recommended by health care professionals in the prevention and management of chronic health conditions. However, there has long been a concern that such promotion could lead to a rise in hip and knee OA – the leading impediment to physical disability in older adults, and a disease with a high and increasing prevalence, as outlined in Chapter 2. Knowledge that sport/recreational activities are safe for the joints at the population level contributes further evidence in support of the public health promotion of exercise, as well as provides physicians and other health care providers with evidence that exercise is safe for the joints and can be pursued for its myriad of other health benefits.

Chapters 5 and 7 contribute new evidence regarding the potentially important role of household-activity related joint force and knee OA. Very few PA-OA studies to

date have considered household activity, and only one case-control study has considered historic household activity (180), though it did not completely classify or quantify PA. Nevertheless, the reported OR's for various physically demanding tasks at home from that study were very similar to those reported in Chapter 7. This, combined with the overall high lifetime joint force in women reported in Chapter 5, provides evidence that further epidemiologic study is required, and may contribute to the unexplained higher prevalence of knee OA in women.

Lastly, Chapters 6 and 7 reported OR's for knee and hip OA from the highest levels of occupational force that are consistent with numerous studies and several systematic reviews that have found a similar relationship, generally reporting odds ratio of between 2 and 3. Thus, our findings contribute to a growing body of evidence that prevention efforts should be directed at occupations requiring high physical demands.

With regards to local joint factors, the results from Chapter 7 confirm hypothesized relationships between lower limb malalignment and lower coordination and knee OA. These results contribute uniquely to the OA epidemiology literature by demonstrating for the first time the potential utility of self-report measures of local factors in a large population-based study. They provide a novel methodology supporting the recent call for PA-OA studies to include and/or stratify research samples by subsets of individuals with local joint vulnerabilities who may respond to PA in different ways (301). Because these variables were developed and/or used for the first time in a population-based OA study, these data should be considered exploratory and the effects reported here are subject to the limitation discussed below. Nevertheless, knowledge that certain identifiable subgroups within the population are more susceptible to the effects of PA could lead to relatively inexpensive and practical recommendations that maximize the benefits of physical activity without increasing the risks of joint disease. Clinicians could

identify susceptible individuals and inform them on how to modify and perform physical activities that maximize energy expenditure while minimizing joint force. Further, local factors are modifiable. For example, reduced coordination can be enhanced by motor re-training and exercise interventions, and loads associated with malalignment can be modified with medial or lateral ‘unloader’ bracing, or in more severe cases, high tibial osteotomy.

8.3 Strengths and Limitations of the Research

As each manuscript chapter provided its own discussion of study-specific strengths and limitations, this examination will focus on the collective thesis work, and highlight the key strengths and limitations as they apply across studies.

Prospectively following a large number of subjects over the lifetime using an objective in vivo measure of joint force would be the only method to precisely estimate lifetime joint force for an epidemiologic study of PA and OA. Since this is extremely unlikely to happen for ethical, monetary and practical reasons, well-designed observational studies that estimate PA using soundly developed and validated instruments are the second best alternative. A strength of this project was the rigorous methodology utilized to meet the objectives of the thesis in estimating lifetime PA-related joint force, made possible by substantial prior work including recent methodological innovations in lifetime PA questionnaire development and web-based data collection. Another important innovation was the development of a method of converting self-reported PA data to mechanical forces in the joint, as described in Chapter 2 and 5, done with the assistance of a multi-disciplinary team of experts, built on a combination of evidence from the literature and following the principles of construct validity. An extensive study of the measurement properties of the questionnaire used to collect PA data was reported in Chapter 2 and in the *American Journal of Epidemiology* (270). This

allowed for the first time, the use of an historic PA questionnaire that quantitatively captured PA data that can be converted to joint loading units, useful for the quantification of the biomechanical effects and dose-response of physical activities on the hip and knee joint in large population-based studies. The joint loading unit developed, the cumulative peak force index (CPFI), was a time-force-bodyweight product as described in Chapter 5, where the feasibility and face validity of the CPFI in a population-based sample were demonstrated. Chapter 6 added to the construct validity of the CPFI, showing that the CPFI was a stronger predictor of OA than any of its component parts alone.

This thesis study was also the first to evaluate historic hip and knee joint force from all three major physical activity domains. Most studies on the relationship between PA and joint health have focused on sport and/or occupation and have not investigated the combined effect of sport, occupation and household activity (which accounts for most of the weekly PA in women), and have not completely classified PA. Biologically, it seems likely that different activities have a cumulative effect, and that this effect depends on the mechanical forces transmitted through the joint though this theory had never been tested empirically before this thesis project. Therefore, most if not all previous studies, by measuring only one or two domains or not assessing frequency and duration of PA, are vulnerable to missing important exposure information.

Nevertheless, the approach to PA measurement used in this thesis has limitations inherent to observational studies that rely on self-report of past exposure. As discussed in Chapter 5 to 7, self-reported PA measures require cautious interpretation because of large within-person variability and problems with recall (231, 242, 434) that may lead to non-differential misclassification and attenuation of the effect size in analytic studies using the exposure. Despite these limitations, it has been repeatedly shown that

PA questionnaires are both practical and valid when used appropriately for large-scale epidemiologic studies (217, 231, 259, 261). Slattery et al. (461) reported good recall of past activity levels when asked about PA up to three to four years in the past; Blair et al.(462), reported reliability of long-term recall of PA of 10 years in the past, while Falkner studied the reliability of recall of PA in the distant past (30 years) and found acceptable levels of recall (262). In a review on the limitations of physical activity questionnaires, Shephard (231) concluded that while detailed interpretation and attempts to estimate precise dosage are inadvisable, use of data to monitor change in population activity and provide categorical estimates is valuable. If a questionnaire is adequately designed for a particular population and has acceptable reliability and validity, the instrument should be able to rank-order adults by category of activity levels and by sociodemographic strata, providing a relative distribution of historical PA with which to rank order subjects (229, 242). While a more precise measure of current or recent activity would have been possible, it was of little interest given the long induction and asymptomatic latency period of OA and the objectives of this thesis, whereas a less precise categorical measure of historic PA was of considerable interest and may have more utility in the eventual development of prevention programs for OA.

Another potential limitation was that the calculation of the CPFI was based in part on assigning a typical peak force value for given activities or positions (Appendix D), as described in Chapters 3 and 5, for use as a multiplier in the time-force-bodyweight calculation. The typical peak joint force is not the same for every individual and may not precisely represent the forces in our study subjects. However, we used a methodology identical to that used and validated in numerous energy expenditure studies (i.e., the assigning of a typical metabolic equivalent value to specific activities), replacing METs with the typical joint force value. Further, as we were interested in relative and not

absolute or precise values, the biases introduced in the estimates probably did not significantly influence our findings. We tested the selection of the typical peak force value in a sensitivity analysis in Chapter 6, which revealed that the CPFI measure was robust to ±20% variation in the force multiplier for each activity and we found that including the multiplier in the CPFI (versus considering only BW and total PA hours) increased the strength of the association and improved the multivariable analytic models.

Another potential limitation related to recall is the possibility of recall bias, where the ability to recall past exposure is dependent on outcome status. Of note, subjects with OA at baseline may have over-reported prior PA exposure, attributing their OA to their past activity. This could lead to increased risk estimates. In Chapter 7, a cross-sectional design was used, and while justified for the reasons outlined in that chapter, remains most vulnerable to this type of bias. However, risk estimates for sport and occupational exposure as well as other covariates were generally in the expected direction and consistent with the literature including prospective data (14, 24, 42, 116, 129, 130, 181, 185, 204), lending validity to the findings. Regardless, the possibility of this bias must be acknowledged and study results interpreted in light of this. In Chapter 6, the use of a prospective cohort design, which eliminated baseline cases, greatly reduced the possibility of this bias.

A strength of the study was the population-based study design and large sample size, allowing for the assessment of a number of potential covariates that *a priori* scientific knowledge and the conceptual framework of causal pathways to OA suggest are important in the relationship between PA and OA (151). This is important given the burden of OA, and the major public health initiatives calling for increased PA.

While the sample was large, the sampling method may limit the generalizability of the findings. As discussed in Chapter 6, the study sample was fairly well-educated, largely Caucasian, Internet users and probably health seeking. However, the aim of this study was not to describe characteristics of, or estimate disease prevalence in, the general population but rather to assemble subjects to test hypotheses about PA and joint health in a large sample of subjects sampled in the identical way (internal validity). Cohort studies are rarely carried out in a random sample from the general population. Some of the most informative cohort studies have been conducted in occupational groups characterized by moderate or high SES (e.g., nurses, physicians, civil servants, nuns) or other special populations.

The case ascertainment also requires mention. We used self-report items that were based on validated items used in previous studies (101, 166, 418, 419). In a validation sub-study using subjects drawn from the larger cohort, described in detail in Chapter 4, good to very good reliability and validity was demonstrated in comparison to American College of Rheumatology clinical criteria, consistent with or better than other studies. Although it could be argued it would have been preferable to perform baseline and follow-up X-rays on all participants, such a study would be very expensive, and the advantage would likely be relatively small. Our case definition is reproducible and its association with standard diagnostic criteria for OA has been established. While less sensitive than x-rays and thus possibly including some false negatives, using our case definition probably allowed us to capture earlier cases of OA, in contrast to many PA-OA studies, which have used case ascertainment criteria associated with more advanced disease (radiographic or joint replacement). Very little is known about the etiology of early OA where strategies aimed at secondary prevention would be most beneficial. The case definition used contributes etiologic information to this stage of disease. Further, it

is probable that the false positives (those who classified themselves as having OA but did not meet clinical criteria) include subjects with early OA not captured by the ACR criteria, and other causes of hip and knee symptoms. From a patient perspective whatever the cause, these symptoms are relevant, affect quality of life and are potentially linked to the key PA exposures that were the focus of this thesis study.

8.4 Future Research and Recommendations

OA is the major public health problem in musculoskeletal medicine, and the work and findings from this thesis program, together with the current evidence, point to several key future research directions and recommendations. One of the most important to emphasize is that lifelong physical activity is by and large safe for healthy hip and knee joints, and that in particular, exercise levels from sport and recreation measured at the population level in this thesis work show no association with knee or hip OA. Therefore, the current recommendations by Health Canada and other major public health agencies in western countries worldwide encouraging 30-60 minutes of moderate to vigorous exercise on most days should continue without reservations regarding hip and knee health. Health educators and clinicians should continue to encourage healthy people to engage in regular PA. However, the evidence from Chapter 7, of an approximate 3-fold increase in knee OA from injury, confirms a substantial body of previous epidemiologic and basic science data that the biomechanical and physiologic changes post-injury place these joints at a high risk for OA, perhaps even in a pre-osteoarthritic state. These individuals should be advised of this and their PA recommendations adjusted to focus on exercise choices that place less strain on the knee joints. The evidence is much less strong and consistent at the hip, though this thesis provided prospective evidence that there was a similar risk from previous hip injury for hip OA. Further research should focus on clarifying this relationship and

identifying more clearly the effect of other factors that play a role in the PA-OA relationship.

The relationships between joint force and OA described in this thesis require confirmation in other populations. The findings regarding the risk from occupational force are consistent with most of the previous literature. The evidence is sufficiently strong and supports the urgent call by Rossignol et al. (21) for future studies to focus on implementing and evaluating prevention efforts in occupations requiring high physical demands. The findings from high lifelong household activity-related joint force in women are novel, and future etiologic research should focus on confirming this relationship, particularly as the consistently higher prevalence of knee OA in women remain unexplained.

The decision to include inactive individuals and/or to use the lowest quintile of joint force as the referent category, (potential risk groups for OA in both the knee and hip studies) may have resulted in attenuation of the force effect and masked a possible risk of OA from inactivity. Low joint loading associated with physical inactivity and/or a sedentary lifestyle have not been the subject of epidemiologic research into the PA-OA relationship, though there is some evidence from animal studies and from studies on humans subject to immobilization (e.g., spinal cord injured, post-operatively) (20, 439-441) that cartilage health is threatened by low loads. Future research should consider how to categorize or analyze physical activity data in order to investigate the possible risk of OA from reduced loading.

It is generally agreed that those with knee and hip OA comprise a heterogeneous population, and there is growing evidence that a number of individual characteristics are important variables in understanding the PA – OA relationship. While we identified and measured two individual characteristics (malalignment and neuromuscular control) that

are known to be associated with OA but not adjusted for in any previous epidemiologic PA - OA studies, we used novel measures drawn from other research areas. Future research should both delineate various causal pathways to OA based on subsets of the population who vary on characteristics known to affect concentration of mechanical stress on the articular surface (e.g., obesity, injury, malalignment, neuromuscular control, femoroacetabular impingement, congenital abnormality) and work towards the standardized measurement of such characteristics for use in population-based research. While gold standards will no doubt be clinically based, the development of inexpensive and practical methods to assess large samples is important to be able to stratify on these characteristics and assess interactions with PA.

Finally, there is also a need for improved outcome measurement that can more accurately identify OA, especially pre-symptomatic or those with early OA. The current gold standard requires x-ray change, which is associated with moderate or late disease and is expensive and impractical for large studies. Since OA takes decades to manifest and secondary prevention efforts require early identification, cost-effective, sensitive measures for earliest and early OA are needed (463).

8.5 Conclusion

In summary, a newly proposed measure of lifetime mechanical hip and knee force was used to plot lifetime trajectories and investigate its relationship with self-reported, medically diagnosed hip and knee OA. It was shown that women, when combining PA from occupation, household and sport/recreation have higher lifetime levels than men. Taken collectively, the results adjusted for covariates, show that most lifelong physical activity is generally safe for the hip and knee, and the promotion of exercise as a major public health initiative should continue without concern for increased rates of hip and knee OA. Very high levels of lifetime force from all domains combined

was a risk factor for hip and knee OA, while very high levels of occupational force in men and household force in women were risks for knee OA. This latter finding in women, together with the higher lifetime levels of PA, sheds potential light on the consistently reported, but unexplained, higher prevalence of OA in women. This thesis also provides novel, though preliminary, evidence that higher levels of neuromuscular control as measured by coordination protect against knee OA.

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APPENDIX A: PHYSICAL SELF-DESCRIPTION QUESTIONNAIRE (PSDQ): COORDINATION SCALE

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Please **circle the number** which is the **most correct** statement about you.

STATEMENT	False	Mostly False	More false than true	More true than false	Mostly true	True
I feel confident when doing coordinated movements	1	2	3	4	5	6
Controlling movements of my body comes easily to me	1	2	3	4	5	6
I am good at coordinated movements	1	2	3	4	5	6
I can perform movements smoothly in most physical activities	1	2	3	4	5	6
I find my body handles coordinated movements with ease	1	2	3	4	5	6
I am graceful and coordinated when I do sports and activities	1	2	3	4	5	6

APPENDIX B: HYPERMOBILITY QUESTIONNAIRE

Hypermobility Questionnaire

Please answer the following questions Yes or No by marking an 'X' in the appropriate column.

	YES	NO
1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?		
2. Can you now (or could you ever) bend your thumb to touch your forearm?		
3. As a child did you amuse your friends by contorting your body into strange shapes OR could you do the splits?		
4. As a child or teenager did your shoulder or kneecap dislocate on more than one occasion?		
5. Do you consider yourself double-jointed?		
TOTAL		

Total score: /5

A score of ≥ 2/5 meets the criteria for joint hypermobility syndrome (JHS)

APPENDIX C: SAMPLE QUESTIONS FROM THREE DOMAINS OF PHYSICAL ACTIVITY

(Survey was online using skip logic technology)

Sports / Recreation *(Using the first item in the L-PAQ sports domain, "Aerobics," as an example)*			
Purpose of Questions		**Specific Questions**	**Units**
Questions on duration of participation in each sports activity	**Q1**	At what age did you start participating in Aerobics?	**YOP:** Years of participation
	Q2	At what age did you stop participating in Aerobics? If you are still participating in Aerobics, please fill in your current age.	
Questions on frequency of participation in each sports activity	**Q3**	How many months per year did you participate in Aerobics?	**WPY:** Months per year converted to Weeks per year
	Q4	How often did you participate (per week, per month, per year)?	**OPW:** Occasions per week (all units converted)
Questions on length of time of participation in one occasion of sports activity	**Q5**	On average, how long did you participate on each occasion (minutes, hours)?	**HPO**: Hours per occasion (all units converted)
Questions on hip joint movements (e.g.time spent in given activity- e.g., walk, stand, run/jog, squat, lift, jump etc.)	**Q6**	When participating in Aerobics, how much time did you spend doing the following activities, on average?	(Ordinal radio button responses in min/hr –none, 1-5 min, <15, 15-30….45-60)
Occupation *(UsingJob #1 from L-PAQ occupational domain, as an example)*			
Purpose of Questions		**Specific Questions**	**Units**
Identify occupation	**Q1**	Please list Job #1	
Questions on duration of participation in each occupation	**Q2**	At what age did you start participating in Job#1?	**YOP:** Years of participation
	Q3	At what age did you stop participating in Job#1? If you are still in Job#1, fill in your current age.	

Occupation *(UsingJob #1 from L-PAQ occupational domain, as an example*			
Questions on <u>frequency</u> of participation in each occupation	**Q4**	What type of employment was Job# 1 (full-time, part-time, seasonal)?	**WPY:** Weeks per year (all units converted)
	Q5	How long was a season on average?	
Questions on <u>length of time</u> of participation in one occasion of occupation	**Q6**	How many hours per week did you work on average?	**HPW**: Hours per week
Questions on <u>hip joint movements</u> (e.g. time spent in given activity- e.g., walk, stand, lift, carry, use heavy tools, squat, lift etc.)	**Q7**	When performing this job #1 how much time did you spend doing the following activities, on average?	(Ordinal radio button responses in min/hr – none, 1-5 min, <15, 15-30….45-60)
Household *Using "caring for children" from L-PAQ household domain, as an example)*			
Purpose of Questions		**Specific Questions**	**Units**
Questions on <u>duration</u> of participation of domestic activity	**Q1**	At what age did you begin caring for children?	**YOP:** Years of participation
	Q2	At what age did you stop caring for children? If you are still caring for children, fill in your current age.	
Questions on <u>frequency</u> of participation of domestic activity	**-**	**Assumed at 52 weeks per year*	
Questions on <u>length of time</u> performing domestic activity	**Q3**	How many hours per week did you care for children on average?	**HPW**: Hours per week
Questions on <u>hip joint movements</u> (e.g. time spent in given activity-e.g., walk, stand, lift, carry, squat, etc.)	**Q4**	When caring for children, how much time did you spend doing the following activities, on average?	(Ordinal radio button responses in min/hr – none, 1-5 min, <15, 15-30….45-60)

APPENDIX D: FORCE VALUE ASSIGNED TO EACH ACTIVITY IN THE CPFI FORMULA

Average Hip Force (x Body Weight (BW))

Activity	Hip Force (BW)
Stand	1
Walk	3
Run	7
Stand and hold object>23 kg	1+23 kg
Walk and carry object > 23kg	3 +23 kg
Push	3
Heavy Tool	1
Kneel	0.75
Squat	1.5

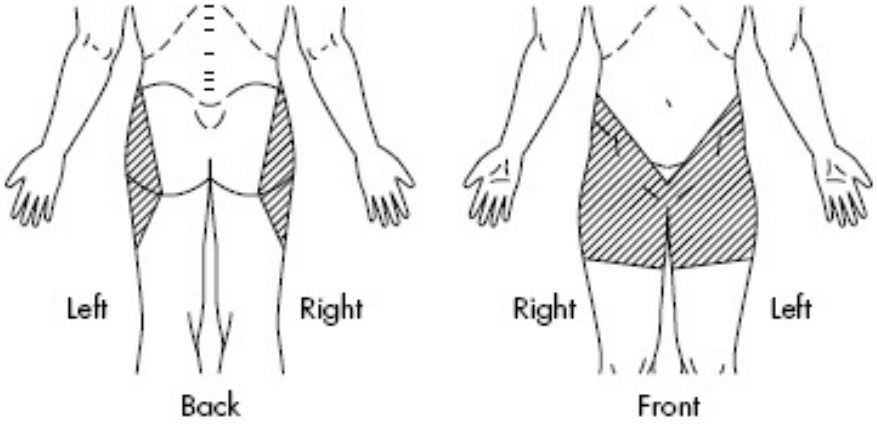
Average Knee (tibio-femoral) Force (x Body Weight (BW))

Activity	Knee Force (BW)
Stand	1
Walk	3
Run	6
Stand and hold object>23 kg	1+23 kg
Walk and carry object > 23kg	3 +23 kg
Push	3
Heavy Tool	1
Kneel	0
Squat	5

APPENDIX E: CASE ASCERTAINMENT HIP – QUESTIONNAIRE ITEMS FROM BASELINE SURVEY

Screenshot 1

Have you had any pain in the shaded area of the diagram below over the past month lasting one day or longer?



Screenshot 2

On most days, do you have pain, aching, or stiffness in your groin or upper thigh?

- ◉ Yes
- ○ No

Next Question | Back

CHANGE ANSWER

Exit

Screenshot 3

Have you ever been diagnosed by a health professional with OSTEOARTHRITIS of the hip? (Please note that osteoarthritis, rheumatoid arthritis, and osteoporosis are different conditions.)

- (●) Yes
- ( ) No

[Next Question] [Back]

[CHANGE ANSWER]

[Exit]

Screenshot 4

Have you ever been diagnosed by a health professional with OSTEOARTHRITIS of the hip? (Please note that osteoarthritis, rheumatoid arthritis, and osteoporosis are different conditions.)

This questions is very important, please confirm your answer

- (●) Yes
- ( ) No

[Next Question] [Back]

[CHANGE ANSWER]

[Exit]

APPENDIX F: CASE ASCERTAINMENT KNEE – QUESTIONNAIRE ITEMS FROM BASELINE SURVEY

Screenshot 1

On most days, do you have pain, aching, or stiffness in either of your knees?

- ◉ Yes
- ○ No

Next Question | Back

CHANGE ANSWER

Exit

Screenshot 2

Have you ever been diagnosed by a health professional with OSTEOARTHRITIS of the knee? (Please note that osteoarthritis, rheumatoid arthritis, and osteoporosis are different conditions.)

- ◉ Yes
- ○ No

Next Question | Back

CHANGE ANSWER

Exit

Screenshot 3

Have you ever been diagnosed by a health professional with OSTEOARTHRITIS of the knee? (Please note that osteoarthritis, rheumatoid arthritis, and osteoporosis are different conditions.)

This questions is very important, please confirm your answer

- (●) Yes
- ( ) No

Next Question | Back

CHANGE ANSWER

Exit

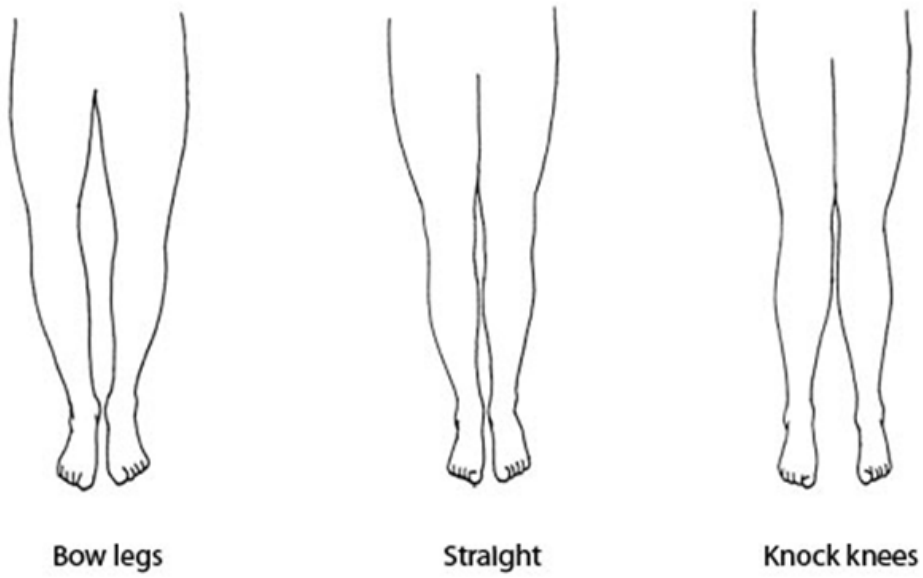
APPENDIX G: LEG ALIGNMENT

Screenshot 1

Leg Shape

The following section contains a question about the shape of your legs.
An example of leg shape is shown in the picture below.

If you are not sure about the shape of your legs, you may need to stand with your legs as close together as possible - until your knees or feet/ankles are touching. Put equal weight on both legs and straighten your knees as much as you can.



Screenshot 2

The scale below helps us measure the shape of your legs at your current age and at age 20. It ranges from strongly bow-legged to strongly knock-kneed. The middle of the scale represents straight legs. Please select the option that best corresponds to the shape of your legs when you are standing.

	Strongly bow-legged					Straight					Strongly knock-kneed
Currently	○	○	○	○	○	◉	○	○	○	○	○
At age 20	○	○	○	○	○	◉	○	○	○	○	○

APPENDIX H: NINE-POINT BEIGHTON SCORE FOR JOINT HYPERMOBILITY SYNDROME

One point is gained for each side of the body for the first four manoeuvres listed below, such that the hypermobility score is a maximum of 9 if all are positive.

1. Passive dorsiflexion of the fifth metacarpophalangeal joint to ≥90°
 (1 point for left; 1 point for right)

2. Opposition of the thumb to the volar aspect of the ipsilateral forearm
(1 point for left; 1 point for right)

3. Hyperextension of the elbow to ≥10°
(1 point for left; 1 point for right)

4. Hyperextension of the knee to ≥10°
(1 point for left; 1 point for right)

5. Placing of hands flat on the floor without bending the knees (1 point)

Total score: /9

A score of ≥ 4/9 meets the criteria for joint hypermobility syndrome (JHS)