DO LOWER EXTREMITY BIOMECHANICS DURING GAIT PREDICT PROGRESSION TO TOTAL KNEE ARTHROPLASTY?

by

Gillian Hatfield

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

at

Dalhousie University
Halifax, Nova Scotia
December 2013

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Introduction: Gait biomechanics are associated with knee osteoarthritis (OA) structural progression, but no studies have included: i) all three lower extremity joints, ii) non-frontal plane factors, iii) temporal loading patterns, and iv) progression from structural and symptomatic perspectives. This dissertation addressed gaps in our understanding of lower limb biomechanics and their implication for determining whether we have identified and are targeting the most effective biomechanical variables in the development and evaluation of conservative interventions to slow knee OA structural and symptom progression (progression to TKA).

Methods: 54 patients with knee OA underwent baseline gait analysis. Three-dimensional hip, knee, and ankle angles and moments were calculated. Waveform characteristics were determined using Principal Component Analysis (PCA), and knee adduction moment (KAM) peak and impulse were calculated. At follow-up 5-8 years later, 26 patients reported undergoing total knee arthroplasty (TKA). Unpaired Student's t-tests detected differences in baseline demographic and gait characteristics between TKA and no-TKA groups. Receiver operating curve analysis determined discriminative abilities of these differences. Stepwise discrimination analysis determined which multivariate combination best classified the TKA group. Logistic regression analysis determined the predictive ability of the multivariate model.

Results: There were no baseline differences in clinical and spatiotemporal gait characteristics, but the TKA group showed significant gait biomechanical differences, including higher KAM magnitude (KAMPC1), less difference between early and mid-stance KAM (KAMPC2), higher KAM peak and impulse, reduced early stance knee flexion and late stance knee extension moments (KFMPC2), and reduced stance dorsiflexion moments (AFMPC4). The multivariate discriminant function with the highest classification rate (74.1%) combined KAMPC1, KFMPC2, and AFMPC4, with sensitivity of 84.6 and specificity of 71.4. A one-unit increase in the model score increased risk of progression to TKA six-fold.

Conclusion: Higher KAMPC1 scores suggest higher overall loading during gait. Lower KFMPC2 and AFMPC4 scores suggest inability to unload the knee and therefore sustained loading. Interventions reducing overall load and altering patterns of loading (i.e. increase unloading) may reduce risk of progression to TKA. Future research should determine how components of the discriminant model can be altered conservatively, and what impact alterations have on the risk of progression to TKA.

LIST OF ABBREVIATIONS USED

AFAPC3	Ankle flexion angle principal component 3
AFMPC4	Ankle flexion moment principal component 4
ARMPC2	Ankle rotation moment principal component 2
ASIS	Anterior superior iliac spine
AUC	Area under curve
BMI	Body mass index
HAAPC2	Hip adduction angle principal component 2
HKA	Hip-knee-ankle
HS	Heel strike
Hz	Hertz
ICC	Intra-class correlation coefficient
JSN	Joint space narrowing
KAM	Knee adduction moment
KAMPC1	Knee adduction moment principal component 1
KAMPC2	Knee adduction moment principal component 2
KFMPC2	Knee flexion moment principal component 2
Kg	Kilograms
KL	Kellgren and Lawrence
m	Metre
MET	Metabolic equivalent
MRI	Magnetic resonance imaging
N	Newton
OA	Osteoarthritis
PC	Principal component
PCA	Principal component analysis
RMS	Root mean squared
ROC	Receiver operating characteristic
s	Second
SKI	Standardized knee imaging

TKA	Total knee arthroplasty
US	Ultrasound
WOMAC	Western Ontario and McMasters Universities Osteoarthritis Index

ACKNOWLEDGEMENTS

I would like to express my deepest appreciation to all those who have helped throughout my long academic journey. First and foremost, thank you to my supervisor, Dr. Cheryl Kozey, who has provided guidance and support for almost 10 years: from my early days as a summer research student while in Physiotherapy school, through my Masters degree, and now throughout my doctoral degree. Henri Poincare said that "Science is built of facts the way a house is built of bricks: but an accumulation of facts is no more science than a pile of bricks is a house". Thank you, Cheryl, for pushing me to go beyond accumulating facts by forcing me to answer the tough questions such as "… but what does this *mean*?" and always reminding me that doctoral research is "a process". From our formal and informal meetings, to our golf games in Halifax and away at conferences (even when the course was being raided by armed police), to your fantastic parties (with your equally fantastic ice cream cake), you have been my mentor, as well as my friend.

Thank you to the rest of my supervisory committee. Thank you, Dr. William Stanish, for your kind words, warm smile, and helping me see where my research fits in the "big picture." Thank you, Dr. Michael Dunbar, for your constant encouragement and for our chats on research and life in general. You are one of the most interesting people I know, and I have thoroughly enjoyed learning from you. Thank you, Dr. Scott Landry, for your positivity. When I was considering doing a Masters you encouraged me to pursue graduate studies, even though it was at the very end of your doctoral degree (where I've learned some frustration can creep in).

I also wish to thank the many undergraduate and graduate students that have worked in the Dynamics of Human Motion laboratory during my time at Dalhousie. I can honestly say that I've enjoyed coming to work each day because I've gotten to meet and become friends with so many great people.

Last, but certainly not least, I wish to thank my parents for their endless love, encouragement, and support throughout this journey. Finally, after 13 years of University, you can say your daughter is no longer a professional student!

CHAPTER 1 INTRODUCTION

1.1 BACKGROUND AND RATIONALE

Arthritis is a significant problem in industrialized countries (Wong et al, 2010). It is the most common cause of disability in Canadians, with osteoarthritis (OA) being the most prevalent type of arthritis (Arthritis Alliance of Canada, 2011). OA is a progressive disease of the synovial joints that represents the failed repair of joint damage, resulting in the degradation of articular cartilage and subchondral bone (Lane et al, 2011). The knee is the joint most often affected by OA (Dillon et al, 2006), particularly the medial tibiofemoral compartment (Lane et al, 2011; Dillon et al, 2006). Knee OA results in pain, stiffness, muscle strength deficits, and joint instability, with the long-term effects reducing an individual's mobility. Along with the personal burden of knee OA, there is a tremendous economic burden. In 2003, $328.1 billion was spent on direct care related to arthritic conditions in the United States (Yelin et al 2007). In Canada, direct and indirect costs are expected to reach $550 billion and $909 billion, respectively, by 2040 (Arthritis Alliance of Canada, 2011). Unfortunately, due to the aging population and the current obesity epidemic, the prevalence of knee OA is increasing dramatically. By 2025, it is expected that 16% of Canadian men and 25% of Canadian women will be diagnosed with knee OA (Lagace et al, 2003). In the United States 30% of the population is expected to have knee OA by 2030 (Lawrence et al, 2008). The reduced mobility resulting from knee OA leads to an increased risk of cardiovascular disease, poor quality of life, and a loss of function (Conn et al, 2008). Specifically, knee OA results in more difficulty with activities of daily living, such as walking or climbing stairs, than any other medical condition for people over the age of 65 years (Hunter and Felson, 2006).

There is currently no cure for knee OA, and as a consequence of the increasing prevalence, the demand for total knee arthroplasty (TKA) surgery has also grown. In Canada, the number of knee replacements performed grew by 125% over a ten-year

period (from 1994-5 to 2004-5) (Canadian Joint Registry, 2006). Similarly, in the United States, the demand is expected to increase by 631% by 2030 (Kurtz et al, 2007). The largest percentage increase in the rate of TKA surgery in Canada and the United States has been in younger patients (Canadian Joint Registry, 2006; Jain et al, 2005), so with the limited lifespan of the implants (83% survival rate at 16 years post-TKA (Buechel et al, 2001)), the revision rates are also expected to rise steeply in the future. TKA is considered the end-stage treatment for those with severe knee OA so ideally conservative treatments should be developed with the goal of delaying or preventing the need for TKA. Biomechanics research has affected various aspects of human health (Zernicke et al, 2012), and biomechanical conservative interventions (specifically braces and insoles) have been recommended in international OA management guidelines (Zhang et al, 2010). However, the main outcome measure used to determine the level of evidence for the recommendation was pain. The biomechanical loading environment of the knee joint was not considered. The main research question this dissertation addresses is whether we have a comprehensive understanding of the biomechanical environment and hence are targeting biomechanical variables in the development and evaluation of conservative management strategies that have the potential to slow or prevent the progression of knee OA to TKA.

The Arthritis Alliance of Canada released a statement in 2011 listing three management strategies for OA that should be prioritized, as they were thought to offer the greatest return on public investment. Along with joint replacement, these interventions included obesity reduction and pain management (Arthritis Alliance of Canada, 2011). While these three interventions were projected to save an estimated $717 billion over the next 30 years, they (with the exception of obesity reduction) do not clearly address underlying mechanisms of OA progression, focusing instead on a symptom-based approach. This is problematic because structural changes are poorly correlated with knee OA symptoms (Creamer et al, 2000; Barker et al, 2004). In fact, it has been proposed that there are two components of knee OA: the “illness” component, consisting of the symptoms of knee OA, and the “disease” component, consisting of the structural changes associated with knee OA (Lane et al, 2011). Additionally, relief of pain in those with moderate knee OA

has been associated with increased knee loading (Henriksen et al, 2006), and prolonged non-steroidal anti-inflammatory use has been linked to an increased risk of structural progression (Reijman et al, 2005). Thus, conservative interventions must not just aim for symptom reduction. They must address *mechanisms* of knee OA progression.

It is recognized that both biomechanical and biochemical factors play roles in knee OA progression (Brandt et al, 2006). Brandt, in an overview on OA, stated that OA can be a mechanically induced disorder, where abnormal joint mechanics lead to biological effects that are mediated biochemically (Brandt et al, 2006). Thus, conservative interventions targeting the biomechanical environment of the knee joint have been the focus of significant research effort (Lane et al, 2011; Buckwalter et al, 2001; Gross and Hillstrom, 2008). The importance of biomechanics in the structural progression of knee OA has been demonstrated with evidence from animal models (Radin et al, 1984; Chen et al, 1999), theoretical models (Andriacchi et al, 2004), and clinical research (Miyazaki et al, 2002; Bennell et al, 2011). However, biomechanical factors driving symptom progression may differ from those driving structural progression, since the two aspects of knee OA are so poorly correlated (Creamer et al, 2000; Barker et al, 2004). Determining how biomechanical factors relate to an outcome measure that captures both aspects of knee OA progression (TKA) is the focus of this dissertation. TKA provides a clear endpoint that includes both symptom and structural aspects of progression, since patient complaints of pain and functional deficits as well as imaging techniques to establish joint structural changes are used in surgical decision making (Gossec et al, 2011). Determining how biomechanical factors relate to a measure that captures both aspects of knee OA progression could refine the development of biomechanical targets used in the development of conservative management strategies.

Most of what we know about biomechanical risk factors in human knee OA progression have been identified from large-scale epidemiological studies, and include obesity (Cooper et al, 2000; Yusuf et al, 2011), knee joint alignment (Yusuf et al, 2011; Sharma et al, 2010), previous anterior cruciate ligament injury (Lohmander et al, 2004; von Porat et al, 2004), quadriceps weakness (in women) (Segal et al, 2010), radiographic disease

severity (Gossec et al, 2011; Conaghan et al, 2010; Riddle et al, 2009), and knee pain (Gossec et al, 2011; Conaghan et al, 2010). While they may play a role in knee OA progression, some of these risk factors are difficult to modify, and in general none consider the dynamic loading environment of the knee. The dynamic loading environment is important because repetitive impulse loading can initiate articular cartilage damage and subchondral bone changes (Radin et al, 1984), increase the production of inflammatory chemicals (Wang et al, 2007) that have been linked to increased knee pain (Stannus et al, 2013), and decrease joint lubrication (Abusara et al, 2013). Sustained compressive load can lead to cartilage degradation (Chen et al, 1999), an upregulation of inflammatory chemicals (Wang et al, 2007) linked to knee pain (Stannus et al, 2013), and an increased risk of cartilage and subchondral bone damage from normal, physiological impulse loads following the sustained loading (Kim et al, 2012). Thus, repetitive, high-magnitude cartilage loading and sustained cartilage loading both provide potential biomechanical pathways for knee OA progression (both structural and symptom), highlighting the importance of looking at the local, dynamic biomechanical loading environment of the knee.

In humans, gait is used as a model to study the local, dynamic biomechanical loading environment of the knee, because it is an activity that is often reported as difficult by those with knee OA (Hunter and Felson, 2006), because the chronic and repetitive loading occurring during gait is thought to dominate the biological and structural response of cartilage (Andriacchi et al, 2004), and because there is empirical evidence from four longitudinal studies that biomechanical factors during gait have the potential to increase the risk of knee OA structural progression (i.e. damage to the articular cartilage) (Miyazaki et al, 2002; Bennell et al, 2011; Chang et al, 2007; Chang et al, 2005). To our knowledge, no studies have looked at gait biomechanics and progression to TKA, therefore looking at knee OA progression from both a structural *and* symptom perspective, and capturing both the “illness” and “disease” components of knee OA (Lane et al, 2011).

The four longitudinal studies on structural progression focused on frontal plane mechanics and specifically the knee adduction moment (KAM) or factors that could affect the KAM. The KAM has traditionally been the focus in the knee OA literature because knee OA is more common in the medial compartment than the lateral compartment (Frontera and Silver, 2002; Thomas et al, 1975), and the KAM is the external moment acting to adduct the knee, or put it in a more varus alignment, thereby increasing the load on the medial compartment (Yang et al, 2010). In the studies directly examining knee biomechanics, it was found that higher KAM peaks (Miyazaki et al, 2002) and higher KAM impulses (Bennell et al, 2011) were associated with an increased risk of knee OA structural progression. The other two longitudinal studies on gait biomechanics and knee OA progression risk focused on the hip (Chang et al, 2005) and ankle (Chang et al, 2007) joints. Greater peak internal hip abduction moments (i.e. greater peak external hip adduction moments) and greater toe-out angles during gait were both associated with a decreased risk of knee OA structural progression. The decreased progression risk was hypothesized to be due to the resulting effect on the KAM during gait. This provides evidence that interrelationships among the lower extremity joints in the kinetic chain can impact knee joint mechanics, and should be studied to fully understand how changes to the local, dynamic biomechanical loading environment of the knee can be achieved.

This focus on the KAM in the literature has led to the development of a plethora of conservative management strategies targeting this feature. Orthotic devices (Gaasbeek et al, 2007; Gross and Hillstrom, 2008; Lindenfeld et al, 1997; Pollo et al, 2002; Radzimski et al, 2012; Self et al, 2000), muscle strengthening exercise (Chang et al, 2005), and gait modifications (Chang et al, 2007; Fregly et al, 2007; Hunt et al, 2011; Mundermann et al, 2004; Schache et al, 2008; Simic et al, 2012) have all been recommended to reduce the magnitude of the KAM. Most studies have focused on altering the peak KAM. While the peak KAM has been linked to structural progression (Miyazaki et al, 2002), it only considers the magnitude of knee loading at one point in the gait cycle. In contrast, the KAM impulse gives an indication of both the magnitude and duration of loading throughout the gait cycle (Thorp et al, 2006). Only one study has related a conservative

intervention to the KAM impulse. Increased lateral trunk lean during gait was found to decrease this variable (Simic et al, 2012).

The results of the clinical intervention studies are equivocal with respect to reducing these discrete KAM features (Fantini Pagani et al, 2010; Gaasbeek et al, 2007; Haladik et al, 2013; Schache et al, 2008; Simic et al, 2011), and no longitudinal studies have examined their effect on structural progression, although they have been found to reduce pain (Pollo et al, 2002; Lindenfeld et al, 1997). So, the question is whether the KAM peak and KAM impulse are the best biomechanical targets for conservative interventions. Differences in study methodologies, particularly the method of amplitude normalization (Simic et al, 2011), may be one reason for equivocal results. Two common methods of moment amplitude-normalization are used in the knee OA literature: normalizing to body mass, and normalizing to body size (body weight times height). How the different methods of amplitude-normalization affect gait outcome measures and the differences associated with knee OA progression would facilitate comparison and interpretation of results between studies. Furthermore, neither the KAM impulse or KAM peak provides an indication of dynamic loading characteristics (i.e. pattern of loading). Principal component analysis (PCA) is one waveform analysis tool that considers the entire waveform, and can extract the main dynamic patterns in the data (principal components, PCs), considering both amplitude and temporal information (Jackson, 2003). PCA has previously been used to identify biomechanical waveform patterns relevant to various aspects of knee OA (Astephen et al, 2008; Astephen Wilson et al, 2011; Astephen Wilson et al, 2010; Gaudreault et al, 2011; Hatfield et al, 2011; Landry et al, 2007; Smith et al, 2004). Specific extracted PCs have been shown to be highly reliable metrics, particularly sagittal angles and moments and frontal plane moments (Robbins et al, 2013). Furthermore, specific PCs have been shown to be unaffected by which anatomical reference frame is used to express joint moments (Newell et al, 2008; Brandon et al, 2011), making it a robust analysis technique. In addition, although the vast majority of conservative interventions target the KAM (particularly the peak KAM), decreases in the peak can be offset by increases in the peak knee flexion moment, which act to keep medial compartment loading the same (Walter et al, 2010). Also, transverse mechanics

should not be neglected when considering the local biomechanical environment of the knee, as altered rotational kinematics (Andriacchi et al, 2004) and excessive shear forces (Wilson et al, 2003; Hashimoto et al, 2009) may cause articular cartilage damage. The four longitudinal studies relating gait biomechanics to knee OA structural progression did not include non-frontal plane biomechanics in their prediction models, and no studies have looked at three-dimensional gait biomechanics and progression to TKA. Since non-frontal plane biomechanics contribute to the function and overall loading of a joint, at present we do not have a comprehensive understanding of the local, dynamic biomechanical environment during gait, and how this environment plays a role in knee OA progression. We also do not know how mechanics in multiple planes interact to influence risk of progression to TKA, as all prediction modeling thus far has included only one gait variable in the model.

An additional factor not taken into consideration in the four longitudinal studies on structural progression was physical activity or a measure of the frequency of loading. Higher frequency of joint loading, even at low force levels, has been related to cartilage properties in animal models (Waldman et al, 2004; Horisberger et al, 2012; Horisberger et al, 2013) and in humans (Racunica et al, 2007), and physical activity has been shown to improve function and decrease pain in those with knee OA (Dunlop et al, 2011; Ettinger et al, 1997; Messier et al, 2004). In those with knee OA, it has been found that frequency of knee loading explains a significant proportion of the variance (9%) in knee pain scores (Robbins et al, 2011). Because loading frequency affects cartilage properties and symptoms, it could play a role in both symptom and structural progression. Thus, in addition to demographic and clinical risk factors, a measure of loading frequency should be included in longitudinal knee OA progression studies.

To summarize, while dynamic lower extremity biomechanics during gait have been linked to knee OA structural progression, there are significant gaps in the literature that limit our understanding of the relationship between lower extremity biomechanics and knee OA progression. First, no longitudinal gait biomechanics studies have examined progression in terms of progression to TKA, therefore capturing progression from a

structural and symptomatic perspective. Second, to our knowledge, no studies have examined the interrelationship among all three lower extremity joints to determine how the loads are distributed throughout the kinetic chain and their potential impact on the mechanical environment of the knee joint. Third, previous progression studies have used discrete waveform features, such as KAM peaks and impulses, neither of which provide information about the temporal (dynamic) biomechanical patterns. Finally, previous progression studies have focused on univariate frontal plane factors, even though sagittal plane features can affect medial compartment loading, and kinematic and kinetic changes in the transverse plane can affect cartilage integrity.

1.2 Research Objectives and Hypotheses

The following three inter-related objectives form a systematic approach to address the main research question of this dissertation.

Objective 1

To determine if three-dimensional lower extremity (i.e. hip, knee, and ankle) amplitude and temporal biomechanical features during gait were different at baseline between those with moderate medial compartment knee OA who progressed to TKA versus those that did not at follow up. Two sub-objectives that helped address the primary objective were:

a) To determine the relation between measures of static frontal plane alignment calculated using motion capture data and calculated using full-leg radiographs.
b) To determine the relation between self-reported physical activity level and objectively measured physical activity level.

Rationale: Given that dynamic loading characteristics have been associated with altered joint loading and an increased risk of knee OA structural progression, between-group differences in three-dimensional lower extremity gait biomechanics at baseline would provide objective data on which to develop multivariate prediction models of OA progression. These models could provide the foundation for targeted biomechanical conservative interventions.

Hypothesis: It was hypothesized that three-dimensional lower extremity biomechanical features during gait would be different between the TKA and no-TKA groups, with the TKA group exhibiting mechanical factors that would increase overall knee joint loading, support a sustained load, and indicate altered rotational mechanics.

Objective 2

To determine how the KAM features extracted using PCA compared to the discrete features already linked to structural progression (i.e. KAM peak and KAM impulse). Sub-objectives were:

a) To determine whether discrete knee biomechanical gait variables previously associated with structural progression were associated with progression to TKA.
b) To determine what effect amplitude normalization had on these features (i.e. would they still differ between the TKA and no-TKA groups using different methods of amplitude normalization).

Rationale: The gait biomechanics literature on structural progression has focused primarily on the KAM peak with more recent studies calculating the KAM impulse in an attempt to determine a more comprehensive measure of the frontal plane mechanics. However, neither captures the dynamic loading characteristics throughout the gait cycle. Determining whether there is a relationship between discrete KAM features and those extracted using PCA would allow for easier comparison between different aspects of the KAM waveform that have been presented in different studies. If poor relationships were found, it would indicate that KAM features extracted through PCA are contributing unique information with respect to knee loading during gait. Determining if discrete measures associated with structural progression are also related to progression to TKA will improve our understanding of mechanisms of knee OA progression, and provide insight as to whether conservative interventions are targeting the most effective biomechanical features.

Hypothesis: It was hypothesized that KAMPC1 would be significantly related to the KAM impulse since both capture the overall magnitude of the KAM, but that KAMPC2 would be unrelated to either discrete measure, since it captures a temporal aspect of the waveform. It was hypothesized that the KAM peak and KAM impulse would be higher at baseline in the TKA group than in the no-TKA group, as structural progression is a factor in the TKA decision-making process (Gossec et al, 2011). Finally, it was hypothesized that the results would be consistent, regardless of amplitude-normalization method.

Objective 3

To determine how well three-dimensional lower extremity biomechanical features identified as significantly different between the group who progressed to TKA and the group that did not (objectives 1 and 2) *predicted* progression to TKA. Sub-objectives were:

a) To determine how well individual (univariate) three-dimensional biomechanical features during gait (KAM peak and KAM impulse, and features extracted using PCA) classified those who progressed to TKA versus those that did not.
b) To determine if a multivariate model including multiple gait features improved the classification ability over univariate models.
c) To determine how well the gait biomechanical features that best classified the two groups *predicted* progression to TKA.

Rationale: While large epidemiological studies include numerous features in prediction models, none of these studies include biomechanical gait features. Prediction models developed using biomechanical gait data have only included one gait variable to predict structural progression. Determining the best combination of biomechanical gait features would identify biomechanical risk factors for OA progression that could be potential targets for conservative interventions, which thus far have focused only on discrete features from the KAM waveforms.

Hypothesis: It was hypothesized that a multivariate model capturing different, uncorrelated dynamic loading features would provide a better prediction of progression to TKA than any univariate model.

1.3 DISSERTATION OUTLINE

This PhD dissertation consists of seven chapters. In Chapter 2, relevant background literature is presented. Chapter 3 contains a detailed description of the study methodology and how the study hypotheses were statistically tested. The results for each research objective are presented in Chapters 4-6, which are organized as self-contained journal format papers. The overall study results are synthesized and discussed in Chapter 7, which also contains a section proposing clinical implications and directions for future research.

CHAPTER 2 BACKGROUND LITERATURE

This chapter contains a discussion of the background literature relevant to this dissertation. First, knee osteoarthritis (OA) will be defined, followed by criteria for its diagnosis. Next, various definitions of knee OA progression are presented, including the definition used in this dissertation: progression to total knee arthroplasty. The subsequent sections describe in detail biomechanical risk factors for knee OA, and discuss their role in mechanisms of knee OA progression.

2.1 KNEE OSTEOARTHRITIS

OA has been defined as a progressive disease of the synovial joints, resulting in the breakdown of articular cartilage and bone, and leading to pain, stiffness and impaired function (Lane et al, 2011). The long-term effects of these symptoms jeopardize an individual's mobility. OA is a huge problem in industrialized countries (Wong et al, 2010). Currently, over 4.4 million Canadians (including 49% of adults over 70 years) are living with OA, with the knee being the most common joint affected (Dillon et al, 2006), particularly the medial tibiofemoral compartment (Frontera and Silver, 2002; Thomas et al, 1975). With the aging population and the obesity epidemic, the number of Canadians with OA is expected to reach 10.4 million (71% of adults over 70) by 2040 (Arthritis Alliance of Canada, 2011). In the United States 30% of the population is expected to have knee OA by 2030 (Lawrence et al, 2008). The reduced mobility resulting from knee OA leads to an increased risk of cardiovascular disease, poor quality of life, and a loss of function (Conn et al, 2008). Specifically, knee OA results in more difficulty with activities of daily living, such as walking or climbing stairs, than any other medical condition for people over the age of 65 years (Hunter and Felson, 2006). Along with the personal burden of OA there is a tremendous economic cost. In 2003, $328.1 billion was spent on direct care related to arthritic conditions in the United States (Yelin et al, 2007). In Canada in 2010, the estimated direct and indirect healthcare costs associated with OA were $10 billion and $17 billion, respectively. Cumulatively, by 2040, the direct and

indirect costs are expected to be $550 billion and $909 billion, respectively (Arthritis Alliance of Canada, 2011).

There is currently no cure for knee OA, with total knee arthroplasty (TKA) being the end-stage treatment of choice for those with severe knee OA. As a result of the rising prevalence of knee OA, the number of TKA surgeries has increased dramatically. In Canada, the rate of TKA increased 125% from 1994-5 to 2004-5 (Canadian Joint Registry, 2006). In the United States the demand is expected to increase by 631% by 2030 (Kurtz et al, 2007). Because implants have a limited lifespan, and the largest increase in the rate of TKA surgery in North America has been in younger patients (Canadian Joint Registry, 2006; Jain et al, 2005), the revision rates are expected to rise steeply in the future. Furthermore, not all patients are satisfied with the results of TKA (Robertsson et al, 2000). Thus, there is a need to develop conservative management strategies to slow knee OA progression and prevent or delay the need for TKA surgery.

In order to evaluate the effectiveness of conservative interventions in slowing knee OA progression, the term "progression" must first be defined. The following section will discuss ways to assess knee OA progression.

2.2 Defining Knee Osteoarthritis Progression

Traditionally, knee OA had been characterized by the degradation of articular cartilage (Altman et al, 1986), but it is now recognized that knee OA affects the whole joint, with damage of the articular cartilage, but also the subchondral bone, ligaments, menisci, periarticular muscles, peripheral nerves, and the synovium (Brandt et al, 2006; Lane et al, 2011). The damage to these different aspects of the knee joint constitutes the structural changes associated with knee OA, or the "disease" component of knee OA (Lane et al, 2011). In addition to the structural changes, there are the symptoms associated with knee OA: the pain, stiffness and impaired function. This aspect is considered the "illness" component of knee OA (Lane et al, 2011). Because of the lack of relationship between structural changes and symptoms (Barker et al, 2004; Creamer et al, 2000), the

Osteoarthritis Research Society International has proposed that research studies should consider the structural changes and symptoms as two separate components of knee OA (Lane et al, 2011).

The American College of Rheumatology has defined knee OA in terms of structural changes and symptoms using three sets of criteria: i) clinical and laboratory, ii) clinical and radiographic, and iii) clinical (Table 2.1), with the clinical and radiographic criteria having the highest combination of sensitivity and specificity (Altman et al, 1986). In terms of defining progression, since the hallmark of knee OA is the degradation of articular cartilage and changes in the surrounding bone and soft tissue, most studies looking at progression have defined it from a structural perspective (i.e. cartilage degeneration, osteophtye formation, or joint space narrowing). However, structural changes are poorly correlated with knee OA symptoms (Barker et al, 2004; Creamer et al, 2000), and symptoms are what lead patients to seek medical attention. This section will describe how to assess progression based on these two different aspects of knee OA.

Table 2.1: Definitions of knee OA proposed by the American College of Rheumatology (Altman et al, 1986).

Clinical and Laboratory	Clinical and Radiographic	Clinical
Knee pain At least 5 of 9: • Age > 50 years • Stiffness < 30 minutes • Crepitus • Bony tenderness • Bony enlargement • No palpable warmth • Erythrocyte sedimentation rate <40 mm/hour • Rheumatoid factor <1:40 • Synovial fluid signs of OA (clear, viscous, or white blood cell count <2000/mm^3	Knee pain At least 1 of 3: • Age > 50 years • Stiffness < 30 minutes • Crepitus • Osteophytes	Knee pain At least 3 of 6: • Age > 50 years • Stiffness < 30 minutes • Crepitus • Bony tenderness • Bony enlargement • No palpable warmth

2.2.1 Knee OA Structural Progression- "Disease Component"

Structural progression can be examined using arthroscopy as well as imaging techniques such as radiography, magnetic resonance imaging (MRI), and ultrasound (US). This section will provide a brief overview of each technique.

Knee arthroscopy is a minimally invasive surgery in which an arthroscope is inserted into the knee joint through a small incision. The arthroscope allows a direct and magnified view of the inside of the knee joint, thus arthroscopic surgery is considered the "gold standard" for assessing structural damage; particularly damage to articular cartilage (Ayral, 1996). Various arthroscopic classification schemes have been proposed in the literature, but the most commonly used classifications are the Outerbridge scale (Outerbridge, 1961) and the Noyes and Stabler scale (Noyes and Stabler, 1989). Both scales focus primarily on damage to the articular cartilage, rather than changes to the entire joint. While arthroscopy is considered the "gold standard" for assessing structural damage, it is a surgical procedure. While some of the cost can be balanced by the fact that you can perform treatment and diagnosis simultaneously, this tool is not practical for monitoring structural progression, particularly in research studies. For this reason, non-invasive imaging techniques are utilized.

Radiography is the most prevalent imaging tool used to assess knee OA structural progression, with the Kellgren and Lawrence (KL) scale (Kellgren and Lawrence, 1957) the most common radiographic outcome measure. This scale has five discrete grades, outlined in Table 2.2. Typically, a diagnosis of knee OA is given when a patient receives a Grade 2 on the scale. The reliability of KL grades has been reported in the literature. Interrater reliability, assessed as percent agreement between two raters by Scott et al (1993), was found to be 51.4% (Scott et al, 1993). Interrater reliability, assessed using intraclass correlation coefficients (ICCs), has been reported to be 0.59-0.81 (Gunther and Sun, 1999; McKean et al, 2007), whereas intrarater reliability has been found to be 0.85-0.93 (Gunther and Sun, 1999).

A problem with the KL scale is that it was not designed to assess structural progression (Altman and Gold, 2007; Felson et al, 2011). Although it is a five-point scale, only grades 2-4 apply to those with knee OA. Most studies define structural progression as an increase of at least one grade, but a lot of structural damage may occur within one grade (Felson et al, 2011). For example, KL3 requires definite joint space narrowing, but this could range from mild to bone-on-bone. The scale is also vague with defining structural progression from one grade to another. For example, when does an osteophyte move from "moderate" to "large," or when does "some" sclerosis turn into "severe" sclerosis? As a result, the scale is not very sensitive in detecting structural progression.

Table 2.2: Kellgren and Lawrence criteria for knee OA (Kellgren and Lawrence, 1957).

Grade	**Description**
Grade 0	No osteoarthritis
Grade 1	Doubtful narrowing of joint space and possible osteophytic lipping
Grade 2	Definite osteophytes and possible narrowing of joint space
Grade 3	Moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends
Grade 4	Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends

Due to these limitations, it has been recommended that knee OA structural progression be assessed by grading individual pathological features of the disease process, such as osteophytes and joint space narrowing (Felson et al, 2011). Scott et al (1993) have developed a grading scale for individual radiographic features of knee OA, including medial and lateral osteophytes, medial and lateral joint space narrowing, medial and lateral subchondral sclerosis, and chondrocalcinosis (Scott et al, 1993). The Scott Feature Based score system has shown comparable (or higher) interrater reliability with the KL scale. Percent agreement between pairs of readers ranged from 70.8%-97.5% for individual features (Scott et al, 1993). Interrater reliability assessed using ICCs ranged from 0.25-0.71 (Scott et al, 1993). Medial compartment joint space narrowing had the

best interrater reliability, with an ICC of 0.70. The ICC for medial compartment osteophytes was 0.60.

Altman et al (1987) looked at how sensitive different radiographic features were for detecting knee OA structural progression (Altman et al, 1987). Eight experts with over 12 years of clinical experience graded 32 pairs of knee radiographs, with the time between radiographs ranging from one month to eight years. The experts were blinded to the temporal order of the pairs. The radiographs showed a wide range of structural progression. Nine features were graded on a 0-3 scale (0 = normal, 1 = mild, 2 = moderate, 3 = severe): medial and lateral compartment joint space narrowing, medial and lateral compartment osteophytes, medial and lateral compartment sclerosis, medial and lateral compartment cysts, and alignment. According to the experts' opinion, joint space narrowing was the most useful feature to detect knee OA structural progression. Interrater reliability and the correct identification of the time sequence of the pairs of radiographs confirmed this; medial joint space narrowing was the best variable to detect knee OA structural progression, followed by medial compartment osteophytes, varus alignment, and medial sclerosis (Altman et al, 1987). Gossec et al (2008) also found that joint space narrowing was more responsive to detecting change over time when compared to KL grades for 50 pairs of radiographs with a between-radiograph interval of 30 months (Gossec et al, 2008).

Grading the individual features can still suffer from the same limitations as grading the entire joint. For example, a lot of change in joint space narrowing can occur before the patient moves into the next ordinal category. Felson et al (2008) have recommended going one step further by using half grades for joint space narrowing to increase sensitivity in assessing structural progression (Felson et al, 2008). Using joint space narrowing as a continuous measure by measuring joint space width in millimetres has also been advocated (Ornetti et al, 2009), however interrater and intrarater reliability for this technique has been found to be lower than for grading joint space narrowing using a categorical scale (Gossec et al, 2008). Astephen Wilson et al (2011) have also used a radiographic visual analogue scale to capture a complete picture of radiographic changes

(i.e. joint space narrowing, osteophytes, sclerosis, and joint deformity) on a continuous scale. This tool showed higher interrater reliability than the KL score, medial compartment joint space narrowing, and medial compartment osteophytes graded on ordinal scales (Astephen Wilson et al, 2011).

Regardless of the grading scale used, the primary limitation of radiography in assessing knee OA structural progression is that a radiograph does not provide information about all of the pathological changes occurring at the joint. Changes to the soft tissue, such as the articular cartilage, ligaments, and menisci, which are part of the knee OA process cannot be visualized (Lane et al, 2011; Peterfy et al, 2004). Joint space narrowing has been used as a surrogate measure of cartilage degeneration, however this may not always be a valid assumption. Felson et al (2008) describe the scenario of pseudo widening, where structural progression of OA in the lateral compartment causes lateral joint space narrowing and concomitant medial compartment widening (Felson et al, 2008). This pseudo widening can artificially slow the appearance of medial compartment narrowing in those affected in both compartments, or may even make it appear that the medial compartment is improving.

Additionally, radiographs expose patients to radiation. MRI and US have both been proposed as non-invasive imaging alternatives that can visualize soft tissue and do not rely on ionizing radiation (Iagnocco, 2010; Lane et al, 2011). However, both are fairly new imaging techniques in the field of knee OA, and thus little work has been done to validate these imaging modalities for monitoring structural progression. With respect to MRI, compared to radiography, validity has been shown for using the change in cartilage thickness to monitor structural progression (Bruyere et al, 2007). The change in cartilage volume has shown questionable validity for monitoring structural progression (Raynauld et al, 2004, Raynauld et al, 2006). Clearly, more validation studies are needed to determine what MRI outcome measure is best. Continuous outcome measures like cartilage volume and thickness also are very time-intensive to determine. Specialized software must be used, and tissue boundaries must be segmented throughout a large series of slices (Eckstein and Wirth, 2011). Also, the cost and limited availability of MRI

scanners make them difficult to use routinely in research and clinical practice (Iagnocco, 2010). Unlike MRI scanners, US scanners are cheaper, portable, and readily available. It is conceivable that family physicians could one day have portable devices in their clinics to monitor structural progression, rather than sending patients to hospitals for radiographs or MRI scans. However, very little work on the measurement properties of US has been done. Before this imaging modality can be used routinely in knee OA research or clinical practice, standardized grading systems or continuous measures must be developed, and the reliability, sensitivity, specificity, and validity of these outcome measures must be determined.

In summary, although MRI and US are both promising imaging tools for the assessment of knee OA structural progression, much research needs to be done on their measurement properties and how to best assess structural progression. Currently, the recommended imaging modality for assessing structural progression, according to the Osteoarthritis Research Society International, is radiography, specifically joint space narrowing (Ornetti et al, 2009).

2.2.2 Knee OA Symptom Progression- "Illness Component"

Knee OA symptoms, or the "illness" component of knee OA, are mainly evaluated using self-report questionnaires. Examples of these questionnaires include the visual analogue scale, the Oxford 12 Item Knee Score, the Knee Osteoarthritis Outcome Score, and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The primary limitation with these measures is that scores can be influenced by a number of other factors, including sex (women report more severe symptoms) (Elbaz et al, 2011), body mass index (BMI, obese individuals report more severe symptoms) (Elbaz et al, 2011), short-term fluctuations in symptoms (Conner-Spady et al, 2004), co-morbidities (those with more co-morbidities report more severe symptoms) (Dunbar et al, 2004), and coping style (Lane et al, 2011). While there are inherent limitations with using self-report questionnaires to assess the "illness" component of knee OA, they do provide a measure of the symptoms that a patient is experiencing. This is important, because it is the symptoms of knee OA that lead patients to their physicians, and progression of symptoms

is a part of the decision-making process when considering a patient for TKA (Gossec et al, 2011).

Objectively measuring the "illness" component of knee OA is difficult. Gait analysis has been used as one method to do so. Astephen Wilson et al (2011) used multiple regression analysis to determine which biomechanical and neuromuscular gait variables were associated with self-reported pain (determined via WOMAC) (Astephen Wilson et al, 2011). The only significant term in the pain regression model was gait speed, which accounted for 28.2% of the variance. There were also significant correlations ($r = 0.41$ and $r = 0.32$) between pain and dynamic characteristics from the lateral gastrocnemius and medial hamstrings muscle activation patterns (capturing the difference between early and late stance activation and the magnitude of activation during early stance and toe off, respectively), but these terms did not remain significant when entered into the multiple regression model (Astephen Wilson et al, 2011). The results of this study indicate that gait speed, and to a lesser extent muscle activation patterns, may be an objective way to measure the "illness" component of knee OA.

2.2.3 Knee Osteoarthritis Progression- Total Knee Arthroplasty

As indicated in the above sections, knee OA progression has been defined in terms of structural progression (i.e. the "disease" component) and in terms of symptom progression (i.e. the "illness" component). Structural progression is monitored using imaging modalities, and joint space narrowing measured via radiographs is presently the recommended metric (Ornetti et al, 2009). Symptom progression is typically measured using self-report questionnaires.

For the purpose of this dissertation, knee OA progression was defined as progression to TKA. TKA was chosen as the outcome measure because it is a clear endpoint that includes both structural and symptomatic aspects of knee OA progression. Worse radiographic disease severity and worse pain and function are factors that go into the clinical decision-making process as to whether a patient should receive TKA (Gossec et al, 2011). Therefore, this metric captures both the "disease" component of knee OA (i.e.

structural changes), as well as the "illness" component (i.e. symptoms). However, it is recognized that there are limitations in using TKA as a metric of knee OA progression, as considerable clinical decision-making is involved when selecting an appropriate TKA candidate. Additionally, a factor in TKA decision-making is a patient's willingness to undergo the procedure (Hawker et al, 2006). Ideally, when using TKA as a metric of progression, clinical decision-making variability should be reduced by sampling patients of one orthopaedic surgeon (however this may limit sample size), and an outcome measure should be included that assesses willingness to have TKA.

A knee OA progression outcome measure capturing structural and symptomatic progression was used in this dissertation because a main purpose was to understand *mechanisms* of knee OA progression. Including both aspects of progression is important because factors driving symptom progression may be different than those driving structural progression. This understanding would provide objective data on which to develop new and assess targeted biomechanical interventions. The next section discusses the etiology of knee OA, including proposed mechanisms of knee OA progression.

2.3 ETIOLOGY OF KNEE OSTEOARTHRITIS

Knee OA has both a biochemical and biomechanical etiology. Brandt et al (2006) proposed that there are two pathways to OA development: i) the biomaterials that comprise the joint are normal, but the mechanical stresses are excessive, and ii) the loads placed on the joint are normal, but the biomaterials are abnormal (for example, due to genetic abnormalities) (Brandt et al, 2006). Brandt's first pathway describes the biomechanical etiology of knee OA initiation. Brandt's second pathway involves biochemical mechanisms of knee OA development. However, neither mechanism occurs in isolation. Brandt acknowledged that OA is a mechanically induced disorder, where abnormal joint mechanics lead to biological effects that are mediated biochemically (Brandt et al, 2006). Thus, the biochemical and biomechanical etiologies of knee OA will be discussed together. Various risk factors for knee OA initiation and progression have been identified in the literature, including obesity, joint injury, varus alignment, and gait

biomechanics. The role of these risk factors in the structural and symptomatic progression of knee OA will be discussed in the following sections, from biochemical and biomechanical perspectives.

2.3.1 Obesity

Large-scale epidemiological studies have shown that obesity is one of the major risk factors for knee OA initiation and progression (Cooper et al, 2000; Felson et al, 1992; Holmberg et al, 2005; Yusuf et al, 2011). Laberge et al (2011) reported that cartilage defects were found more frequently in overweight and obese subjects with no radiographic evidence or symptoms of knee OA than in normal weight controls. The lesions were also found to increase in severity more frequently in obese subjects compared to normal weight controls (Laberge et al, 2012). Cooper et al (2000) found that subjects with the greatest body mass index (BMI) at baseline had a nine-fold increased risk of developing mild radiographic knee OA, and an 18-fold increased risk of developing moderate radiographic knee OA (Cooper et al, 2000). BMI also predicted osteophyte and joint space narrowing (i.e. structural) progression. The increased risk of knee OA initiation and progression in those who are obese is thought to be due to biochemical and biomechanical factors.

Biomechanically, obesity has been hypothesized to produce an excess loading effect on the knee cartilage (Pottie et al, 2006; Wang et al, 2009). Body mass alone has been found to explain 33% of the variance in the first peak of the knee adduction moment (KAM) waveform (Segal et al, 2009), and modelling work has shown that weight reduction causes a decrease in knee compressive loads (Messier et al, 2011). Increased BMI has also been associated with an inability to unload the knee during stance (indicated by a decreased difference between the early and mid-stance KAM magnitudes) (Harding et al, 2012). At a cellular level, increased body mass is thought to inhibit matrix formation and increase cartilage degradation by activating load-sensitive mechanoreceptors on the surface of chondrocytes (Pottie et al, 2006).

In addition to the effects of obesity later in life, it has been found that overweight and obese children show trends toward decreased cartilage volume (Jones et al, 2003). This means that adults who have been overweight or obese their whole life may experience a negative loading environment due to their current weight, but also may have less cartilage to withstand these loads than an adult of normal weight. This reasoning is supported by a 1999 study by Gelber et al, who found that greater BMI in young men (aged 20-29 years) was associated with an increased risk of developing knee OA later in life (Gelber et al, 1999). One important factor not taken into consideration in these studies was physical activity. The amount of physical activity an individual engages in is important because it gives an indication of the frequency of joint loading, which has been related to cartilage properties in animal models. Waldman et al (2004) found that the long-term application of cyclical compressive loads resulted in more extracellular matrix (30% more proteoglycans and 40% more collagen), a two-fold increase in load-bearing capacity, and a three-fold increase in bovine cartilage stiffness (Waldman et al, 2004). Similar results were found for shear loading: bovine cartilage stimulated for four weeks with cyclic shear loading accumulated more extracellular matrix (35% more proteoglycans and 40% more collagen), had a three-fold increase in load-bearing capacity, and a six-fold increase in stiffness compared to unstimulated controls (Waldman et al, 2003). However, prolonged periods of cyclic loading are able to cause chondrocyte death (Horisberger et al, 2012). In humans, in a cross sectional study, Racunica et al (2007) found that there was a positive association between the number of weekly episodes of vigorous physical activity performed and tibial cartilage volume in asymptomatic adults, and no association with pathological features such as cartilage defects or bone marrow lesions (Racunica et al, 2007). Thus, those who have had lifelong obesity may have decreased cartilage volume compared to normal weight controls due to decreased physical activity levels (and therefore decreased loading frequency), rather than from an increased magnitude of load over time. The findings that cyclical loading and regular physical activity are associated with increased cartilage volume highlight the need to include a measure of physical activity or loading frequency in models of knee OA initiation and progression.

Obesity also has a biochemical effect, since adipose tissue is a biochemically active tissue. Brunner et al (2010) reported that a high fat diet in animals led to knee OA development, independent of body weight. They fed rabbits either a high fat (17%) or a low fat (2%) diet and found that, even though there was no difference in weight between the two groups, the high fat diet group had more cartilage degradation than the low fat diet group (Brunner et al, 2010). In humans, adipose tissue is considered to be an endocrine organ, secreting adipokines such as leptin, adiponectin, resistin, and vistatin (Dumond et al, 2003; Pottie et al, 2006). It is hypothesized that leptin plays an important role in the pathophysiology of knee OA, as it and its functional receptor have been identified in human chondrocytes (Pottie et al, 2006). Leptin has also been found at high levels in osteoarthritic cartilage and in osteophytes in patients undergoing arthroscopy or TKA (Dumond et al, 2003). The level of leptin correlated with the severity of cartilage damage. Leptin reportedly stimulates cartilage anabolism, and may contribute to osteophyte formation by promoting fetal-like skeletal development processes and inhibiting extracellular matrix synthesis (Dumond et al, 2003; Pottie et al, 2006). Hui et al (2011) found that leptin alone could stimulate cartilage degradation via the up regulation of matrix metalloproteinases, and that it behaved synergistically with the pro-inflammatory cytokines interleukin-1 and tumor necrosis factor-α to degrade cartilage (Hui et al, 2012).

Leptin is not the only chemical secreted by adipose tissue that has been implicated in the etiology of knee OA. While the disease is primarily considered a non-inflammatory arthropathy, pro-inflammatory cytokines secreted by the adipose tissue such as tumor necrosis factor-α and interleukin-1, interleukin-6 and interleukin-17 have all been implicated in knee OA progression (Malemud, 2004; Pottie et al, 2006; Valdes and Spector, 2009). Specifically, these chemicals upregulate the expression of matrix metalloproteinases, nitric oxide, and prostaglandin-2. Matrix metalloproteinases are involved in altering the metabolism of articular cartilage and the synovial membrane, and nitric oxide and prostaglandin-2 are able to alter chondrocyte homeostatis (Malemud, 2004). Pro-inflammatory cytokines such as interleukin-1β and tumor necrosis factor-α have also been found to be independent predictors of worsening knee pain over 5 years in

those with knee OA (Stannus et al, 2013). In summary, obesity is a known risk factor for knee OA initiation and progression, with the increased risk in those who are obese due to a combination of biomechanical and biochemical factors. Although they have been discussed separately above, in reality they cannot be separated.

2.3.2 Joint Injury

Previous joint injury is another major biomechanical risk factor for knee OA. An increased prevalence of knee OA has been reported in those sustaining anterior cruciate ligament and meniscal injuries in the past (Hootman et al, 2003; Lohmander et al, 2004; Lohmander et al, 2007; von Porat et al, 2004). Like obesity, the increased risk associated with previous joint injury can be attributed to biomechanical and biochemical factors. Biochemically, in the acute phase, joint injuries cause the release of oxygen free radicals from the chondrocytes, triggering chondrocyte death and matrix degradation. Inflammatory chemicals such as cytokines, tumor necrosis factor-α, interleukin-1, nitric oxide, and matrix metalloproteinases are also released into the synovial fluid, which can lead to cartilage degradation (Anderson et al, 2011). Biomechanically, the mechanical forces associated with the injury can cause immediate damage to the articular cartilage and subchondral bone (Anderson et al, 2011). In the longer-term, kinematic alterations caused by the injury can lead to cartilage degradation (Andriacchi et al, 2004). It is thought that the change in gait kinematics following knee injury shifts the load bearing to unconditioned regions of cartilage, initiating the degenerative process by destroying chondrocytes and disrupting the extracellular matrix (Andriacchi et al, 2004; Andriacchi et al, 2009; Wilson et al, 2009). Using computer simulations, Andriacchi et al (2006) showed that a five degree internal tibial rotation offset (associated with anterior cruciate ligament deficiency) predicted patterns of cartilage thinning which were consistent with patterns seen in knee OA. Thus, to understand mechanisms of primary knee OA development and progression, it is important to only study participants with no previous history of joint injury.

2.3.3 Knee Alignment

Another risk factor for knee OA initiation and progression that has been identified from epidemiological studies is static frontal plane alignment. Using data from the Multicentre Osteoarthritis Study cohort, a large group of individuals with knee OA or risk factors for knee OA, Sharma et al found that a varus hip-knee-ankle (HKA) angle (≤ 178 degrees) at baseline resulted in a slightly increased risk for medial knee OA structural development (odds ratio of 1.49), and a greatly increased risk for medial knee OA structural progression (odds ratio 3.59), 30 months later compared to neutral knees (179-181 degrees) (Sharma et al, 2010). Similarly, Yusuf et al (2011) found a relative risk of medial knee OA structural progression over 6 years of 2.3 in those with varus knees (Yusuf et al, 2011). The increased risk of varus alignment is thought to be due to load distribution. Greater varus alignment would increase the moment arm length of the ground reaction force in the frontal plane, therefore increasing the KAM. However, these studies looked at knee alignment statically. Static knee alignment obtained from radiographs is not significantly correlated with dynamic knee alignment during gait, or with the peak KAM or KAM impulse (Barrios et al, 2012). The following section will explain why the dynamic loading environment of the knee is important to study.

2.3.4 Gait Biomechanics

The link between mechanical loading and knee OA structural and symptom progression has been established dynamically in animal models (Chen et al, 1999; Kim et al, 2012; O'Connor and Brandt, 1993; Radin et al, 1984; Walker et al, 1991). Work in animal models has shown that repetitive impulse loading is enough to initiate articular cartilage damage and changes in the subchondral bone consistent with changes found in knee OA (Radin et al, 1984), and increase the production of inflammatory chemicals (Wang et al, 2007) that have been linked to increased knee pain (Stannus et al, 2013). Animal modelling has also shown that sustained compressive load can lead to cartilage degradation (Chen et al, 1999), and an increased risk of cartilage and subchondral bone damage from normal, physiological impulse loads following the sustained loading (Kim et al, 2012). This is thought to be because the accumulated strain energy eventually exceeds the energy of the covalent bonds of the collagen in the cartilage matrix, initiating

damage (Chen et al, 1999), and also because biosynthetic activity is reduced during conditions of sustained compressive loading (Arokoski et al, 2000; Wong et al, 1999). Sustained loading also causes an upregulation of inflammatory chemicals (Wang et al, 2007) linked to knee pain (Stannus et al, 2013). Less studied is knee OA progression due to shear loading, however theoretical evidence indicates that excessive shear forces are able to cause cartilage damage (Wilson et al, 2003), and in vitro experiments using human chrondrocytes have shown that shear strain results in increased expression of p53, a protein responsible for chondrocyte apoptosis (Hashimoto et al, 2009). Thus, there are three different dynamic loading mechanisms that have been associated with knee OA structural and symptom progression: repetitive impulse loading, sustained compressive loading, and shear loading.

Gait is the most common model used to establish links between biomechanics and knee OA initiation and progression because dynamic loading occurs with more frequency during gait than any other activity of daily living, and also because walking is the activity most commonly reported as difficult by those with knee OA (Andriacchi et al, 2009; Guccione et al, 1994). Andriacchi has proposed a model of knee OA initiation and structural progression based on gait mechanics (Andriacchi et al, 2004; Andriacchi and Mundermann, 2006; Andriacchi et al, 2009). According to the model, in a healthy joint the articular cartilage becomes conditioned to the repetitive loading during gait and no damage occurs. The finding that the thickest articular cartilage occurs in the load-bearing areas of the tibiofemoral joint supports this hypothesis (Andriacchi et al, 2009). However, the degenerative process may be initiated if there is a change to the normal gait pattern, to the structure of the knee, or to the articular cartilage (Andriacchi and Mundermann, 2006; Andriacchi et al, 2009). Structural progression occurs due to altered knee loading on already damaged cartilage (Andriacchi et al, 2004).

Much of what we know about the role of dynamic biomechanics in knee OA progression has come from cross-sectional gait studies. With respect to knee kinematics, decreased knee flexion angles during stance have been reported (peak, overall magnitude, and flexion range of motion) (Astephen et al, 2008, Astephen et al, 2008b; Deluzio and

Astephen, 2007; Rudolph et al, 2007), as has varus thrust, an abnormal frontal plane knee motion characterized by a rapid transition from valgus to varus alignment (Kuroyanagi et al, 2012). Varus thrust has been shown to be related to radiographic disease severity, and is thought to be caused primarily by ligament laxity (Kuroyanagi et al, 2012). It is hypothesized that this gait abnormality acutely increases the load on the medial compartment with each step (Kuroyanagi et al, 2012), therefore causing structural progression due to the repetitive impulse loading mechanism of cartilage degradation (Radin et al, 1984).

Kinetically, decreased knee flexion moments (peak and overall magnitude) (Astephen et al, 2008; Deluzio and Astephen, 2007; Gaudreault et al, 2011; Kaufman et al, 2001; Landry et al, 2007; Rudolph et al, 2007), increased KAM (peak, overall magnitude, mid-stance magnitude, and impulse) (Astephen et al, 2008; Astephen et al, 2008b; Deluzio and Astephen, 2007; Landry et al, 2007; Rudolph et al, 2007; Baliunas et al, 2002; Maly et al, 2013; Mundermann et al, 2005), decreased differences between the early stance and mid-stance magnitudes of the KAM (Landry et al, 2007), and decreased knee external rotation moments (Landry et al, 2007) have been reported in those with knee OA compared to asymptomatic controls. There are also knee kinetic changes associated with increasing knee OA severity. These changes include decreased knee flexion and extension moments (Astephen et al, 2008), increased KAM mid-stance amplitudes (Astephen et al, 2008), and increased KAM impulses (Thorp et al, 2006). The decrease in the knee flexion moment is thought to indicate decreased load dissipation during stance (Kaufman et al, 2001), or may reflect a knee stiffening strategy (i.e. “stiff gait”) to combat self-perceived instability during walking, thus reflecting sustained compressive loading. Higher KAM peaks, overall magnitudes, and impulses indicate higher ratios of medial compartment loading relative to total knee joint loading (Zhao et al, 2007) either during weight-acceptance (peak KAM) or throughout stance (overall magnitude and impulse). Higher mid-stance KAM magnitudes and smaller differences between the early and mid-stance KAM magnitudes indicates that the medial compartment is loaded throughout stance, rather than unloaded during mid-stance, thus suggesting sustained cartilage loading.

Less well studied are the changes in hip and ankle biomechanics and their potential influence on knee joint mechanics. Biomechanical alterations at the hip and ankle in those with knee OA include decreased hip internal/external rotation moments (Astephen et al, 2008b; McKean et al, 2007), and adduction moments (Mundermann et al, 2005), more hip internal rotation (McKean et al, 2007) and abduction during stance (Weidow et al, 2006), decreased ankle dorsiflexion moments during stance (Astephen et al, 2008b; McKean et al, 2007), and decreased plantar flexion at toe off (McKean et al, 2007). But, whether these changes drive knee OA progression or are compensations related to the changes occurring at the knee joint has been subject to minimal inquiry. Greater peak internal hip abduction moments (i.e. greater peak external hip adduction moments) and greater toe-out angles during gait have both been associated with a decreased risk of medial compartment knee OA structural progression (Chang et al, 2005; Chang et al, 2007). The effect of these gait alterations has been hypothesized to be due to their effect on medial knee joint loading, specifically the KAM, during gait. However, hip abductor strengthening programs have not been shown to be effective in reducing the KAM (Bennell et al, 2010), and the toe-out angle during gait is correlated with the second peak or late stance KAM, rather than with the first peak or early stance KAM (the KAM variable linked to structural progression) (Rutherford et al, 2008; Schache et al, 2008). Nonetheless, these studies provide evidence that interrelationships among the lower extremity joints in the kinetic chain can impact knee joint mechanics, and should be studied to fully understand how changes to the local, dynamic biomechanical loading environment of the knee can be achieved.

While cross-sectional studies have shown that there are alterations in knee (and to a lesser extent hip and ankle) biomechanics during gait in those with knee OA, the findings of these studies cannot be extrapolated to mechanisms of knee OA structural and symptomatic progression. Only four longitudinal studies have linked gait biomechanics to knee OA progression, and all four studied structural progression only. In the most widely cited study on knee biomechanics during gait and knee OA structural progression, Miyazaki et al (2002) found that the peak KAM at baseline was able to predict structural

progression (defined as an increase in radiographically determined joint space narrowing) over 6 years in a group of 74 participants with medial compartment knee OA with a sensitivity of 88% and a specificity of 83% (Miyazaki et al, 2002). For every 1% increase in the peak KAM, the risk of progression increased 6.46 times. In a more recent study looking at knee kinetics and knee OA structural progression, Bennell et al found that a higher KAM impulse at baseline was associated with a greater loss of tibial cartilage volume (detected via MRI) over 12 months in a large group of subjects with moderate knee OA (Bennell et al, 2011). This relation remained significant after controlling for alignment. Medial tibial cartilage volume loss is moderately correlated with medial compartment joint space narrowing over one (Bruyere et al, 2007) and two years (Raynauld et al, 2004), therefore the interpretation of the cartilage volume loss was that the KAM impulse was related to structural OA progression. No correlation between cartilage volume change and the peak KAM was found. Differences in methodologies between the two studies, including the study population age, body size, follow-up time, and structural progression outcome measure make it difficult to directly compare the results as well as draw definitive conclusions related to the mechanism for knee OA structural progression. Mechanistically, a high KAM impulse is likely a risk factor for knee OA progression because it gives an indication of loading throughout the gait cycle, and therefore loading of different areas of cartilage as the position of the tibia relative to the femur changes. Conversely, the peak KAM only captures loading at one discrete point in the gait cycle. While repetitive impulse loading has been shown to initiate cartilage damage (Radin et al, 1984), the damage may only occur at one location (i.e. a focal lesion). These ideas have been supported in preliminary work by Maly et al (2013). The peak KAM was associated with focal thinning in the tibia and femur, whereas the KAM impulse was related to total tibia and femur cartilage surface area (Maly et al, 2013). Additionally, since the KAM impulse considers the entire stance portion of the waveform, it captures both the magnitude and duration of knee load during each step.

The two other longitudinal studies linking gait biomechanics to knee OA structural progression focused on the hip and ankle, although they both interpreted their results in the context of what resulting effect the differences would have on the KAM. Chang et al

(2005) found that greater peak internal hip abductor moments were protective against medial compartment knee OA structural progression (Chang et al, 2005). For each unit increase in the hip abduction moment, the odds of medial knee OA structural progression were reduced by 50%. They theorized that the protection was due to the greater hip abductor torque enabling the pelvis to remain level during gait. In those with weak hip abductors it is thought that the weakness allows the contralateral side of the pelvis to drop during single leg stance, shifting the body's centre of mass toward the swing limb. This increases the moment arm length and therefore the magnitude of the external KAM (Chang et al, 2005). However, more recent work has shown that hip abductor strength is not related to the external hip adduction moment during gait (Rutherford et al, 2009). Furthermore, hip abductor strengthening programs have not been shown to be effective in reducing the KAM (Bennell et al, 2010). With respect to ankle biomechanics, a greater toe-out angle at baseline was associated with a reduced likelihood of medial knee OA structural progression over 18 months (odds ratio of 0.60) (Chang et al, 2007). The protective effect was thought to be because toeing out shifts the ground reaction force vector closer to the knee centre of rotation, decreasing the moment arm length and therefore decreasing the KAM. However, the toe-out angle during gait is actually correlated with the second peak or late stance KAM, rather than with the first peak or early stance KAM (Rutherford et al, 2008; Schache et al, 2008).

Because only frontal plane biomechanics (specifically the KAM, or other frontal plane variables that would affect the KAM) have been associated with knee OA structural progression in longitudinal studies, most biomechanical conservative interventions have targeted the frontal plane. Orthotic devices, such as canes (Gross and Hillstrom, 2008), lateral wedge orthotics (Gross and Hillstrom, 2008; Radzimski et al, 2012), and unloader braces (Gaasbeek et al, 2007; Gross and Hillstrom, 2008; Lindenfeld et al, 1997; Pollo et al, 2002; Self et al, 2000), hip abductor strengthening (Chang et al, 2005), and gait modifications such as reduced walking speed (Mundermann et al, 2004), increased trunk lateral lean (Hunt et al, 2011; Simic et al, 2012), toe-ing out (Chang et al, 2007; Schache et al, 2008), and "medial thrust" (Fregly et al, 2007; Schache et al, 2008) all target the KAM; mostly the peak KAM. However, focusing only on the frontal plane has

limitations. The KAM has frequently been used in the knee OA literature as a surrogate measure of medial compartment loading, because peak medial cartilage stress has been found to occur at the same point in the gait cycle as the peak KAM (Yang et al, 2010), and the KAM has been found to correlate with the ratio of medial compartment loading relative to total knee joint loading measured in vivo using an instrumented knee prosthesis ($r = 0.94$) (Zhao et al, 2007). However, caution must be exercised when linking the KAM directly to medial compartment contact forces. Research done using instrumented knee prostheses to get an actual measure of medial compartment contact force has found that decreases in the peak KAM are not necessarily associated with decreases in medial compartment loading (Walter et al, 2010). Concomitant increases in the peak knee flexion moment can offset peak KAM decreases to keep medial compartment loading the same. It was found that the best prediction model for medial compartment loading included the knee adduction and flexion moments (Walter et al, 2010). This evidence, combined with the modeling and in vitro work showing that shear forces can also lead to cartilage degradation (Hashimoto et al, 2009; Wilson et al, 2003), and the cross-sectional evidence showing alterations in other planes that are associated with knee OA severity indicate that to get a better understanding of the dynamic loading environment of the knee, three-dimensional knee biomechanics should be studied. However, no longitudinal studies on gait biomechanics and knee OA progression have considered non-frontal plane variables. As Wilson et al (2009) concluded in their review on how joint mechanics affect the knee OA process, we do not yet know enough about which biomechanical variables are most important in knee OA etiology, nor do we know how the different biomechanical factors interact (Wilson et al, 2009).

2.3.5 Etiology of Knee Osteoarthritis- Summary

In summary, knee OA has both a biomechanical and biochemical etiology. However, biomechanics are likely more important in those with primary knee OA (i.e. no history of previous joint injury), as dynamic loading (repetitive impulse loading, sustained loading, and shear loading) has been associated with cartilage degradation and the production of inflammatory chemicals associated with increased knee pain. Gait is typically used as a model to study dynamic loading in humans. Knee (and to a lesser extent hip and ankle)

biomechanical differences during gait have been found in those with knee OA, and some gait characteristics have been linked to increasing knee OA severity. While some have tried to extrapolate the results of cross-sectional studies to mechanisms of disease progression, only four longitudinal studies have related gait biomechanics to an increased risk of knee OA progression. All four have focused on frontal plane kinetics, and all four have focused on structural progression. Two focused on discrete aspects of the KAM, and the other two studies, which looked at the hip and ankle, interpreted the results in the context of the KAM. As a result of the focus on the KAM in the knee OA literature, conservative interventions have targeted this feature. However, gait alterations in those with knee OA are not just present in the frontal plane, sagittal knee kinetics can offset changes in the KAM, and animal models have shown that shear forces can result in cartilage degradation. Therefore, by focusing on the frontal plane, we are limiting our understanding of biomechanical mechanisms of knee OA progression. Further, other variables, such as obesity, physical activity, and frontal plane alignment have been associated with the biomechanical etiology of knee OA, and therefore need to be considered in progression studies.

2.4 SUMMARY

To summarize, knee OA has both a biomechanical and biochemical etiology, with biomechanical factors likely playing a stronger role in the structural progression of primary knee OA, as dynamic loading has clearly been linked to cartilage degradation and increased expression of pain-producing inflammatory chemicals. Gait is used as a model to study dynamic loading in humans. Biomechanical differences during gait have been found in those with knee OA, have been linked to increasing knee OA severity, and have been related to knee OA structural progression. The majority of knee OA literature (and all four studies on gait biomechanics and knee OA structural progression) has focused on the frontal plane, specifically the KAM. This has resulted in the vast majority of conservative interventions targeting this feature. However, gait alterations in those with knee OA are not just present in the frontal plane, sagittal knee kinetics can offset changes in the KAM, and animal models have shown that shear forces can result in

cartilage degradation. Therefore, by focusing on the frontal plane, we are limiting our understanding of biomechanical mechanisms of knee OA structural progression. Additionally, all of the longitudinal progression studies have looked at risk factors for structural progression. Knee OA progression can also be defined in terms of symptom progression, and the biomechanical factors driving this type of progression may be different than those driving structural progression. Specifically, sustained loading may be more likely to increase the risk of symptom progression. TKA can be a valuable outcome measure for assessing knee OA progression as this metric captures both the "disease" component of knee OA (i.e. structural changes), as well as the "illness" component (i.e. symptoms). However, no studies relating gait biomechanics to knee OA progression have used an outcome measure that considers both symptom and structural progression.

CHAPTER 3 METHODS

The goal of this dissertation was to improve our understanding of the relation between lower extremity biomechanics and mechanisms of knee osteoarthritis (OA) symptom and structural progression (defined as progression to total knee arthroplasty, TKA), with the aim of identifying effective targets for designing and evaluating conservative interventions. This chapter provides an overview of the detailed methodologies used in the following three results papers to address the main objectives and sub-objectives of the dissertation.

3.1 PARTICIPANTS

Data for this dissertation were collected as part of an on-going follow-up study on a group of 90 asymptomatic participants and a group of 80 participants with moderate medial compartment knee OA that underwent gait assessment in the Dynamics of Human Motion laboratory at Dalhousie University between 2003 and 2008. OA participants were originally recruited from the clinical practice of one high-volume orthopaedic surgeon. All were diagnosed with medial compartment knee OA based on radiographic criteria (medial compartment joint space narrowing grade was equal to or greater than the lateral compartment grade, based on the Scott Feature Based score system (Scott et al, 1993)). They were further classified as having moderate knee OA as none were candidates for TKA at the time of baseline testing, and all met the functional criteria of being able to jog 5 metres, walk a city block, and climb stairs reciprocally (Hubley-Kozey et al, 2006). Furthermore, all were clinically managed using non-surgical interventions, with the exception of debridement using arthroscopic techniques, which had to be completed at least one year prior to gait assessment. None of the participants had a history of anterior cruciate ligament injury, a significant risk factor for knee OA (Lohmander et al, 2004; von Porat et al, 2004), and all had been given a diagnosis of primary (i.e. non-traumatic) knee OA.

At least five years (mean 8 (2), range 5-8) following their baseline assessments, participants were sent an introductory letter or email describing the follow-up study, and were contacted by phone 1-2 weeks later for an initial screening. Figure 3.1 depicts the results of the telephone screening; of the 80 baseline participants with moderate medial compartment knee OA, 64 could be reached by telephone to inquire whether they were willing to undergo a follow up gait analysis. Twenty-eight participants agreed to the follow up gait analysis and reported that they had not had TKA surgery since their original testing session ("no-TKA" group). The "TKA" group consisted of 26 participants who reported that they had undergone TKA surgery since their baseline testing session. Nine participants denied undergoing TKA surgery since baseline, but were not interested in coming in for a follow-up gait analysis, and one participant had high tibial osteotomy surgery since baseline.

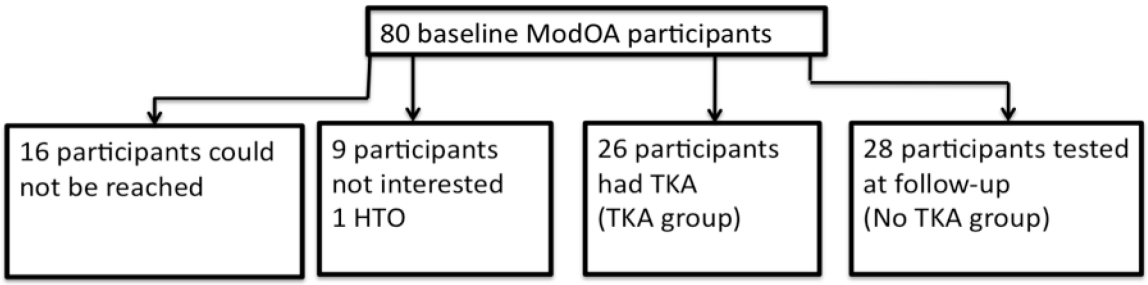

Figure 3.1: Participant recruitment overview for the on-going follow-up study being conducted in the Dynamics of Human Motion Laboratory.

At baseline, participants received a standard gait assessment (Section 3.2.1) and standard, weight-bearing anterior-posterior and lateral radiographs were performed (Section 3.2.2). Radiographs were also taken at the follow-up gait analysis for the no-TKA group (8 (2) years after baseline), and prior to TKA for the TKA group (4 (3) years after baseline) to determine the proportion of participants who progressed structurally. The gait assessment consisted of the collection of three-dimensional motion and ground reaction force data, surface electromyograms from seven lower extremity muscles, and maximal voluntary isometric contraction torques from the knee extensor, flexor, and plantar flexor muscle groups. Participants also filled out the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (Bellamy et al, 1988) to get a subjective

measure of pain, stiffness, and physical function (Section 3.2.3). Physical activity was assessed via self-report (Section 3.2.4). While surface electromyograms and strength data were collected as part of the comprehensive gait assessment, this dissertation focuses only on joint biomechanics and progression to TKA. Therefore, the surface electromyography and strength testing methodology and results are not presented.

3.2 STUDY PROCEDURE

3.2.1 Gait Analysis

This study used baseline data from the on-going, longitudinal follow-up study, which were collected between 2003 and 2008. At baseline, after signing consent forms approved by the Dalhousie University and Capital Health Research Ethics Boards, participants began the gait assessment. This was conducted using a standardized protocol. Demographic (age, sex) and anthropometric data (thigh and calf circumferences, foot width, body mass, and height) were recorded. To monitor segmental motion during gait, 16 infrared-emitting diodes were placed on specific anatomical landmarks on each participant (Figure 3.2). Triads were placed on the pelvis, thigh, shank, and foot segments, and individual markers were placed on the shoulder, greater trochanter, lateral epicondyle, and lateral malleolus. The locations of eight virtual points (right and left anterior superior iliac spines (ASIS), medial epicondyle, fibular head, tibial tuberosity, medial malleolus, second metatarsal, and heel) were recorded in quiet standing.

The three-dimensional motions of the markers during gait were collected using a two-camera Optotrak™ 3020 motion capture system (Northern Digital Inc, Waterloo ON) sampling at 100 Hz. Three-dimensional ground reaction forces were recorded at 1000 Hz using an AMTI™ force platform (Advanced Medical Technology Inc, Watertown MA) embedded in the lab floor (Figure 3.2). Prior to the gait trials, a standing calibration trial was performed. This trial provided the reference joint angles. All angles during gait were calculated with respect to the angles recorded in the standing calibration trial. The standing calibration trial also was used to calculate static frontal plane knee alignment by looking at the angle formed between: i) the line connecting the ASIS and the knee joint

centre (midpoint between the medial and lateral epicondyles), and ii) the line connecting the knee joint centre and the ankle joint centre (midpoint between the medial and lateral malleoli). This measure of alignment was found to correlate best with the mechanical axis of the lower extremity derived from standing full-leg radiographs on a subset of 35 participants (Appendix 1). Larger ASIS-knee-ankle angles (i.e. closer to 180 degrees) were more varus, with an ASIS-knee-ankle angle of approximately 175 degrees corresponding to neutral alignment, based on the full-leg radiographs.

For the gait trials, participants were asked to walk at a self-selected pace across a five-metre walkway. A trial was considered successful if the participant's foot on the tested leg came into full contact with the force platform, and the foot on the untested leg did not contact the force platform. At least five successful trials were recorded for each participant.

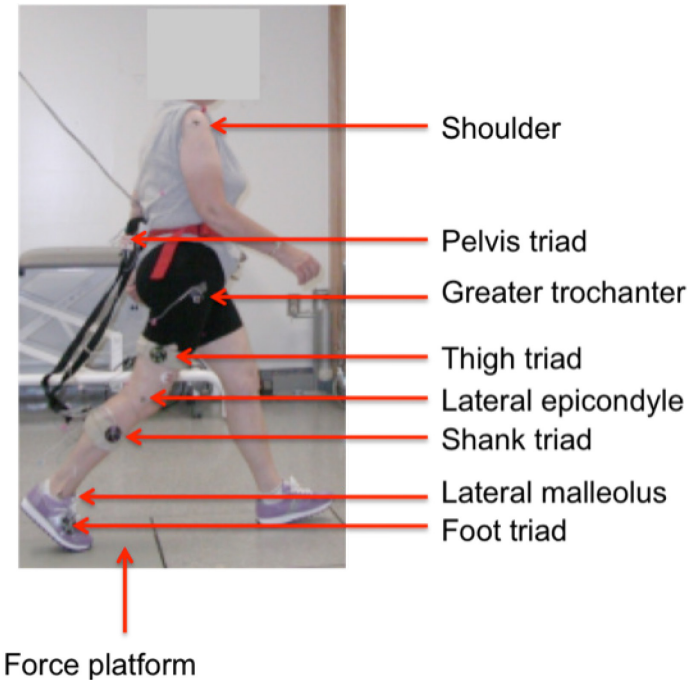

Figure 3.2: Infrared light emitting diode and force platform set up for the gait trials.

3.2.2 Radiographs

All participants received standard, weight-bearing anterior-posterior and lateral radiographs at baseline. Radiographs were also taken at the follow-up gait assessment for the no-TKA group (8 (2) years after baseline), and prior to TKA for the TKA group (4 (3) years after baseline) to determine the proportion of participants who progressed structurally. One high-volume orthopaedic surgeon graded the baseline radiographs twice using the Kellgren and Lawrence (KL) grading scale (Kellgren and Lawrence, 1957) and the Scott Feature Based score system (Scott et al, 1993). The first grading was done at the baseline time of recruitment into the study and the second grading was done after follow-up phone interviews 5-8 years later to determine inclusion in the follow up study. This surgeon showed high intra-rater reliability, with percent agreements between these two gradings of 95% for the overall KL grade and 98% and 93% for the medial and lateral joint space narrowing grades of the Scott Feature Based score system, respectively. Weighted kappa coefficients of 0.91, 0.99, and 0.91 were found for the KL grade, and medial and lateral joint space narrowing grades, respectively (Appendix 2). Follow-up radiographs were graded once. Structural progression was defined as an increase in the medial compartment joint space narrowing grade of the Scott Feature Based score system (Scott et al, 1993). Inter-rater reliability of three independent surgeons (including the surgeon that performed the grading for the present study) for the KL grade and Scott Feature Based score system was high (ICC >0.73) for all features and grades except presence of sclerosis in the tibiofemoral and patellofemoral joints (McKean et al, 2007).

3.2.3 Subjective Outcome Measure

Participants filled out the WOMAC questionnaire at the baseline testing session to get a measure of self-reported pain, stiffness, and physical function (Bellamy et al, 1988). This questionnaire is widely used in the knee OA literature, and has been shown to be reliable and valid for those with knee OA (Bellamy et al, 1988; Bellamy et al, 1997). The no-TKA group also filled out this questionnaire at their follow-up gait assessment to get a measure of progression of symptoms.

3.2.4 Physical Activity

Physical activity was measured via self-report. As part of the initial baseline telephone screening, participants were asked four questions about their current physical activity level (Table 3.1). The questions were based on the American College of Sports Medicine's recommendations for adequate levels of physical activity (American College of Sports Medicine, 2006). It is acknowledged that self-report questionnaires can suffer from social desirability bias (the tendency for individuals to portray themselves in keeping with perceived cultural norms (Adams et al, 2005)), resulting in an over-estimation of physical activity level. Accelerometers are the preferred method of objectively assessing physical activity, and have been shown to be valid, with activity counts correlating significantly with energy expenditure estimates obtained using the gold standard doubly labelled water technique (Plasqui and Westerterp, 2007; Rothney et al, 2008). However, a validation study on our self-report physical activity questionnaire indicated that it significantly differentiated between active and sedentary physical activity levels based on minutes spent in moderate physical activity determined using accelerometer data (Appendix 3).

Table 3.1: Telephone screening baseline and follow-up physical activity questions.

Question	Possible Answers
Over a typical 7-day period (one week), how many times do you engage in physical activity that is sufficiently prolonged and intense to cause sweating and a rapid heart rate?	• At least 3 times • Normally once or twice • Rarely or never
When you engage in physical activity do you have the impression that you:	• Make an intense effort • Make a moderate effort • Make a light effort
In a general fashion, would you say that your current physical fitness is:	• Very good • Good • Average • Poor • Very poor
Are you an active member of a walking group? For how long?	

3.3 DATA ANALYSIS

3.3.1 Kinematics and Kinetics

Custom software written in Matlab (Mathworks Inc, Natick MA) was used to process the gait data. The motion and force data were digitally filtered (recursive fourth order Butterworth) at 8 Hz and 60 Hz respectively, and used to identify heel strike and toe-off to define one gait cycle (heel strike to heel strike on the same foot). Heel strike was defined when the vertical force from the force platform was non-zero. Toe-off was determined as the point where the maximal vertical force from the force platform occurred after heel strike. The vertical location of the lateral malleolus marker at heel strike was used to identify the second heel strike of the same foot (Costigan et al, 1992;

Deluzio et al, 1993; Li et al, 1993). The three-dimensional angles at the hip, knee and ankle were calculated using a least squares optimization routine (Challis, 1995) and expressed in the joint coordinate system (Grood and Suntay, 1983). The angle waveforms were time-normalized to a percentage of the gait cycle (i.e. 101 data points) using a linear interpolation technique (Astephen et al, 2008; Astephen et al, 2008b; Deluzio and Astephen, 2007; Landry et al, 2007). Three-dimensional hip, knee, and ankle external moments were calculated using inverse dynamics (Costigan et al, 1992; Deluzio et al, 1993; Li et al, 1993) and also expressed in the joint coordinate system (Grood and Suntay, 1983). For inverse dynamics, a link-segment model was used, where each segment acted independently, influenced by either ground or joint reaction forces, gravitational forces and net moments of force at either end of the segment (Costigan et al, 1992; Deluzio et al, 1993; Li et al, 1993).

Inverse dynamics modelling was started at the foot, where the distal ground reaction forces were obtained from the force platform data. Using the Newtonian equation $\sum F=ma$, where 'm' is the segment mass (Winter, 1979) and 'a' is the segment acceleration (obtained from motion data) the three-dimensional proximal foot forces were determined. The same process was followed to determine the knee and hip forces. Using these forces, the moments of force about the centre of mass of each segment were calculated using the equation $\sum M=I\alpha$, where 'I' is the moment of inertia of each segment and 'α' is the segment angular acceleration. Moments of inertia were calculated using an optimization method based on work by Vaughan et al (Vaughan et al, 1992; Vaughan et al, 1982), and the segment accelerations were obtained from the motion data. Joint reaction forces were converted into moments of force using segment lengths (obtained from motion data) and previously published data on locations of segment centres of mass (Winter, 1979). As with the forces, modelling started at the foot and continued up the kinetic chain.

Moment waveforms used in the principal component analysis (PCA) models (Chapter 4), and used to calculate the knee adduction moment (KAM) peak (Chapter 5), were time-normalized to a percentage of the gait cycle (i.e. 101 data points) using a linear

interpolation technique (Astephen et al, 2008; Astephen et al, 2008b; Deluzio and Astephen, 2007; Landry et al, 2007). Waveforms were not time-normalized for the calculation of the KAM impulse (i.e. the area under the positive stance portion of the KAM waveform, Chapter 5), as this variable is meant to capture the total magnitude and duration of load that the knee experiences over time.

In terms of moment amplitude-normalization, the two previous studies linking knee biomechanics to knee OA structural progression amplitude-normalized the KAM to body size by dividing the external moment by body weight times height. The units would be Nm/Nm, therefore the moments were expressed as a percentage (Miyazaki et al, 2002; Bennell et al, 2011). Cross-sectional studies looking at the KAM peak (Baliunas et al, 2002; Lewek et al, 2004; Mundermann et al, 2005) and KAM impulse (Kean et al, 2012; Thorp et al, 2006) have also normalized to body weight times height. Normalization to body weight times height is performed to get at abnormally high knee loading above that which would occur due to increased body size. However, it has been advocated that normalizing to just body mass is sufficient, because there is less variability in height than in mass (Pierrynowski and Galea, 2001), and normalizing to body mass will still capture loading above that which would occur due to increased mass. Other studies looking at the peak KAM (Astephen et al, 2008b), and the studies using PCA to extract moment waveform features have used waveforms amplitude-normalized to body mass (Astephen et al, 2008; Hatfield et al, 2011; Landry et al, 2007; Robbins et al, 2013; Smith et al, 2004). Robbins et al (2011b) argued that if the purpose of examining moment waveforms is to get an absolute measure of the magnitude of load the knee is experiencing, amplitude-normalizing removes some of that signal. They found that the non-amplitude-normalized peak KAM was better able to distinguish between knee OA severities (Robbins et al, 2011b). Because discrepancy exists in the literature as to the best method to amplitude-normalize moment waveforms, three normalization methods were used. Moment waveforms were kept in their original units (Nm), normalized to body mass (Nm/kg), and normalized to body size (Nm/Nm)%.

For the time-normalized data used in the PCA analysis, waveforms for each trial were averaged to create ensemble average profiles for each participant (Winter and Yack, 1987). Three-dimensional angle and moment PCs were calculated based on the ensemble averages. The peak KAM (peak occurring in the first 40% of the gait cycle (Robbins et al, 2013)) and KAM impulses (area under the positive portion of the stance phase of the gait cycle (Equation 3.1)) were determined for each trial for each participant individually, and then averaged to get the mean KAM peak or impulse for each participant. The KAM peak and impulse have been shown to be reliable metrics, with test-retest intraclass correlation coefficients of 0.91 and 0.89, respectively (Robbins et al, 2013; Robbins et al, 2009).

$$\text{Impulse} = \int_{a}^{b} KAM(t)dt \qquad \text{Equation 3.1}$$

where KAM(t) = the external KAM at time (t); a = time (t) at heel strike; b = time (t) at toe off (Robbins et al, 2009).

3.3.2 Principal Component Analysis

Three-dimensional hip, knee, and ankle angle and moment waveforms were analyzed using PCA. This is a pattern recognition technique that has been used in the literature to reduce gait waveform data to a limited number of patterns (PCs) that explain the majority of variation in the data (Deluzio and Astephen, 2007; Hubley-Kozey et al, 2006; Hubley-Kozey et al, 2008; Landry et al, 2007). The technique is advantageous as it considers both amplitude and temporal information (Deluzio and Astephen, 2007). Specific features extracted from knee biomechanical gait data have been found to be reliable, particularly sagittal angles and moments and frontal plane moments (Robbins et al, 2013). A schematic of PCA is shown in Figure 3.3.

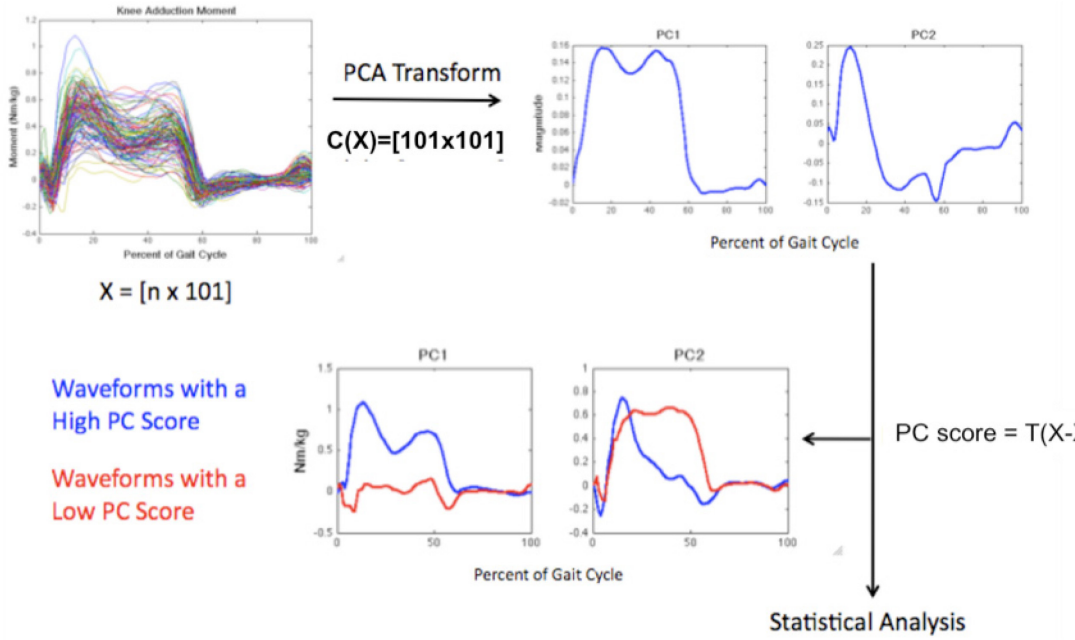

Figure 3.3: Principal component analysis (PCA), using the knee adduction moment (KAM) as an example.

The first step in PCA was to form an nx101 matrix (**X**) for each variable, consisting of the ensemble average profile for each participant (n) for that given variable. For this study, the matrices were constructed from a larger dataset of 149 baseline and follow-up waveforms for asymptomatic and moderate knee OA participants in the larger longitudinal follow-up study. Therefore, the matrices were 149x101. Generating the PCs from a larger dataset increased the robustness of the patterns extracted (Osborne and Costello, 2004). Next, a covariance matrix (**C**) was formed (Astephen et al, 2008; Deluzio and Astephen, 2007; Landry et al, 2007) and eigenvector-eigenvalue decomposition of **C** was performed, resulting in a transform matrix (**T**, 101x101) of the PCs (eigenvectors), and **Λ,** a diagonal of the associated variances (eigenvalues). Scores were then calculated for each participant's original waveform. For this dissertation, PC scores were calculated for the baseline waveforms for the 54 participants in the study. These PC scores were weighting coefficients based on how much of the variability in a participant's waveform was accounted for by a particular PC. Statistical analyses were done on these scores.

PCA was performed on each of the three-dimensional angles and moments from each joint individually. PCs that accounted for a total of 90% of the variance of the large dataset (but did not contribute less than 1% of the variance) were retained for statistical hypothesis testing (Deluzio and Astephen, 2007). Typically only 3 or 4 PCs were retained for each gait variable. In order to ensure that the extracted PCs accurately represented the original waveforms from this smaller subset, waveforms for the 54 participants in this dissertation were reconstructed by the linear combination of the PCs multiplied by the corresponding PC scores. The root mean squared error was then calculated for the reconstructed waveforms (Appendix 4). Based on these reconstructions, it was found that the moment PCs better represented the waveforms than the angle PCs, for all of the joints. Non-sagittal plane angle reconstruction was considerably worse than sagittal reconstruction. The poor reconstruction in the adduction and rotation angles may have been due to the increased variability in these measures, perhaps due to kinematic crosstalk. The moment reconstruction appeared to be particularly good for the stance phase of gait, which is most important, since that is where the majority of joint loading took place.

3.4 Statistical Analysis

The statistical analyses are listed below in the order of the research objectives (Section 1.2). For each dependent variable, the assumptions of normality and equal variances were examined using the Kolmogorov-Smirnov and Levene's tests, respectively. For all hypothesis testing, the significance level (α) was 0.05. The receiver operating characteristic (ROC) curve analyses (Objective 3, Chapter 6) were performed using MedCalc software (Version 12.5.0, Mariakerke, Belgium), and the discriminant analyses (Objective 3, Chapter 6) were completed using SPSS Statistics (Version 20.0.0, IBM Corporation, Armonk, NY). All other analyses (unpaired Student's t-tests (Objectives 1 and 2, Chapters 4 and 5), correlation analyses (Objective 2, Chapter 5), and logistic regression analyses (Objective 3, Chapter 6)) were done using Minitab™ (Version 16, Minitab Inc, State College PA).

3.4.1 Statistical Hypotheses Testing

Objective 1:

To determine if three-dimensional lower extremity biomechanical features during gait were different between those with moderate medial compartment knee OA who progressed to TKA versus those that did not, unpaired Student's t-tests were used to detect significant differences in PC scores for each variable between the TKA and no-TKA groups.

Objective 2:

To determine whether knee biomechanical gait variables previously associated with knee OA structural progression (i.e. KAM peak and KAM impulse) were also associated with progression to TKA, unpaired Student's t-tests were used to detect significant differences in the KAM peak and KAM impulse between the TKA and no-TKA groups. To then determine how the KAM features extracted using PCA compared to the discrete features already linked to structural progression, Pearson product moment correlation coefficients were used to determine relations between KAMPC1 and KAMPC2 and the KAM peak and KAM impulse. To determine what effect amplitude-normalization had on these between-group differences and relations between variables, the statistical analyses were performed with the KAM waveforms amplitude-normalized three different ways: i) unnormalized (units of Nm), ii) normalized to body mass (units of Nm/kg), and iii) normalized to body weight times height (units of Nm/Nm, converted to a percentage).

Objective 3:

To determine how well the individual (i.e. univariate models) three-dimensional biomechanical features during gait that were significantly different between the two groups classified those who progressed to TKA, ROC curve analyses were performed. The area under the curve (AUC) was calculated and used to quantify the overall "diagnostic accuracy" of each of the variables (McNeil and Hanley, 1984). Next, to determine how well multivariate models discriminated between the two groups, stepwise multivariate linear discriminant analyses were performed using three combinations of baseline biomechanical gait features: i) a "discrete" model using discrete (i.e. KAM peak

and impulse) variables, ii) a "PCA" model using PC scores found to be different between the TKA and no-TKA groups (Objective 1), and iii) a "combined" model, using variables identified from models 1 and 2 that significantly discriminated between the two groups. Models were performed using moment data amplitude-normalized to body mass, and to body weight times height, making a total of 6 models. The relative importance of each term in the multivariate models was quantified with the magnitude of the coefficients in the discriminant function. Group separation was quantified with correct classification rates for all original cases, and model over-training was estimated with cross-validation (iterations of all cases except one) classification rates (Lachenbruch, 1975). The multivariate discriminant functions were used to calculate discriminant function scores for all participants. Standardized scores (z-scores) for the gait variables were used in the calculations, and were determined according to equation 3.2. These discriminant function scores were used as input for additional ROC curve analyses to determine optimal cut-points that distinguished between the two groups, and the associated sensitivities (number of participants correctly classified as being in the TKA group divided by the total number of participants in the TKA group) and specificities (number of participants correctly classified as being in the no-TKA group divided by the total number of participants in the no-TKA group). Finally, scores were entered into logistic regression models to determine the predictive ability of the discriminant functions.

$$\text{Z Score} = \frac{x - \mu}{\theta} \qquad \text{Equation 3.2}$$

Where "x" is the participant's value for a given gait variable, μ is the sample mean, and θ is the sample standard deviation

CHAPTER 4 THREE-DIMENSIONAL BIOMECHANICAL GAIT CHARACTERISTICS ASSOCIATED WITH KNEE OSTEOARTHRITIS PROGRESSION

4.1 INTRODUCTION

Osteoarthritis (OA) is a significant problem in industrialized countries resulting in a huge economic burden (Arthritis Alliance of Canada, 2011). The knee is the most common joint affected, with 12% of adults over the age of 60 years having symptomatic knee OA (Dillon et al, 2006). With the aging population and current obesity epidemic, the prevalence is expected to increase. Knee OA results in pain, stiffness, muscle strength deficits, and joint instability, with the long-term effects reducing an individual's mobility. Reduced mobility from knee OA can lead to increased risk of cardiovascular disease, poor quality of life, and loss of function (Conn et al, 2008). There is currently no cure for knee OA, with total knee arthroplasty (TKA) being the end-stage treatment for those in the severe disease stage. Because there is no cure, for more than a decade conservative interventions aimed at slowing OA progression have been a focus of significant research effort (Buckwalter et al, 2001; Gross and Hillstrom, 2008; Lane et al, 2011).

Both biomechanical and biochemical factors play roles in knee OA progression (Brandt et al, 2006). Evidence from animal models (Abusara et al, 2013; Chen et al, 1999; Kim et al, 2012; Radin et al, 1984), theoretical models (Andriacchi et al, 2004), and clinical research (Bennell et al, 2011; Miyazaki et al, 2002) highlights the importance of biomechanics in the structural progression of knee OA. Repetitive impulse loading has been shown to be enough to initiate articular cartilage damage and cause changes in the subchondral bone (Radin et al, 1984), and decrease proteoglycan-4 secretion into the synovial joint fluid, a vital protein for joint lubrication (Abusara et al, 2013). Sustained compressive load can lead to cartilage degradation (Chen et al, 1999) and an increased risk of cartilage and subchondral bone damage from normal, physiological impulse loads following the sustained loading (Kim et al, 2012). Finally, shear strain results in

increased expression of p53, a protein responsible for chondrocyte apoptosis (Hashimoto et al, 2009). While articular cartilage degradation is a hallmark of OA, assessing structural progression only captures the "disease" component of knee OA, and the relation with the "illness" component (Lane et al, 2011) is not evident, as symptoms are poorly correlated with structural changes (Barker et al, 2004). Thus, biomechanical factors driving symptom progression (i.e. progression of the "illness" component) may differ from those driving structural progression. Repetitive impulse loading, detrimental to articular cartilage (Radin et al, 1984; Wang et al, 2007), increases gene expression for inflammatory chemicals (Wang et al, 2007) that have been linked to increased knee pain (Stannus et al, 2013). However, higher levels of inflammatory chemical gene expression were seen during conditions of static loading compared to dynamic loading (Wang et al, 2007). Thus, sustained loading may cause increased knee pain, and increase the risk of symptom progression. Determining how biomechanical factors relate to an outcome measure that captures both aspects of knee OA progression is the focus of the present study. While there are limitations associated with surgical decision-making and patient willingness to undergo surgery, TKA provides a clear endpoint that includes both symptom and structural aspects of progression, since patient complaints of pain and functional deficits as well as imaging techniques to establish joint structural changes are used in surgical decision making (Gossec et al, 2011).

Biomechanical risk factors for knee OA progression have been identified from epidemiological studies, and include obesity (Yusuf et al, 2011), frontal plane alignment (Yusuf et al, 2011), previous anterior cruciate ligament injury (Lohmander et al, 2004), radiographic disease severity (Gossec et al, 2011), and knee pain (Gossec et al, 2011). While these risk factors can provide potential targets for interventions, some are not easily modifiable. Furthermore, they do not provide a clear indication of dynamic aspects of loading such as repetitive impulse loading (Radin et al, 1984; Wang et al, 2007), sustained compressive loading (Arokoski et al, 2000; Chen et al, 1999; Wang et al, 2007), and shear loading (Hashimoto et al, 2009), which can lead to cartilage degradation and/or increased symptoms. Hence there is a need to understand the dynamic biomechanical environment of the knee joint.

Gait is frequently used as a model to study the knee dynamic biomechanical environment because it is an activity often reported as difficult by those with knee OA and chronic and repetitive loading occurring during gait is thought to dominate the biological and structural response of cartilage (Andriacchi et al, 2004). Much of what we know about specific gait alterations in those with knee OA is from cross–sectional studies, which have shown that gait biomechanics change with increasing knee OA severity. At the knee, there are alterations in frontal plane kinetics throughout the gait cycle (Astephen et al, 2008; Thorp et al, 2006) and reduced sagittal plane kinetics and kinematics (Astephen et al, 2008). Hip and ankle alterations are less well-studied, but include altered hip frontal and sagittal plane kinetics and kinematics (Astephen et al, 2008b), decreased ankle sagittal kinetics and kinematics (Astephen et al, 2008b), and alterations in ankle rotation moments (Astephen et al, 2008). Collectively, these cross-sectional studies show that lower extremity biomechanics are related to knee OA severity, but findings cannot be extrapolated to determine mechanisms of progression. Only four longitudinal studies provide empirical evidence that lower extremity biomechanical factors during gait increase the risk of knee OA progression, and all four focused on structural progression only (Bennell et al, 2011; Chang et al, 2007; Chang et al, 2005; Miyazaki et al, 2002). In the most widely-cited study, a 1% peak knee adduction moment (KAM) increase was associated with a six-fold increased risk of structural progression (radiographic joint space narrowing) over 6 years (Miyazaki et al, 2002). More recently, a higher KAM impulse (but not a higher KAM peak) was associated with greater medial tibial cartilage volume loss over one year (Bennell et al, 2011). Medial tibial cartilage volume loss is moderately correlated with medial compartment joint space narrowing (Bruyere et al, 2007; Raynauld et al, 2004), and thus has been used as a structural progression outcome measure. Methodological differences, including population age (subjects in the Miyazaki et al study were over 70 years of age), body size, follow-up time, and structural progression outcome measure could account for differences in conclusions related to mechanisms for structural progression. The other two longitudinal studies examined the hip (Chang et al, 2005) and ankle (Chang et al, 2007) joints, and interpreted their results in the context of knee loading. Greater peak internal hip abduction moments and greater

toe-out angles (both hypothesized to decrease the KAM during gait) were associated with decreased risk of structural progression (radiographic joint space narrowing) over 18 months, but direct links to knee joint loads were not made (Chang et al, 2007; Chang et al, 2005).

Although gait is used as a model to study the knee dynamic biomechanical environment, reporting discrete variables (peaks or impulses) does not capture dynamic loading characteristics *throughout* the gait cycle. Capturing temporal features has been accomplished through principal component analysis (PCA), which considers the entire waveform by extracting temporal and amplitude information (principal components, PCs) (Deluzio and Astephen, 2007). PCA has been applied to identify biomechanical waveform patterns relevant to various aspects of knee OA (Astephen et al, 2008; Landry et al, 2007), but has not been used in a longitudinal study assessing knee OA progression.

An additional factor not taken into consideration in the longitudinal studies was physical activity or a measure of the frequency of loading. Higher frequency of joint loading has been related to cartilage properties in animal models (Horisberger et al, 2012; Waldman et al, 2004) and in humans (Racunica et al, 2007). In terms of knee symptoms, physical activity improves function and decreases pain in those with knee OA (Dunlop et al, 2011; Ettinger et al, 1997; Messier et al, 2004), however it has also been found that the frequency of knee loading in those with knee OA explains a significant proportion of the variance (9%) in knee pain scores (Robbins et al, 2011). Because loading frequency affects cartilage properties and pain, it could play a role in both symptom and structural progression. Thus, in addition to demographic and clinical risk factors, a measure of loading frequency should be included in longitudinal knee OA progression studies.

Together, the few longitudinal studies and cross-sectional findings have provided a framework for developing mechanically based interventions. Most aim to reduce KAM magnitudes, primarily the peak KAM, and include orthotic devices (Gross and Hillstrom, 2008), muscle strengthening (Chang et al, 2005), and gait modifications (Chang et al, 2007; Hunt et al, 2011; Mundermann et al, 2004; Schache et al, 2008). Efficacy of these

interventions has been equivocal (Fantini Pagani et al, 2010; Gaasbeek et al, 2007; Haladik et al, 2013; Schache et al, 2008; Simic et al, 2011), and while the KAM has been correlated with medial compartment contact force (Zhao et al, 2007), medial load has been shown to remain constant with changes in KAM and knee flexion moments (Walter et al, 2010). Furthermore, transverse biomechanics have been neglected in longitudinal studies, even though excessive shear forces can cause cartilage damage (Hashimoto et al, 2009) and rotational kinematics have been theorized to contribute to knee OA initiation (Andriacchi et al, 2004).

The overall research question for this study was to determine whether a comprehensive understanding of the three-dimensional, dynamic biomechanical environment during gait would provide insight into mechanisms of knee OA progression. The specific objective was to determine if lower extremity (hip, knee, ankle joint) biomechanical gait features were different between those with moderate medial knee OA who progressed to TKA versus those that did not. The overarching hypothesis was that lower extremity gait dynamic biomechanical characteristics would differ between TKA and no-TKA groups, with the TKA group exhibiting mechanical factors that would increase overall knee joint loading, support a sustained load, and indicate altered rotational mechanics. This understanding could provide objective data on which to develop new and assess targeted biomechanical interventions.

4.2 METHODS

4.2.1 Participants

Data were collected as part of a larger, on-going longitudinal study on 90 asymptomatic participants and 80 participants with moderate medial knee OA that underwent baseline gait analysis in the Dynamics of Human Motion laboratory at Dalhousie University between 2003 and 2008. OA participants were recruited from the clinical practice of one high-volume orthopaedic surgeon and were diagnosed with knee OA using radiographic and clinical evidence (Altman et al, 1986). Medial knee OA was based on radiographic criteria (medial compartment joint space narrowing grade equal or greater than lateral

compartment grade, based on Scott's Feature Based score system (Scott et al, 1993)). Moderate severity was based on clinical criteria: none were candidates for TKA at baseline, and all were able to jog 5 metres, walk a city block, and climb stairs reciprocally (Hubley-Kozey et al, 2006). All had primary knee OA as determined from self-report questionnaires of no ligamentous or structural injuries.

Institutional ethics approval (Capital Health Research Ethics Board and Dalhousie University Research Ethics Board) was obtained for this study. Sixty-four OA baseline participants were contacted to inquire whether they were willing to undergo follow-up gait analysis. Twenty-eight agreed, and reported they had not had TKA (no-TKA group). Twenty-six reported they had TKA since baseline testing (TKA group, mean time to TKA was 4 (3) years)). Nine participants did not have TKA, but declined participation in the gait study and radiographic assessment, and one had a high tibial osteotomy since baseline.

4.2.2 Procedure

At baseline, demographic data (age, sex, mass, height), frontal plane alignment (from standing calibration trial), and self-reports of physical activity, pain, and function were recorded. Standard, weight-bearing anterior-posterior and lateral radiographs were taken at baseline and follow-up (no-TKA group) or pre-TKA (TKA group) to determine baseline structural severity and the proportion of participants who progressed structurally (increase in medial joint space narrowing grade (Miyazaki et al, 2002)). One high-volume orthopaedic surgeon graded baseline radiographs twice (baseline and follow-up) using the Kellgren and Lawrence (KL) grading scale (Kellgren and Lawrence, 1957) and the Scott Feature Based score system (Scott et al, 1993). Between-grading agreement was 95%, 98%, and 93% for KL grade, medial, and lateral joint space narrowing grades, with weighted kappa coefficients of 0.91, 0.99, and 0.91 (Appendix 2). Follow-up radiographs were graded once.

Frontal plane alignment was calculated using motion capture data from a standing calibration trial as the angle formed between: i) the line connecting the anterior superior

iliac spine (ASIS) and the knee joint centre (midpoint between medial and lateral epicondyles), and ii) the line connecting the knee and ankle joint centres (midpoint between medial and lateral malleoli). In a subset of 35 participants this alignment measure was found to correlate best with alignment derived from standing full-leg radiographs (56% of variance explained, Appendix 1). Larger ASIS-knee-ankle angles (i.e. closer to 180 degrees) were more varus, with an ASIS-knee-ankle angle of approximately 175 degrees corresponding to neutral alignment, based on the full-leg radiographs.

Physical activity was assessed via self-report. Participants were asked how many times they engaged in physical activity "sufficiently prolonged and intense to cause sweating and a rapid heart rate?" They were classified as active if they answered at least three days/week (American College of Sports Medicine, 2006). A validation study on our self-report physical activity questionnaire on 25 participants indicated that it differentiated between active and sedentary participants based on minutes spent in moderate physical activity measured using accelerometers (Appendix 3). Self-reported pain and function were assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (Bellamy et al, 1988). Baseline gait analysis included collection of three-dimensional motion and ground reaction force data, surface electromyograms from seven lower extremity muscles, and maximal voluntary isometric contraction torques from the knee extensor, flexor, and plantarflexor muscles. Only biomechanics data are presented in this study.

4.2.3 Biomechanical Gait Analysis

To monitor segment motion during gait, 16 infrared-emitting diodes were placed on specific anatomical landmarks using a standardized protocol (Landry et al, 2007). Triads were placed on pelvis, thigh, shank, and foot segments. Individual markers were placed on the shoulder, greater trochanter, lateral epicondyle, and lateral malleolus. The locations of eight virtual points (right and left ASIS, medial epicondyle, fibular head, tibial tuberosity, medial malleolus, second metatarsal, heel) were recorded in quiet standing. Three-dimensional marker motion during gait was collected using a two-camera

Optotrak™ 3020 motion capture system (Northern Digital Inc, Waterloo ON) sampling at 100 Hz. Three-dimensional ground reaction forces were recorded at 1000 Hz using an AMTI™ force platform (Advanced Medical Technology Inc, Watertown MA). Participants performed at least five gait trials at a self-selected pace across a five-metre walkway. A trial was successful if the participant's foot on the tested leg came into full contact with the force platform, and the other foot did not contact the force platform. Specific gait waveform characteristics extracted from knee biomechanical gait data using this protocol have been found to be reliable; particularly sagittal angles and moments and frontal plane moments (ICCs from 0.70-0.94) (Robbins et al, 2013).

4.2.4 Data Analysis

Motion and force data were digitally filtered (recursive fourth order Butterworth) at 8 Hz and 60 Hz respectively, and used to identify heel strike and toe-off to define one gait cycle (heel strike to heel strike on the same foot). Three-dimensional hip, knee, and ankle angles were expressed in the joint coordinate system (Grood and Suntay, 1983). Three-dimensional hip, knee, and ankle external moments were calculated using inverse dynamics (Costigan et al, 1992; Deluzio et al, 1993; Li et al, 1993) and expressed in the joint coordinate system (Grood and Suntay, 1983). Angles and moments were time-normalized to percentage of the gait cycle (i.e. 101 data points) using a linear interpolation technique (Astephen et al, 2008; Astephen et al, 2008b; Landry et al, 2007). To capture loading beyond that associated with increased body mass, moments of force were amplitude-normalized to body mass (Astephen et al, 2008; Astephen et al, 2008b; Landry et al, 2007). Waveforms for each trial for each variable were averaged to create ensemble average profiles for each participant (Winter and Yack, 1987).

4.2.5 Principal Component Analysis

Three-dimensional hip, knee, and ankle angles and moments were analyzed using PCA (Deluzio and Astephen, 2007). An nx101 matrix (**X**) was formed for each gait variable, consisting of the ensemble average profile for participants from a dataset (n=149) of baseline and follow-up waveforms for asymptomatic and moderate knee OA participants

in the follow-up study. Generating PCs from a larger dataset increased robustness of patterns extracted (Osborne and Costello, 2004). Next, a covariance matrix of **X** was formed (**C**). A transform matrix (**T**, 101x101) was calculated by the eigenvector-eigenvalue decomposition of **C**. **T** was a matrix of the PCs (eigenvectors), and **Λ** was a diagonal of the associated variances (eigenvalues). Scores were calculated for baseline waveforms for the 54 participants in this study. Scores were weighting coefficients based on how much variability in a participant's waveform was explained by a particular PC.

PCs accounting for at least 90% of the total variance of the large dataset (but not contributing less than 1% of variance) were retained for statistical hypothesis testing (Deluzio and Astephen, 2007). To ensure that extracted PCs accurately represented the original waveforms, waveforms were reconstructed by the linear combination of the PCs multiplied by corresponding PC scores. The root mean squared error was then calculated for reconstructed waveforms. Custom Matlab (Mathworks Inc, Natick MA) programs were used to process gait data.

4.2.6 Statistical Analysis

Assumptions of normality and equal variances were examined using Kolmogorov-Smirnov and Levene's tests for all continuous variables. Unpaired Student's t-tests were used to test for significant differences in demographics, alignment, walking speed, self-reported pain and function, and PC scores for each gait variable between groups (significance level (α) of 0.05). Analyses were completed using Minitab™ (Minitab Inc, State College PA).

4.3 RESULTS

There were no significant baseline between-group differences in age, mass, body mass index (BMI), or frontal plane alignment, with similar sex distribution and radiographic disease severity between groups (Table 4.1). Both groups had similar numbers of physically active participants. There were no significant between-group differences in

spatiotemporal gait characteristics, or WOMAC scores, indicating similar clinical status. Ten participants in the TKA group and 14 participants in the no-TKA group progressed radiographically.

Based on the waveform reconstructions, moment PCs better represented original waveforms (RMS error 0.01-0.25) than angle PCs (RMS error 1.49-7.13), for all joints (Appendix 4). Non-sagittal plane angle reconstruction was poorer than sagittal reconstruction. Poor reconstruction in adduction and rotation angles was likely due to increased variability in these measures, as well as kinematic crosstalk since errors were most noticeable during the swing phase (Piazza and Cavanagh, 2000).

Mean knee angle and moment waveforms are in Figure 4.1. Interpretations for the extracted knee angle and moment PCs and results of the statistical analyses are in Table 4.2. There were no significant between-group differences for any knee angle PC scores ($p>0.05$). The overall shape and magnitude of the KAM waveform (KAMPC1), the difference between early and mid-stance KAM magnitudes (KAMPC2), and the difference between the early stance knee flexion and late stance knee extension moment (knee flexion moment PC2) were significantly different between groups ($p<0.05$). The TKA group had higher KAM magnitudes, less difference between early and mid-stance KAM, and reduced early stance flexion and late stance extension moments compared to the no-TKA group.

Mean hip and ankle angle and moment waveforms are in Figures 4.2 and 4.3, with interpretations for the extracted angle and moment PCs and statistical results in Tables 4.3 and 4.4. There were significant between-group differences ($p<0.05$) in hip and ankle biomechanics, including: i) the difference between the stance and swing hip adduction angles (hip adduction angle PC2), ii) the difference between the stance and swing ankle flexion angles (ankle flexion angle PC3), iii) the early to mid-stance ankle dorsiflexion moment (ankle flexion moment PC4), and iv) the difference between the early and late stance ankle rotation moments (ankle rotation moment PC2). The TKA group had less hip adduction range of motion, less ankle dorsiflexion in stance, lower dorsiflexion

moments during early to mid-stance, and less of a difference in rotation moments between early and late stance than the no-TKA group.

Table 4.1: Participant demographics, spatiotemporal gait characteristics and self-reported symptoms for the no-TKA and TKA groups. Data are presented as mean (standard deviation).

		No-TKA	TKA
	Sex	9 female	7 female
		19 male	19 male
	Age (years)	57.9 (7.3)	60.2 (9.3)
	Mass (Kg)	95.4 (20.1)	92.9 (13.7)
	BMI (Kg/m^2)	30.8 (5.5)	30.9 (4.7)
	KL Grade	2.5 (0.7)	2.8 (0.8)
		2 KL1	2 KL1
		12 KL2	6 KL2
		12 KL3	13 KL3
		2 KL4	5 KL4
	Medial Joint Space	1.6 (0.8)	2.1 (0.9)
	Alignment (ASIS-Knee-Ankle)[¥]	176.2 (3.0) degrees	174.8 (3.3) degrees
	Physical Activity*	9 Active	12 Active
		11 Sedentary	10 Sedentary
Spatiotemporal Gait Characteristics	Velocity (m/s)	1.3 (0.2)	1.2 (0.2)
	% Stance	63.7 (1.8)	64.7 (2.1)
	% Swing	36.3 (1.8)	35.3 (2.1)
WOMAC Scores	Pain (/20)	6.3 (4.6)	7.6 (3.6)
	Stiffness (/8)	3.2 (1.7)	4.0 (1.4)
	Function (/68)	20.4 (14.5)	24.4 (11.0)
	Total (/96)	30.0 (20.3)	35.7 (15.0)

[¥] Larger angles indicate more varus alignment
* Baseline physical activity questionnaires could not be located for 13 participants

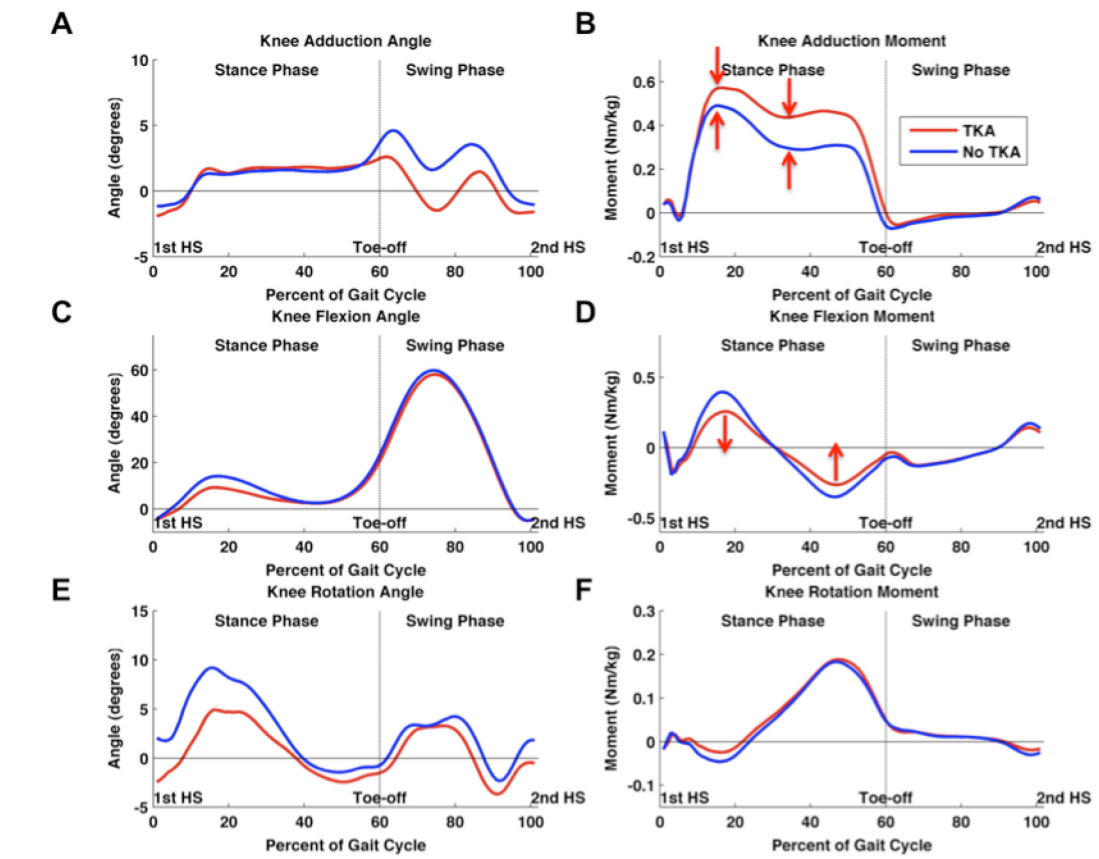

Figure 4.1: Baseline ensemble average knee A) adduction, C) flexion, and E) rotation angles and B) adduction, D) flexion, and F) rotation moments for the TKA (red) and no-TKA (blue) groups. Positive values denote adduction, flexion, and internal rotation angles and moments. The TKA group had a significantly higher overall knee adduction moment magnitude, less of a difference between the early and mid-stance knee adduction moment magnitudes (red arrows), and decreased early stance flexion and late stance extension moments (red arrows) at baseline compared to the no-TKA group ($p<0.05$).

Table 4.2: Three-dimensional knee angle and moment PC scores for the no-TKA and TKA groups. Data are presented as mean (standard deviation).

Gait Variable	PC	Explained Variance (%)*	Interpretation	No TKA	TKA	p-value
Flexion Angle	1	62.8	Overall magnitude	204.9 (41.9)	183.0 (56.1)	0.11
	2	14.7	Phase shift	44.4 (26.5)	51.7 (28.1)	0.33
	3	10.4	Late stance- swing difference	160.5 (22.3)	159.6 (26.4)	0.89
	4	6.5	Early stance-late stance difference	-10.8 (18.8)	-19.7 (18.4)	0.08
Adduction Angle	1	73.5	Overall magnitude	17.9 (30.8)	4.1 (29.7)	0.10
	2	9.9	Early-mid stance and late swing angle	-1.5 (11.7)	-1.9 (10.7)	0.89
	3	6.7	Mid-late stance angle	-6.8 (9.3)	-11.0 (10.0)	0.12
Rotation Angle	1	54.5	Overall magnitude	28.5 (47.0)	6.8 (49.2)	0.10
	2	22.2	Early stance/late swing-late stance/early swing difference	2.3 (32.5)	-3.2 (31.0)	0.53
	3	8.1	Late stance angle	8.0 (17.3)	9.1 (28.1)	0.86
	4	3.7	Stance-swing difference	26.3 (15.6)	19.2 (14.4)	0.09

Gait Variable	PC	Explained Variance (%)*	Interpretation	No TKA	TKA	p-value
Flexion Moment	1	44.1	Overall magnitude	0.36 (0.91)	0.18 (1.29)	0.55
	2	37.9	Flexion-extension moment difference¥	1.74 (1.01)	1.18 (0.86)	0.03
	3	7.1	Phase shift	-0.43 (0.29)	-0.39 (0.30)	0.65
	4	2.4	Heel strike extension moment	0.39 (0.25)	0.32 (0.19)	0.27
Adduction Moment	1	63.7	Overall shape and magnitude¥	2.38 (0.70)	3.21 (1.00)	0.001
	2	15.9	Early-mid stance difference¥	0.44 (0.45)	0.14 (0.45)	0.03
	3	7.0	Mid-late stance difference	-0.34 (0.26)	-0.36 (0.27)	0.73
	4	3.7	Swing magnitude	-0.10 (0.26)	-0.10 (0.25)	0.94
Rotation Moment	1	52.4	External-internal rotation moment difference	0.62 (0.38)	0.59 (0.27)	0.73
	2	34.2	Mid stance moment	0.43 (0.32)	0.51 (0.41)	0.42
	3	5.5	Internal rotation moment phase shift	0.07 (0.10)	0.10 (0.10)	0.26

* Explained variance refers to how much variability in the larger dataset (n=149) was accounted for by a particular principal component.
¥ Indicates a significant between-group difference ($p<0.05$)

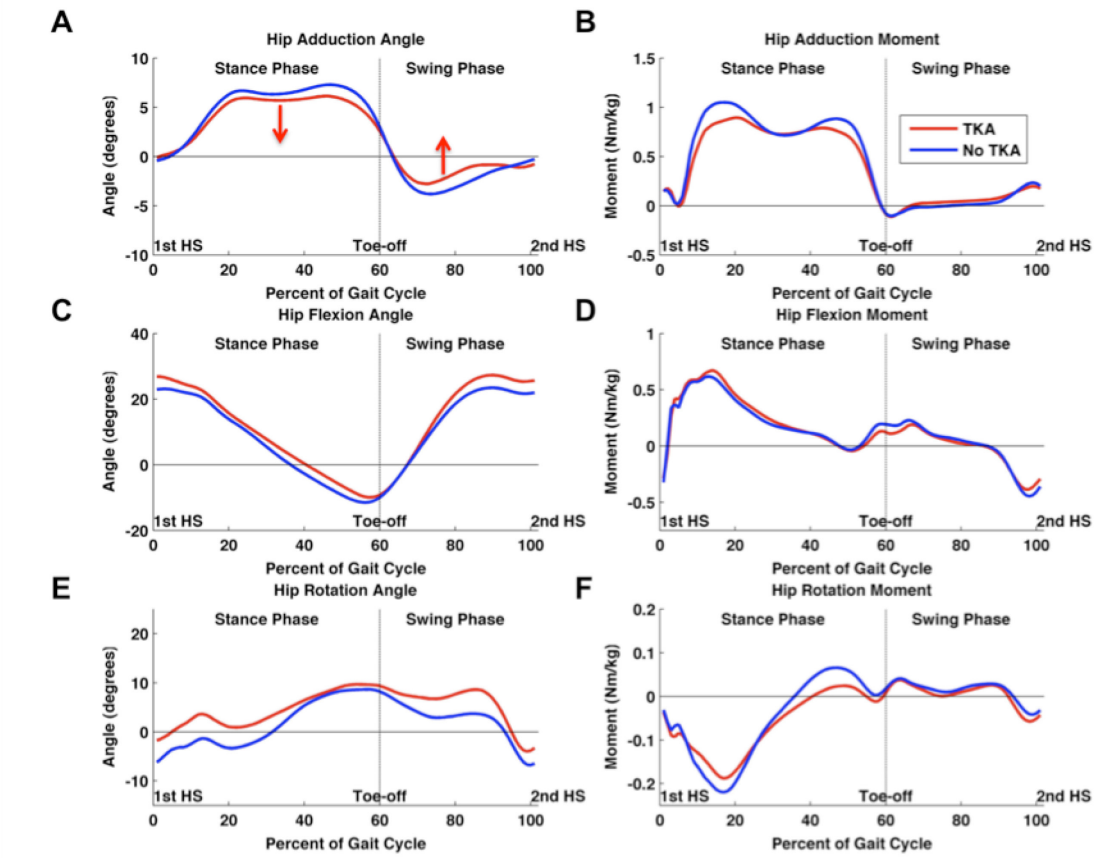

Figure 4.2: Baseline ensemble average hip A) adduction, C) flexion, and E) rotation angles and B) adduction, D) flexion, and F) rotation moments for the TKA (red) and no-TKA (blue) groups. Positive values denote adduction, flexion, and internal rotation angles and moments. The TKA group had less of a difference between the stance and swing hip adduction angles (red arrows) at baseline compared to the no-TKA group ($p<0.05$).

Table 4.3: Three-dimensional hip angle and moment PC scores for the no-TKA and TKA groups. Data are presented as mean (standard deviation).

Gait Variable	PC	Explained Variance (%)*	Interpretation	No TKA	TKA	p-value
Flexion Angle	1	70.3	Overall shape and magnitude	131.1 (68.7)	155.8 (47.0)	0.13
	2	15.0	Late stance extension	78.3 (31.9)	72.7 (24.6)	0.47
	3	7.4	Phase shift	7.1 (15.2)	8.5 (17.2)	0.76
Adduction Angle	1	77.7	Overall magnitude	23.5 (29.6)	21.9 (24.0)	0.83
	2	10.3	Mid stance to swing difference¥	38.3 (12.4)	30.7 (14.0)	0.04
	3	6.2	Early stance to swing difference	9.9 (9.0)	7.8 (10.8)	0.44
Rotation Angle	1	62.4	Late stance to early stance/late swing difference	-11.3 (58.7)	-43.0 (55.4)	0.05
	2	18.2	Late stance/early swing magnitude	44.8 (26.9)	42.1 (30.8)	0.73
	3	6.0	Mid stance to mid swing difference	1.9 (15.2)	4.7 (21.1)	0.58
	4	4.4	Early to late swing difference	-1.7 (13.6)	4.5 (19.1)	0.18

Gait Variable	PC	Explained Variance (%)*	Interpretation	No TKA	TKA	p-value
Flexion Moment	1	60.3	Overall magnitude	1.79 (1.13)	1.91 (1.91)	0.78
	2	12.0	Early stance flexion moment	-1.63 (0.67)	-1.65 (0.49)	0.90
	3	7.7	Late stance to late swing difference	-0.34 (0.58)	-0.01 (0.58)	0.05
	4	5.3	Swing magnitude	1.22 (0.46)	1.26 (0.41)	0.71
Adduction Moment	1	57.5	Overall shape and magnitude	5.45 (1.77)	4.76 (1.62)	0.14
	2	22.2	Phase shift	1.36 (1.05)	0.94 (0.77)	0.10
	3	5.4	Mid-stance magnitude relative to early and late stance magnitude	0.61 (0.46)	0.86 (0.56)	0.08
	4	3.6	Early swing magnitude	-0.59 (0.47)	-0.65 (0.32)	0.59
Rotation Moment	1	57.9	Overall magnitude	-0.40 (0.54)	-0.47 (0.80)	0.71
	2	21.2	Mid stance to late stance difference	0.65 (0.35)	0.46 (0.38)	0.06
	3	5.6	Phase shift	0.11 (0.19)	0.12 (0.21)	0.88
	4	4.0	Early swing magnitude	-0.33 (0.16)	-0.24 (0.15)	0.05

* Explained variance refers to how much variability in the larger dataset (n=149) was explained by a particular principal component.
¥ Indicates a significant between-group difference ($p<0.05$)

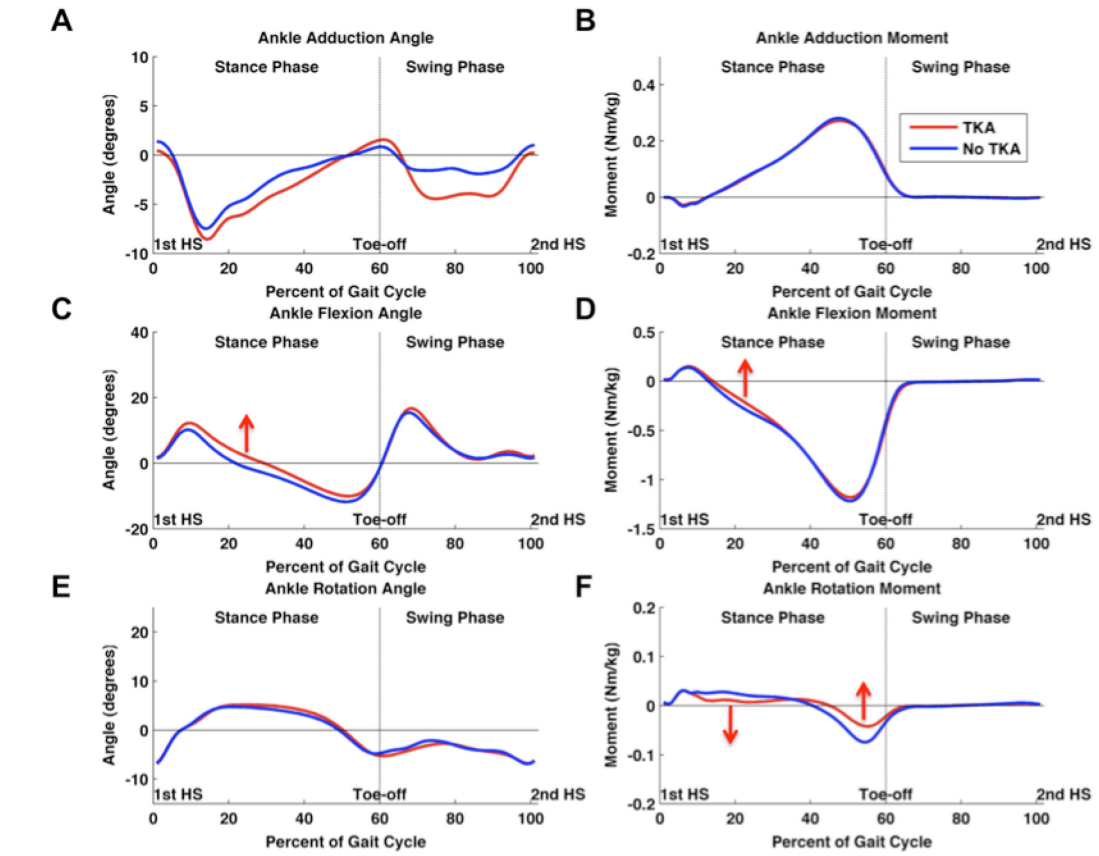

Figure 4.3: Baseline ensemble average ankle A) adduction, C) flexion, and E) rotation angles and B) adduction, D) flexion, and F) rotation moments for the TKA (red) and no-TKA (blue) groups. Positive values denote adduction, plantarflexion, and internal rotation angles and moments. The TKA group had less dorsiflexion during stance (red arrow), decreased dorsiflexion moments during early stance (red arrow), and less of a difference between the early stance internal rotation and late stance external rotation moment (red arrows) at baseline than the no-TKA group ($p<0.05$).

Table 4.4: Three-dimensional ankle angle and moment PC scores for the no-TKA and TKA groups. Data are presented as mean (standard deviation).

Gait Variable	PC	Explained Variance (%)*	Interpretation	No TKA	TKA	p-value
Flexion Angle	1	55.5	Overall magnitude	15.7 (36.2)	27.5 (50.8)	0.33
	2	23.3	Phase shift	0.0 (22.1)	-9.7 (17.8)	0.08
	3	7.7	Stance to swing difference¥	43.9 (13.0)	35.1 (14.4)	0.02
	4	5.4	Early swing magnitude	-23.6 (13.6)	-29.5 (14.3)	0.12
Adduction Angle	1	58.2	Overall magnitude	-15.7 (32.5)	-26.8 (36.1)	0.25
	2	17.4	Mid stance to early & late stance difference	9.3 (16.8)	13.6 (13.2)	0.30
	3	7.3	Mid stance magnitude	17.1 (7.2)	21.0 (11.7)	0.15
	4	4.4	Late swing magnitude	-8.0 (7.3)	-2.7 (12.6)	0.07
Rotation Angle	1	66.6	Stance to swing difference	16.5 (28.1)	17.1 (29.1)	0.94
	2	12.5	Mid stance magnitude	15.7 (17.1)	20.3 (11.8)	0.25
	3	8.5	Early to late stance difference	26.8 (9.2)	27.7 (14.2)	0.76
	4	4.5	Late swing/early stance magnitude	15.1 (6.9)	13.9 (7.9)	0.57

Gait Variable	PC	Explained Variance (%)*	Interpretation	No TKA	TKA	p-value
Flexion Moment	1	48.2	Dorsiflexion magnitude	3.44 (0.89)	3.24 (0.72)	0.36
	2	24.1	Phase shift	-3.05 (0.53)	-2.99 (0.45)	0.64
	3	16.7	Mid to late stance difference	2.02 (0.42)	2.01 (0.52)	0.55
	4	5.8	Early-mid stance dorsiflexion magnitude¥	-0.75 (0.28)	-0.93 (0.19)	0.01
Adduction Moment	1	93.9	Overall shape and magnitude	1.21 (0.58)	1.20 (0.67)	0.95
Rotation Moment	1	75.3	Mid-late stance external rotation magnitude	0.10 (0.39)	0.03 (0.41)	0.58
	2	14.5	Early to late stance difference¥	0.23 (0.17)	0.13 (0.18)	0.03
	3	4.6	Early stance external rotation magnitude	0.05 (0.10)	0.04 (0.08)	0.50

* Explained variance refers to how much variability in the larger dataset (n=149) was explained by a particular principal component.
¥ Indicates a significant between-group difference ($p<0.05$)

4.4 DISCUSSION

This study investigated whether differences existed in three-dimensional lower extremity biomechanical gait patterns between those with moderate medial knee OA who progressed to TKA versus those that did not. Increased structural disease severity has been associated with TKA (Gossec et al, 2011), but both groups had similar radiographic disease severity based on KL and mean joint space narrowing grades. The ASIS-knee-ankle angle showed slight varus alignment, but this was similar between groups (Table 4.1). While full-leg radiographs, the gold-standard for frontal-plane static alignment were not obtained in the present study, the measure of alignment suggests that varus alignment, a risk factor for medial knee OA structural progression (Yusuf et al, 2011), did not explain the differences found in joint biomechanics between groups. The groups did not differ in self-reported pain and function, two factors that influence the need for TKA (Gossec et al, 2011). While the TKA group had higher WOMAC scores, indicating worse perceived symptoms, there were no significant between-group differences, and the difference in scores was less than the minimally clinically important difference (Escobar et al, 2007). Furthermore, similarities between groups in walking velocity and stride characteristics at baseline support comparable symptomatic severity.

While comparable for the above variables, the two groups did have different lower extremity biomechanical patterns at baseline. Differences at the knee were in frontal and sagittal plane moments that affect the local biomechanical loading environment. The hip and ankle differences were found in the sagittal (angle and moment) and transverse (moment) planes at the ankle and only frontal plane motion for the hip joint.

Frontal plane moment alterations have thus far been the only kinetic gait variables linked to knee OA structural progression (Bennell et al, 2011; Chang et al, 2005; Miyazaki et al, 2002). This study also found that frontal plane moment characteristics were different between the two groups, but only at the knee. In contrast to other progression studies, two aspects of the KAM were different, along with the knee flexion moment pattern, for the TKA group. The higher overall KAM magnitude (KAMPC1) in the TKA group captures

increased loading relative to body mass that can affect different areas of cartilage as the position of the tibia relative to the femur changes throughout gait. Less of a difference between early and mid-stance KAM magnitudes (KAMPC2) indicates reduced ability to unload the medial tibiofemoral compartment during walking, and is consistent with the reduced knee flexion and extension moments found (knee flexion moment PC2). Together, these two features support a "stiff gait" pattern, which is consistent with the sustained loading mechanism associated with cartilage degradation (Chen et al, 1999). Sustained compressive loads have been found to reduce biosynthetic activity (Arokoski et al, 2000), and the accumulated strain energy exceeds the energy of the covalent bonds of collagen in the cartilage matrix, causing damage (Chen et al, 1999). In terms of progression of symptoms, static compressive load has been shown to increase expression of inflammatory chemicals, such as interleukin-1β and tumor necrosis factor-α in articular cartilage in animal models more than dynamic load (Wang et al, 2007). Baseline levels of these inflammatory chemicals are independent predictors of worsening knee pain over 5 years in those with knee OA (Stannus et al, 2013). The higher magnitude and sustained duration of compressive loading seen in the TKA group provides a mechanical environment that could lead to an increase in these inflammatory chemicals, perhaps contributing to a more rapid progression of symptoms. The combination of knee joint moment findings supports the interaction between a higher overall magnitude of loading *plus* an inability to unload the joint as a mechanism for OA progression, rather than peak loading at only one point in the gait cycle (i.e. KAM peak) or the combined magnitude and duration of loading (i.e. KAM impulse), neither of which capture the unloading feature.

With "stiff gait" decreased knee flexion range of motion might be expected. While the difference between the early and late stance knee flexion angle (knee flexion angle PC4) was reduced in the TKA group, this difference was not significant ($p = 0.08$). In part this is explained by the high variability, as the difference is 45% in the PC scores, which translates into a difference in range of motion of approximately 5 degrees between the groups. Looking at the mean waveforms (Figure 4.1), this reduction in range of motion occurs mainly at the stance peak. Reductions in the stance peak knee flexion angle have

been found to be approximately 6 degrees more in those with severe knee OA compared to those with moderate knee OA based on knee OA symptomatic and structural severity. (Astephen et al, 2008b). Knee kinetic differences in the TKA group were also consistent with data reported from cross-sectional studies for increased symptomatic and structural severity (Astephen et al, 2008b). Thus, it cannot be ruled out that knee biomechanics are actually a more sensitive metric to assess OA progression, and are picking up severity changes before they appear symptomatically or radiographically. However, alterations in the knee rotation moment were also seen in those with severe knee OA in the study by Astephen et al (Astephen et al, 2008b), which were not seen in the present TKA group. It was surprising that no knee joint rotational variables were different, as was hypothesized, but this could be due to the increased variability in these measures, reducing statistical power. Additionally, reconstruction of these waveforms using the extracted PCs was poor, indicating that PCA may not have adequately captured rotational features. Increased BMI has been associated with an inability to unload the knee during stance (indicated by a decreased difference between the early and mid-stance KAM magnitudes) (Harding et al, 2012), however there were no between-group differences in BMI, indicating that increased BMI was not the reason for the decreased KAMPC2 scores in the TKA group.

The results for the hip and ankle joint biomechanics and their influence on OA progression differed from previous work. Although decreased peak external hip adduction moments were previously associated with structural progression (Chang et al, 2005), there were no between-group differences for the overall magnitude of the hip adduction moment. PC3 for the hip adduction moment, capturing the mid-stance magnitude relative to the early and late stance magnitudes, was greater for the TKA group, but did not reach statistical significance ($p=0.08$), which may have been due to low statistical power, but also this pattern only explained 5.4% of the variance in the waveforms. The higher mid-stance magnitude in the TKA group indicates decreased unloading at the hip during mid-stance, is consistent with findings at the knee, and supports a “stiff gait” in this group. The only hip gait variable that significantly differed between groups was the reduced frontal plane range of motion between the stance and

swing phase for the TKA group, and how that would affect the knee joint mechanical environment and joint loading was not evident. At the ankle, sagittal plane angles and moments and transverse plane moments differed between groups. The reduced stance dorsiflexion angle and moment could indicate a more posterior tibial position, causing the slight reduction in the stance knee flexion angle, and provides additional evidence of "stiff gait" in the TKA group. No transverse plane ankle motion differences in the present study contrasts previous work linking transverse plane angles to structural progression (Chang et al, 2007)). The reduced difference between the early stance internal rotation and late stance external rotation moments has previously been reported in those with severe knee OA compared to those with moderate knee OA (Astephen et al, 2008), but how this alteration relates to the knee biomechanical environment is unclear.

Thus far, most biomechanical-based conservative intervention studies have targeted frontal plane mechanics, particularly the peak KAM, and results from these studies have been equivocal regarding biomechanical changes. This suggests that either the outcome variable or patient selection needs to be evaluated. Perhaps targeting one discrete variable such as a peak or impulse explains some of the inconsistencies between biomechanical and symptomatic changes with these interventional studies. The present results indicate that knee flexion moment patterns and knee joint unloading during stance, which no longitudinal studies have addressed, could be used as outcome measures and/or targets for conservative interventions. Targeting just the peak KAM or KAM impulse may reduce the magnitude of joint loading, but would not affect sustained loading. Altering kinetic patterns associated with sustained loading would address a knee OA progression mechanism thus far neglected in the development and evaluation of conservative interventions. Furthermore, only evaluating the effect of a conservative intervention on the KAM neglects to consider the other dimensions of joint loading.

A strength of the study is that, since less than 50% of the TKA group progressed radiographically, TKA as an outcome measure captured an additional aspect of progression not captured by structural changes alone. However, it is recognized that considerable clinical decision-making is involved when selecting an appropriate TKA

candidate. Surgeon variability in clinical decision-making was reduced by having all participants under the care of the same orthopaedic surgeon at baseline. In addition to the presence of structural damage, two major factors influencing need for surgery are pain and functional deficits (Gossec et al, 2011). Both groups had similar baseline pain and function scores and were being managed conservatively. Pre-TKA WOMAC scores were not available for the TKA group, but there was self-reported improvement or no change in symptoms in 20/28 of no-TKA participants at follow-up. An additional factor in the decision to undergo TKA is a patient's willingness (Hawker et al, 2006). The current study was limited because no metric of willingness to undergo TKA was obtained, but presumably some participants in the no-TKA group would fit this category. This error could result in an underestimation of biomechanical differences. Finally, determining knee joint loading based on inverse dynamics alone has limitations as muscle forces can contribute to the overall load (Herzog et al, 2003; Horisberger et al, 2012) and muscle activation patterns are altered for those with knee OA (Hubley-Kozey et al, 2006). Future work should include electromyography in order to provide insight as to how the periarticular muscles are contributing to the biomechanical differences found.

In conclusion, this study determined that lower extremity gait biomechanics were different between those with moderate medial knee OA who progressed to TKA versus those that did not, despite similar demographic, radiographic, and symptomatic factors at baseline. The TKA group had frontal and sagittal plane knee moment pattern differences that are consistent with higher overall loading of the knee during the stance phase of gait, and reduced ability to unload the joint in mid-stance, at baseline. This combination of higher and more sustained loading is consistent with mechanical mechanisms for both structural and symptomatic OA progression. The differences found have not previously been reported in longitudinal studies on knee OA progression, and provide potential targets for conservative interventions.

CHAPTER 5 RELATION BETWEEN KNEE ADDUCTION MOMENT PATTERNS EXTRACTED USING PRINCIPAL COMPONENT ANALYSIS AND THE KNEE ADDUCTION MOMENT PEAK AND IMPULSE

5.1 INTRODUCTION

Osteoarthritis (OA) is a degenerative disease of synovial joints, for which there is no cure. The knee joint is most often affected by OA (Dillon et al, 2006), and resulting pain, stiffness, weakness, and joint instability can lead to decreased mobility and functional limitations. In fact, more difficulty with typical activities of daily living such as walking and climbing stairs is reported by those with knee OA over the age of 65 years than any other medical condition (Hunter and Felson, 2006). Conservative interventions have been identified as the most important healthcare need for those with knee OA (Buckwalter et al, 2001; Gross and Hillstrom, 2008; Lane et al, 2011). Because of its progressive nature, those with mild to moderate knee OA have the most to gain from interventions that slow OA progression. However, in order to determine the most effective conservative interventions, mechanisms of progression must first be understood. Since dynamic frontal plane knee biomechanical features during walking have been implicated in knee OA structural progression (Bennell et al, 2011; Miyazaki et al, 2002), conservative treatment approaches have aimed to alter these features. The present study focuses on the knee adduction moment (KAM). This gait variable has been a focus in the knee OA literature because it is correlated with the ratio of medial compartment to total knee loading (Zhao et al, 2007) and knee OA is more common in the medial than lateral compartment (Frontera and Silver, 2002; Thomas et al, 1975), and it is also related to pain (Henriksen et al, 2012).

Conservative interventions targeting KAM features are based on only two longitudinal studies that have related increased KAM peaks (Miyazaki et al, 2002) and impulses (Bennell et al, 2011) to an increased risk of knee OA structural progression. Orthotic

devices, such as canes (Gross and Hillstrom, 2008), lateral wedge orthotics (Gross and Hillstrom, 2008; Radzimski et al, 2012), and unloader braces (Gaasbeek et al, 2007; Gross and Hillstrom, 2008; Lindenfeld et al, 1997; Pollo et al, 2002; Self et al, 2000), hip abductor strengthening (Chang et al, 2005), and gait modifications such as reduced walking speed (Mundermann et al, 2004), increased trunk lateral lean (Hunt et al, 2011; Simic et al, 2012), toe-ing out (Chang et al, 2007; Schache et al, 2008), and "medial thrust" (Fregly et al, 2007; Schache et al, 2008) have all been proposed as conservative interventions that reduce the KAM. However, looking only at structural changes (i.e. "disease" component) neglects the symptoms (i.e. "illness" component) of knee OA (Lane et al, 2011), which is important to consider as symptoms are poorly correlated to structural changes (Barker et al, 2004; Creamer et al, 2000). Using total knee arthroplasty (TKA) as a progression outcome measure captures both the symptoms and structural changes associated with knee OA, as both aspects are considered in the clinical decision-making surrounding TKA (Gossec et al, 2011). Knowing whether the KAM peak and impulse are only associated with structural progression, or whether they are also able to differentiate a group whose knee OA progression is based on structural and symptomatic changes, could shed light on biomechanical mechanisms of knee OA progression that would help to evaluate the value of these variables as conservative intervention targets.

In Chapter 4 it was found that both amplitude and temporal characteristics of KAM waveforms extracted using principal component analysis (PCA) were different at baseline between those with moderate medial knee OA that progressed to TKA within 8 years and those that did not. The TKA group had higher overall KAM magnitudes (KAMPC1) and less of a difference between the early and mid-stance KAM (KAMPC2), indicating an inability to unload the knee during mid-stance. Although KAMPC1 is not capturing the same characteristic as the KAM impulse, the two variables should be related, since both get at the overall magnitude of medial compartment loading. The KAM impulse includes a duration of loading component, but the values are not unique since different waveform patterns can give the same numerical value. The benefit of using features extracted using PCA is that amplitude and temporal information are considered. KAMPC1 captures the overall magnitude, but also the shape of the KAM. For example, a KAM waveform with

a high first peak could have the same KAM impulse as a waveform with a high second peak (Figure 5.1), and also could have the same peak KAM value, but the interpretation of the dynamic loading patterns would be different. Features extracted using PCA would capture the different loading patterns, as the waveforms would score very differently for KAMPC1 and KAMPC2. PCA can be difficult to interpret, however, and determining whether simple discrete measures capture similar information would be valuable.

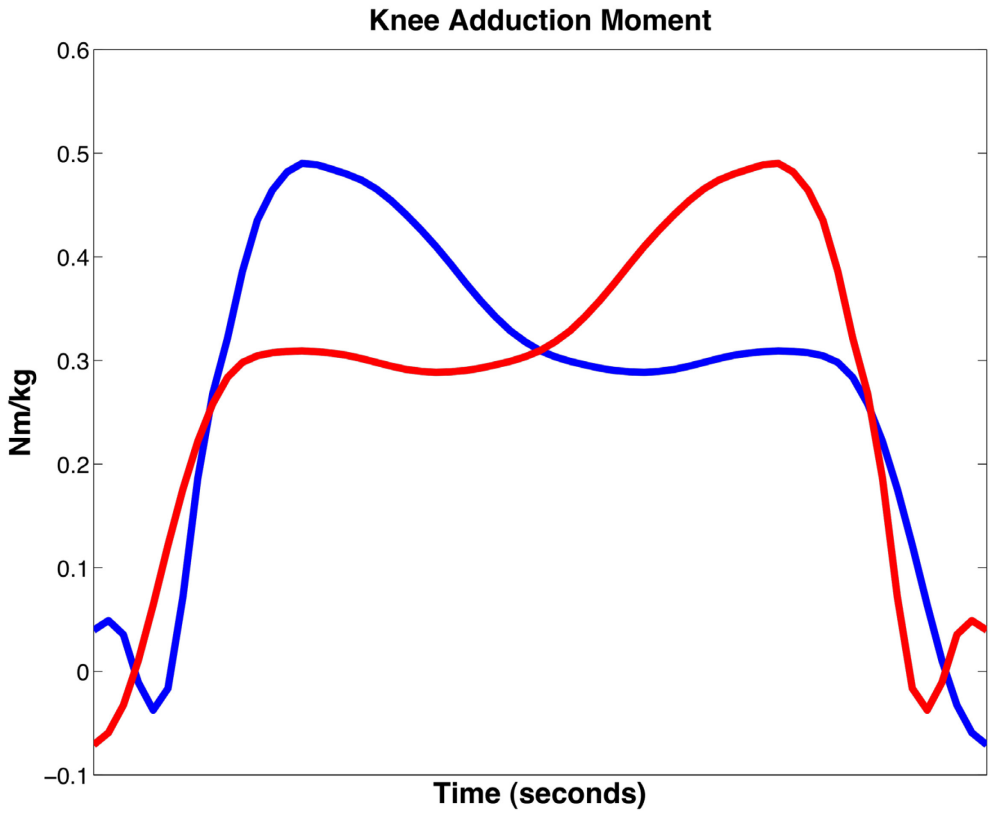

Figure 5.1: Example knee adduction moment waveforms (stance phase shown) that have the same knee adduction moment impulse value, but different shapes and therefore different interpretations.

A second issue related to understanding KAM features is that a variety of amplitude-normalization procedures have been used in the literature, making it sometimes difficult to make comparisons of results between studies. The two previous studies linking KAM discrete features to knee OA structural progression amplitude-normalized the KAM to body weight times height (with units of Nm/Nm expressed as percentages) to control for differences in body size between participants (Bennell et al, 2011; Miyazaki et al, 2002). Cross-sectional studies looking at the KAM peak (Baliunas et al, 2002; Lewek et al, 2004; Mundermann et al, 2005) and impulse (Kean et al, 2012; Thorp et al, 2006) have also normalized to body weight and height. The rationale for this normalization is that taller, heavier people have heavier, longer, and wider body segments, which result in greater segment moments of inertia and moment arm lengths (Roebuck et al, 1975). It has been found that both weight and height have significant correlations with joint moments during gait (Moisio et al, 2003).

In other areas of gait biomechanics the most common method of amplitude-normalization is to normalize to body mass only. This provides an indication of how much loading the joint is experiencing above that associated with body mass alone. The rationale for amplitude-normalizing to mass only, as opposed to including height, is that there is less variability in height than in mass (Pierrynowski and Galea, 2001). Also, it has been found in healthy adults that, since mass and height are significantly correlated, and since mass has higher correlations with joint moments during gait than height, that entering both variables into multiple regression models resulted in only mass emerging as a significant predictor of joint moments (Moisio et al, 2003). Studies looking at the peak KAM (Astephen et al, 2008b) have amplitude-normalized to body mass (units of Nm/kg), and typically studies using PCA to extract gait features have used waveforms amplitude-normalized to body mass (Astephen et al, 2008; Hatfield et al, 2011; Landry et al, 2007; Robbins et al, 2013; Smith et al, 2004).

However, caution needs to be exercised in using and interpreting any amplitude-normalization for the KAM as mass is a major contributor to absolute amplitude of external joint moments (Moisio et al, 2003). Thus, if the overall goal is to quantify the

absolute load the knee is experiencing, amplitude-normalizing removes some of that signal (Robbins et al, 2011b). However, while Robbins et al (2011b) found that non-normalized waveforms were better able to distinguish between knee OA severities, the masses between the different severity groups were also different (Robbins et al, 2011b), highlighting why amplitude-normalization is so common in the gait biomechanics literature. How the different methods of amplitude-normalization impact differences associated with knee OA progression would facilitate comparison and interpretation of results between studies, and shed light on which method of normalization is best to use for longitudinal studies.

The aims of this study were therefore: i) to determine whether baseline differences existed in KAM discrete measures (i.e. peak and impulse) between those with moderate medial knee OA who progressed to TKA and those that did not, ii) to determine relations between KAM discrete measures and KAM features extracted using PCA, and iii) to examine the effects of different methods of KAM amplitude-normalization on the results of the first two aims. With respect to the first aim, it was hypothesized that the KAM peak and impulse would be higher at baseline in the TKA group than in the no-TKA group, as structural progression is a factor in the TKA decision-making process (Bennell et al, 2011). For the second aim, it was hypothesized that KAMPC1 would be significantly related to the KAM impulse, but that KAMPC2 would be unrelated to either discrete measure, since it captures a temporal aspect of the waveform. For the third aim, it was hypothesized that the results of aims i) and ii) would be consistent, regardless of amplitude-normalization method.

5.2 METHODS

5.2.1 Participants

Data for this study were collected as part of a longitudinal study on 80 participants with moderate medial compartment knee OA that underwent baseline gait analysis in the Dynamics of Human Motion laboratory at Dalhousie University between 2003 and 2008. Participants were diagnosed by one orthopaedic surgeon using radiographic and clinical

evidence, as defined by the American College of Rheumatology (Altman et al, 1986). All patients had primary knee OA and none were candidates for TKA at the time of recruitment. At baseline, all participants met the functional criteria of being able to jog 5 metres, walk a city block, and climb stairs reciprocally (Hubley-Kozey et al, 2006). Out of 64 participants who could be reached by telephone to inquire whether they were willing to undergo a follow-up gait analysis, 28 participants agreed and reported they had not had TKA (no-TKA group), and 26 reported they had TKA since their baseline testing session (TKA group). Nine participants were not interested in participating in the follow-up gait analysis, but denied undergoing TKA since baseline, and one participant had undergone high tibial osteotomy since baseline.

5.2.2 Procedure

Institutional ethics approval (Capital Health Research Ethics Board and Dalhousie University Research Ethics Board) was obtained for this study. Demographic data (age, sex, mass, height), static frontal plane alignment (from standing calibration trial, Chapter 4), and self-reports of physical activity (Chapter 4), pain and function (Western Ontario and McMaster Universities Osteoarthritis Index, WOMAC (Bellamy et al, 1988)) were recorded at baseline. Standard, weight-bearing anterior-posterior and lateral radiographs were taken to determine baseline structural severity. One high-volume orthopaedic surgeon graded the radiographs twice using the Kellgren and Lawrence (KL) grading scale (Kellgren and Lawrence, 1957) and the Scott Feature Based score system (Scott et al, 1993). Between-grading agreement was 95%, 98%, and 93% for KL grade, medial, and lateral joint space narrowing grades, with weighted kappa coefficients of 0.91, 0.99, and 0.91 (Appendix 2).

Gait analysis included collection of three-dimensional motion and ground reaction force data, surface electromyograms, and maximal strength measures, but since this chapter focuses on KAM differences between the TKA and no-TKA groups, and on relations between different KAM measures, only biomechanical gait analysis methodology and results are presented.

5.2.3 Gait Analysis

To monitor segment motion during gait, 16 infrared-emitting diodes were placed on specific anatomical landmarks on the participants. Triads were placed on pelvis, thigh, shank, and foot segments. Individual markers were placed on the shoulder, greater trochanter, lateral epicondyle, and lateral malleolus. The locations of eight virtual points (right and left ASIS, medial epicondyle, fibular head, tibial tuberosity, medial malleolus, second metatarsal, and heel) were recorded in quiet standing. The three-dimensional motion of the markers during gait was collected using a two-camera Optotrak™ 3020 motion capture system (Northern Digital Inc, Waterloo ON) sampling at 100 Hz. Three-dimensional ground reaction forces were recorded at 1000 Hz using an AMTI™ force platform (Advanced Medical Technology Inc, Watertown MA). Frontal plane alignment was calculated using motion capture data from a standing calibration trial as the angle formed between: i) the line connecting the anterior superior iliac spine (ASIS) and the knee joint centre, and ii) the line connecting the knee and ankle joint centres (Chapter 4). Participants performed at least five successful gait trials, walking at a self-selected pace, across a five-metre walkway. A trial was considered successful if the participant's foot on the tested leg came into full contact with the force platform, and the foot on the untested leg did not contact the force platform. Gait variables obtained using this standardized protocol, including discrete variables and frontal plane knee moments, have been shown to be reliable (Robbins et al, 2013).

5.2.4 Data Analysis

Custom software written in Matlab (Mathworks Inc, Natick MA) was used to process the gait data. Motion and force data were digitally filtered (recursive fourth order Butterworth) at 8 Hz and 60 Hz respectively, and used to identify heel strike and toe-off to define one gait cycle (heel strike to heel strike on the same foot). Three-dimensional knee external moments were calculated using inverse dynamics (Costigan et al, 1992; Deluzio et al, 1993; Li et al, 1993) and expressed in the joint coordinate system (Grood and Suntay, 1983). For the PCA analysis and the peak KAM, the KAM waveforms were time-normalized to a percentage of the gait cycle (i.e. 101 data points) using a linear interpolation technique (Astephen et al, 2008; Astephen et al, 2008b; Deluzio and

Astephen, 2007; Landry et al, 2007). Waveforms were not time-normalized for the calculation of the KAM impulse, as the variable is meant to capture the load that the knee experiences over time. Three amplitude-normalization methods were used. KAM waveforms were kept in their original units (Nm), amplitude-normalized to body mass (Nm/kg), and amplitude-normalized to body weight and height (Nm/Nm) and expressed as percentages.

The first peak KAM (i.e. peak occurring in the first 40% of the gait cycle (Robbins et al, 2013)) and KAM impulse (area under the positive portion of the stance phase of the non-time normalized waveform, Equation 3.1) were calculated for each trial for each participant, and then averaged to get the mean peak KAM and mean KAM impulse for each participant. For the PCA analysis, time-normalized KAM waveforms for each trial were averaged to create ensemble average profiles for each participant (Winter and Yack, 1987), and PCs were calculated based on the ensemble averages.
Discrete peak KAM and PCs extracted from the KAM waveform have been shown to be highly reliable metrics, with intra-class correlation coefficients ranging from 0.91 to 0.94 (Robbins et al, 2013).

5.2.5 Principal Component Analysis

PCA for gait biomechanical waveforms has been described in detail elsewhere (Deluzio and Astephen, 2007), but a brief description consistent with Chapter 4 is provided. An nx101 matrix (**X**) was formed for the KAM, consisting of the ensemble average profile of walking trials for each participant. For this study, the matrix was constructed from a larger dataset of 149 baseline and follow-up waveforms (**X**=149x101) for asymptomatic and moderate knee OA participants in the follow-up study to improve robustness of patterns extracted (Osborne and Costello, 2004). Next, a covariance (**C**) matrix of **X** was calculated. A transform matrix (**T**, 101x101) was then calculated by the eigenvector-eigenvalue decomposition of **C**. **T** is a matrix of the PCs (eigenvectors), and **Λ** is a diagonal of the associated variances (eigenvalues). Scores were then calculated for the baseline waveforms for the 54 study participants. These scores are weighting coefficients based on how much of the variability in a participant's KAM waveform is explained by a

particular PC. Statistical analyses were done on these scores. For this study, KAMPC1 and KAMPC2 scores were retained for statistical analysis, as these were the KAM features that were associated with progression to TKA (Chapter 4).

5.2.6 Statistical Analysis

Assumptions of normality and equal variances were examined using the Kolmogorov-Smirnov and Levene's tests, respectively. Unpaired Student's t-tests were used to detect significant differences in KAM peaks, KAM impulses, KAMPC1 scores, and KAMPC2 scores between the TKA and no-TKA groups. For the second study aim, Pearson product moment correlation coefficients were used to determine relations between KAMPC1 and KAMPC2 scores and the KAM peak and impulse. In order to address the effect of amplitude-normalization, the above analyses were performed for non-amplitude-normalized KAM waveforms, KAM waveforms amplitude-normalized to body mass, and KAM waveforms amplitude-normalized to body weight times height. For all hypothesis testing, the significance level (α) was 0.05. All analyses were completed using Minitab™ (Minitab Inc, State College PA).

5.3 RESULTS

The first study aim was to determine if there were baseline differences in the KAM peak and impulse between the TKA and no-TKA groups. Participant demographics have been presented in Table 4.1. There were no between-group differences in age, mass, BMI, physical activity level, or frontal plane alignment, with similar sex and radiographic disease severity distribution at baseline. The groups were clinically similar, with no significant between-group differences in WOMAC scores (Table 4.1). The TKA group spent a longer time in stance compared to the no-TKA group (0.76 (0.07) versus 0.70 (0.12)), but this difference was not significant. There were no significant between-group differences in walking velocity (Table 4.1). As hypothesized, significant between-group baseline differences were found for the peak KAM (normalized to body weight times height) and for the KAM impulse. The KAM peak and impulse were significantly higher in the TKA group than the no-TKA group. Percent differences ranged from 13-16% for

the peak KAM, and from 28-30% for the KAM impulse. Group means for these variables are in Tables 5.1 and 5.2, and mean KAM waveforms for both groups are in Figure 4.1.

Table 5.1: Peak knee adduction moment (KAM) for the TKA and no-TKA groups. Moments were non-amplitude-normalized, normalized to mass (kg), and normalized to body weight times height (Nm/Nm). Data presented as mean (standard deviation).

		Peak KAM (Nm)	Peak KAM (Nm/kg)	Peak KAM (Nm/Nm) %
No TKA	Mean (SD)	49.7 (16.1)	0.53 (0.15)	3.10 (0.87)
TKA	Mean (SD)	57.1 (17.7)	0.63 (0.19)	3.67 (1.11)*
	Percent Difference	13%	16%	16%
	p-value	0.12	0.05	0.04

* Indicates a significant between-group difference ($p<0.05$)

Table 5.2: Knee adduction moment impulse (KAM) for the TKA and no-TKA groups. Moments were non-amplitude-normalized, normalized to mass (kg), and normalized to body weight times height (Nm/Nm). Data presented as mean (standard deviation).

		KAM Impulse (Nm*s)	KAM Impulse (Nm/kg*s)	KAM Impulse (Nm/Nm*s) %
No TKA	Mean (SD)	17.1 (6.9)	0.18 (0.06)	1.06 (0.36)
TKA	Mean (SD)	23.7 (8.2)*	0.26 (0.08)*	1.51 (0.48)*
	Percent difference	28%	30%	30%
	p-value	0.002	<0.001	<0.001

* Indicates a significant between-group difference ($p<0.05$)

The second study aim was to determine how well KAMPC1 and KAMPC2 correlated with discrete KAM characteristics (peak and impulse). The correlation coefficients between KAMPC1 and KAMPC2 and the KAM peak and impulse are in Tables 5.3 (non-amplitude-normalized), 5.4 (amplitude-normalized to body mass), and 5.5 (amplitude-normalized to body weight times height). KAMPC1, which captured the overall shape and magnitude of the KAM, was significantly correlated with both the peak KAM and the KAM impulse, regardless of the amplitude-normalization method used. KAMPC2, which captured the difference between the early and mid-stance KAM magnitudes, was not significantly correlated with the KAM impulse, regardless of amplitude-normalization method. It was correlated with the KAM peak, regardless of the method of amplitude-normalization, but the correlation coefficients were small, accounting for only 8-16% of the variance.

Table 5.3: Correlation coefficients between knee adduction moment (KAM) PC1 and PC2 and the KAM peak and impulse. Data non-amplitude-normalized (Nm).

	Peak KAM	KAM Impulse	KAMPC1
Peak KAM		r = 0.768*	r = 0.900*
KAM Impulse	r = 0.768*		r = 0.925*
KAMPC1	r = 0.900*	r = 0.925*	
KAMPC2	r = 0.274*	r = -0.233	r = -0.117

* Indicates a significant correlation ($p<0.05$)

Table 5.4: Correlation coefficients between knee adduction moment (KAM) PC1 and PC2 and the KAM peak and impulse. Data amplitude-normalized to body mass (Nm/kg).

	Peak KAM	KAM Impulse	KAMPC1
Peak KAM		r = 0.756*	r = 0.878*
KAM Impulse	r = 0.756*		r = 0.931*
KAMPC1	r = 0.878*	r = 0.931*	
KAMPC2	r = 0.394*	r = -0.146	r = -0.037

* Indicates a significant correlation ($p<0.05$)

Table 5.5: Correlation coefficients between knee adduction moment (KAM) PC1 and PC2 and the KAM peak and impulse. Data amplitude-normalized to body weight times height (Nm/Nm).

	Peak KAM	KAM Impulse	KAMPC1
Peak KAM		r = 0.766*	r = 0.878*
KAM Impulse	r = 0.766*		r = 0.934*
KAMPC1	r = 0.878*	r = 0.934*	
KAMPC2	r = 0.399*	r = -0.131	r = -0.033

* Indicates a significant correlation ($p<0.05$)

Table 5.6: KAMPC1 and KAMPC2 scores for the TKA and no-TKA groups. Moments were non-amplitude-normalized, normalized to mass (kg), and normalized to body weight times height (Nm/Nm). Data presented as mean (standard deviation).

		TKA	No TKA	P-Value
Non-amplitude-normalized	KAMPC1 score*	296.0 (93.6)	227.9 (77.9)	0.006
	KAMPC2 score*	2.2 (42.6)	32.9 (39.8)	0.009
Amplitude-normalized to body mass	KAMPC1 score*	3.21 (1.00)	2.38 (0.70)	0.001
	KAMPC2 score*	0.14 (0.45)	0.44 (0.45)	0.020
Amplitude-normalized to body weight times height	KAMPC1 score*	0.19 (0.06)	0.14 (0.04)	0.001
	KAMPC2 score*	0.01 (0.03)	0.03 (0.03)	0.028

* Indicates a significant between-group difference ($p<0.05$)

The final study aim was to determine the effect of amplitude-normalization on the results. As seen in Tables 5.3-5.5, the method of amplitude-normalization had no effect on the correlations between variables. Amplitude-normalization also did not affect between-group differences for the KAM impulse, KAMPC1, and KAMPC2; the KAM impulse and KAMPC1 score were higher and KAMPC2 score lower at baseline in the TKA group, regardless of how the KAM waveforms were normalized (Table 5.2 for KAM impulse, Table 5.6 for PC scores). The only variable affected by method of amplitude-normalization was the KAM peak, which only significantly differed between the two groups when normalized to body weight times height (Table 5.1).

5.4 Discussion

The primary aim of this study was to determine if the KAM peak and impulse, two discrete variables previously associated with knee OA structural progression, were also associated with progression to TKA. Confirming the study hypothesis, it was found that the KAM peak was significantly higher in the TKA group than in the no-TKA group when it was amplitude-normalized to body weight times height, and approached significance when amplitude-normalized to body mass. The KAM impulse was higher in the TKA group than no-TKA group for absolute values and both methods of amplitude-normalization. The KAM impulse can be affected by the duration of stance, since it is an integral of the stance phase of the non-time-normalized KAM waveform. There were no significant between-group differences in stance time, however the TKA group spent 0.06 seconds longer in stance each gait cycle: a difference of 8%. The between-group difference in KAM impulse was 30%, thus while a longer stance time may have contributed to the difference, a higher KAM magnitude was likely the greater contributor. The finding that the KAM peak and impulse were higher in the TKA group indicates that these discrete variables are not just factors in knee OA structural progression, but play roles in progression to TKA as well. Structurally, repetitive, high magnitude compressive loading has been shown to decrease proteoglycan-4 secretion into the synovial joint fluid, a vital protein for joint lubrication (Abusara et al, 2013). In terms of symptom progression, high magnitudes of compressive load increase the expression of

inflammatory chemicals, such as interleukin-1β and tumor necrosis factor-α (Wang et al, 2007), which have been found to be independent predictors of increased knee pain over 5 years in those with knee OA (Stannus et al, 2013). Thus, these gait variables could contribute to both structural and symptomatic knee OA progression.

Percent differences for the peak KAM ranged from 13-16%, and from 28-30% for the KAM impulse. The higher percent differences for the KAM impulse compared to the peak, and the finding that significant between-group differences persisted despite the method of amplitude-normalization, suggest that it is a more discriminative progression metric. This is consistent with the findings of Bennell et al (Bennell et al, 2011), who found that the KAM impulse, but not the peak, was able to predict medial tibial cartilage volume loss (i.e. structural progression) over one year. The greater discriminative ability may be because the KAM impulse captures the overall magnitude and exposure to load, rather than loading at only one point in the gait cycle, and therefore reflects loading of different regions of cartilage. It also captures the duration of loading throughout the gait cycle. It may also reflect greater variability in the peak KAM, and thus a lower statistical power. Amplitude-normalizing to both body weight and height removes the most between-subject variability, and could account for why the between-group difference only reached significance when using this normalization method.

Between-group differences in KAMPC1 (overall shape and magnitude) and KAMPC2 (difference between early and mid-stance magnitude) also persisted for non-amplitude-normalized data, as well as data normalized to body mass and body weight times height. The TKA group had higher overall KAM magnitudes (KAMPC1), and less of a difference between the early and mid-stance KAM magnitudes (KAMPC2) than the no-TKA group. The finding that these differences were significant regardless of normalization method highlights the robustness of these measures. In summary, the method of amplitude-normalization did not affect the overall findings for measures that considered the entire waveform, such as the KAM impulse, KAMPC1, and KAMPC2. However, for the KAM peak, which only considers one point in the gait cycle, the method of amplitude-normalization does affect the interpretation of results.

The second aim of this study was to determine how well KAMPC1 and KAMPC2 were related to the KAM peak and impulse. KAMPC1 was related to both the KAM peak and the impulse, with higher correlations for the KAM impulse. The relations were similar for both amplitude-normalizations (i.e. normalized to body mass, and to body weight times height), providing additional evidence that the method of amplitude-normalization does not affect the interpretation of results, particularly for the KAM impulse. The significant correlations between KAMPC1 and the KAM peak and impulse are logical, as all measures capture amplitude features of the KAM. KAMPC1 captures the overall magnitude of the KAM, and if the overall magnitude is higher, the area under the curve (i.e. the impulse) should also be greater. With respect to the peak KAM, an individual with a high overall KAM magnitude should also have a high magnitude in early stance, where the peak KAM occurs. This would especially be true in the moderate knee OA population, where the first peak in the KAM waveform can still be distinguished. By the time the disease reaches the severe state, the early stance magnitude decreases and the mid-stance magnitude increases, making the first peak lower and more difficult to pick out (Astephen et al, 2008b). The higher correlations between KAMPC1 and the KAM impulse, compared to the peak, likely reflect that both KAMPC1 and the KAM impulse consider the entire stance phase.

KAMPC2 was significantly related to the peak KAM, however the correlation coefficients were low, ranging from 0.274-0.399 depending on the method of amplitude-normalization, and thus only explaining between 8-16% of the variance. KAMPC2 was not related to the impulse at all, with correlation coefficients ranging from -0.131 to -0.233. The low correlation coefficients indicate that KAMPC2 is capturing a different characteristic of the KAM waveform (i.e. the ability to unload the knee from early to mid-stance). Thus, with respect to cartilage loading and progression of pain this feature captures sustained joint loading. A high KAMPC2 score would only be achieved with a specific KAM waveform shape: a high early stance magnitude and low mid-stance magnitude, whereas a high KAM peak or impulse could occur with a variety of KAM waveform shapes. KAMPC2 was not related to KAMPC1 either, with correlation

coefficients between -0.033 and -0.117, again reflecting that it captured a unique aspect of the KAM waveform- a temporal feature rather than an amplitude feature. This finding indicates that analysis of KAM waveforms using PCA provides different information. Determining whether this alters the predictive ability of KAM features is unknown.

While considerable clinical decision-making is involved when selecting an appropriate TKA candidate, in the present study surgeon variability in clinical decision-making was reduced by having all participants under the care of the same orthopaedic surgeon at baseline. In addition to the presence of structural damage, two major factors influencing need for surgery are pain and functional deficits (Gossec et al, 2011). Both groups had similar baseline pain and function scores and were being managed conservatively. An additional factor in the decision to undergo TKA is a patient's willingness (Hawker et al, 2006). The current study was limited because no metric of willingness to undergo TKA was obtained, but presumably some participants in the no-TKA group would fit this category. This error could result in an underestimation of between-group differences in the KAM outcome measures. While these limitations may have affected the between-group differences, they would not have affected the relations between the different KAM measures, nor would they have affected the findings with respect to the methods of amplitude-normalization.

In conclusion, the KAM impulse was higher at baseline in those who progressed to TKA compared to those who did not progress, regardless of normalization, whereas only the normalized peak KAMs were different. The robustness of this finding along with the more than two-fold percent difference between groups for the KAM impulse supports that the total loading exposure captured from the amplitude and duration measure may be a more discriminatory metric for progression to TKA. Given the minimal difference between the results for the two amplitude normalization approaches for both discrete and PCA variables, neither method is superior. The correlations between discrete variables and the PCA variables suggest that the KAM impulse and the overall magnitude (KAMPC1) could be interchangeable, but the peak and the relative ability to unload the joint from early to mid-stance (KAMPC2) are capturing different features. Thus

prediction models of progression to TKA would likely benefit from the inclusion of variables capturing the magnitude and duration of loading, as well as the unloading feature.

CHAPTER 6 KNEE BIOMECHANICS DURING GAIT PREDICT KNEE OSTEOARTHRITIS PROGRESSION

6.1 INTRODUCTION

Knee osteoarthritis (OA) is a progressive, degenerative disease with a tremendous economic cost (Arthritis Alliance of Canada, 2011). In 2011 the Arthritis Alliance of Canada released a statement listing three interventions for OA that should be prioritized, as they were thought to offer the greatest return on public investment. These interventions were: i) total joint replacement, ii) obesity reduction, and iii) adequate pain management (Arthritis Alliance of Canada, 2011). While these three interventions were projected to save an estimated $717 billion over the next 30 years, they (excepting obesity reduction) do not address underlying mechanisms of OA progression, focusing instead on a symptom-based approach. Furthermore, total knee replacement/arthroplasty (TKA) is considered the end-stage treatment for those with severe knee OA. Ideally, conservative treatments should be developed with the goal of delaying or preventing the need for TKA. However, in order to develop interventions that slow or prevent the progression to TKA, mechanisms of progression must first be understood.

Progression to TKA involves both structural and symptomatic mechanisms of progression, as structural disease severity and patient reports of pain and function are involved in the surgical decision-making process (Gossec et al, 2011). Most risk factors for knee OA structural and/or symptomatic progression have been identified from large-scale epidemiological studies, such as the Multicenter Osteoarthritis Study, the Osteoarthritis Initiative, and the European League Against Rheumatism cohort, or from countrywide surveys. These risk factors include obesity (Cooper et al, 2000; Yusuf et al, 2011), knee joint alignment (Sharma et al, 2010; Yusuf et al, 2011), previous anterior cruciate ligament injury (Lohmander et al, 2004; von Porat et al, 2004), quadriceps weakness (in women) (Segal et al, 2010), radiographic disease severity (Conaghan et al, 2010; Gossec et al, 2011; Riddle et al, 2009), and knee pain (Conaghan et al, 2010;

Gossec et al, 2011). While some of these risk factors do provide targets for conservative interventions, in general they do not consider the dynamic loading environment of the knee. There is both theoretical modelling (Andriacchi et al, 2004) and animal model (Chen et al, 1999; O'Connor and Brandt, 1993; Radin et al, 1984; Walker et al, 1991) evidence that dynamic biomechanics play a role in knee OA initiation and progression. However, only four longitudinal studies have included dynamic lower extremity biomechanical features in knee OA progression prediction models, and these focused on structural progression only: two on the knee joint (Bennell et al, 2011; Miyazaki et al, 2002), one on hip biomechanics (Chang et al, 2005), and one on ankle biomechanics (Chang et al, 2007). All four examined only frontal plane variables during walking, and all included only one discrete measure from the biomechanical waveforms in prediction models. Higher knee adduction moment (KAM) peaks (Miyazaki et al, 2002) and KAM impulses (Bennell et al, 2011) normalized to body size (body weight times height) were related to an increased risk of structural progression, whereas higher internal hip abduction moments (Chang et al, 2005) and greater toe-out angles (Chang et al, 2007) were associated with a reduced risk of structural progression. The latter two were thought to be due to their resulting effects on the KAM magnitude.

While the amplitude-normalized KAM peak and impulse were significantly higher at baseline in a group of participants with moderate medial compartment knee OA who progressed to TKA compared to a group that did not (Chapter 5), the only non-normalized KAM variable that was higher in the TKA group was the KAM impulse. These groups were similar on all other variables, including demographics, clinical characteristics, spatiotemporal gait characteristics, radiographic disease severity, and frontal plane alignment. Furthermore, temporal features extracted using principal component analysis (PCA), a statistical pattern recognition technique, were different between those who progressed to TKA and those who did not (Chapter 4). The group that progressed to TKA had higher KAM magnitudes (KAMPC1), less difference between early and mid-stance KAM (KAMPC2), and reduced early stance flexion and late stance extension moments (KFMPC2) at baseline than the no-TKA group. At the other lower extremity joints, the TKA group had less hip adduction range of motion (HAAPC2), less

ankle dorsiflexion in stance (AFAPC3), lower dorsiflexion moments (AFMPC4) during early to mid-stance, and less of a difference in ankle rotation moments between early and late stance (ARMPC2) than the no-TKA group. PCA examines amplitude as well as temporal patterns throughout the gait cycle not captured by discrete variables. This was demonstrated through correlation analyses between discrete and PCA variables from the KAM waveform (Chapter 5). It was found that the overall KAM magnitude (KAMPC1) was correlated with the KAM impulse (86% variance explained) and KAM peak (77% variance explained), but the second pattern extracted from the KAM waveform (KAMPC2) captured a unique characteristic that was not well correlated with either the KAM peak or KAM impulse.

Given that univariate prediction models that included KAM characteristics (normalized to body size only) have been previously examined for structural progression, and the relatively poor correlations between KAM discrete measures and certain dynamic features from PCA, this paper aimed to determine which biomechanical variables or combination of variables best predicted increased risk of progression to TKA. The purpose was three-fold: i) to determine how well individual (univariate) three-dimensional lower extremity biomechanical gait features discriminated between those who progressed to TKA and those that did not, ii) to determine if a multivariate model including multiple gait features improved the discrimination ability over univariate models, and iii) to determine how well the gait biomechanical features that best discriminated between the two groups *predicted* knee OA progression. It was hypothesized that a multivariate model capturing different, uncorrelated dynamic loading features would provide a better prediction of progression to TKA than any univariate model. This would illustrate that a combination of loading characteristics are involved in progression to TKA, and would identify potential targets for conservative interventions.

6.2 METHODS

6.2.1 Participants

Data for this study were collected as part of a longitudinal study on 80 participants with moderate, medial compartment knee OA that underwent baseline gait analysis in the Dynamics of Human Motion laboratory at Dalhousie University between 2003 and 2008. Of the 80 participants, 64 could be reached by telephone to inquire whether they were willing to undergo follow-up gait analysis. Twenty-eight participants agreed, and reported they had not had TKA (no-TKA group). Twenty-six participants reported they had TKA since their baseline gait analysis (TKA group). Nine participants did not have TKA, but declined participation in the gait study and radiographic assessment, and one had a high tibial osteotomy since baseline. All participants were patients of one high-volume orthopaedic surgeon, and were diagnosed using radiographic and clinical evidence, as defined by the American College of Rheumatology (Altman et al, 1986). They were diagnosed as having medial compartment knee OA if medial compartment joint space narrowing was greater than or equal to lateral compartment joint space narrowing, according to the Scott Feature Based score system (Scott et al, 1993). A classification of moderate knee OA was given because all participants were being managed conservatively, none were candidates for TKA at baseline, and all met the functional criteria of being able to jog 5 metres, walk a city block, and climb stairs reciprocally (Hubley-Kozey et al, 2006).

6.2.2 Procedure

Institutional ethics approval (Capital Health Research Ethics Board and Dalhousie University Research Ethics Board) was obtained for this study. At baseline, demographic data (age, sex, mass, height) were collected. Structural severity at baseline was determined using standard, weight-bearing anterior-posterior and lateral radiographs. One high-volume orthopaedic surgeon graded baseline radiographs twice using the Kellgren and Lawrence (KL) grading scale (Kellgren and Lawrence, 1957) and the Scott Feature Based score system (Scott et al, 1993). Between-grading agreement was 95%, 98%, and 93% for KL grade, medial, and lateral joint space narrowing grades, with weighted kappa

coefficients of 0.91, 0.99, and 0.91. Static frontal plane alignment was calculated using marker position data from a standing calibration trial performed prior to gait analysis (Chapter 4).

Physical activity, pain, and function were assessed via self-report. Participants were classified as active if they reported engaging in physical activity "sufficiently prolonged and intense to cause sweating and a rapid heart rate" at least three days/week (American College of Sports Medicine, 2006) (Chapter 4). Self-reported pain and function were assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (Bellamy et al, 1988).

Three-dimensional motion and ground reaction force data, surface electromyograms from seven lower extremity muscles, and strength data from the knee extensor, flexor, and plantarflexor muscle groups were collected as part of the baseline gait analysis. However, because this paper focuses on gait biomechanical predictors for progression to TKA, only the kinematic and kinetic methodology will be presented.

6.2.3 Gait Analysis

The gait analysis was conducted using a standard protocol (Landry et al, 2007). To monitor three-dimensional motion, 16 infrared emitting diodes were placed on specific anatomical landmarks. Triads were placed on the pelvis, thigh, shank, and foot segments. Individual markers were placed on the shoulder, greater trochanter, lateral epicondyle, and lateral malleolus. The locations of eight virtual points (right and left ASIS, medial epicondyle, fibular head, tibial tuberosity, medial malleolus, second metatarsal, and heel) were recorded in quiet standing. Motion of the markers was collected using a two-camera Optotrak™ 3020 motion capture system (Northern Digital Inc, Waterloo ON) sampling at 100 Hz. Three-dimensional ground reaction forces were recorded at 1000 Hz using an AMTI™ force platform (Advanced Medical Technology Inc, Watertown MA). Participants performed at least five gait trials at a self-selected pace across a five-metre walkway. A trial was successful if the participant's foot on the tested leg came into full contact with the force platform, and the foot on the untested leg did not contact the force

platform. Gait variables obtained using this standardized protocol, particularly discrete variables, sagittal knee angles, and sagittal and frontal knee moments, have been shown to be reliable (Robbins et al, 2013).

6.2.4 Data Analysis

Custom software written in Matlab (Mathworks Inc, Natick MA) was used to process the gait data. Motion and force data were digitally filtered (recursive fourth order Butterworth) at 8 Hz and 60 Hz respectively, and used to identify heel strike and toe-off to define one gait cycle (heel strike to heel strike on the same foot). Three-dimensional hip, knee, and ankle joint angles were expressed in the joint coordinate system (Grood and Suntay, 1983). Three-dimensional external hip, knee, and ankle joint moments were calculated using inverse dynamics (Costigan et al, 1992; Deluzio et al, 1993; Li et al, 1993) and also expressed in the joint coordinate system (Grood and Suntay, 1983).

To calculate the KAM peak and perform PCA, waveforms were time-normalized to a percentage of the gait cycle (i.e. 101 data points) using a linear interpolation technique (Astephen et al, 2008; Astephen et al, 2008b; Deluzio and Astephen, 2007; Landry et al, 2007). The KAM waveforms were not time-normalized for calculation of the KAM impulse, as this variable is meant to capture the total exposure of load that the knee experiences over time.

In order to capture loading beyond that associated with increased body mass or increased body size, and because between-group KAM peak differences were not significant when left in their original units (Nm, Chapter 5), moment waveforms were amplitude-normalized. Amplitude-normalization was done in two ways. Moment waveforms were amplitude-normalized to body mass (units of Nm/kg), and amplitude-normalized to body weight times height (units of Nm/Nm and expressed as percentages).

KAM peaks and impulses were determined for each trial for each participant individually, and then averaged to get the mean value for each participant. KAM peaks were calculated as the maximal amplitude of the KAM occurring in the first 40% of the

gait cycle (Robbins et al, 2013), and KAM impulses were determined by calculating the area under the positive portion of the stance phase of the KAM waveform (Equation 3.1). For the time-normalized data used in the PCA analysis, waveforms for each trial were averaged to create ensemble average profiles for each participant (Winter and Yack, 1987). PCA was performed on the ensemble averages.

6.2.5 Principal Component Analysis

Three-dimensional hip, knee, and ankle joint angle and moment waveforms were analyzed using PCA. An nx101 matrix (**X**) was formed for each variable, consisting of the ensemble average profile for each participant for that given variable. For this study, the matrices were constructed from a larger dataset of 149 baseline and follow-up waveforms (X = 149x101) for asymptomatic and moderate knee OA participants in the follow-up study to increase the robustness of the patterns extracted (Osborne and Costello, 2004). Covariance matrices of **X** were then formed (**C**). Transform matrices (**T**, 101x101) were calculated by the eigenvector-eigenvalue decomposition of **C**. **T** is a matrix of the PCs (eigenvectors), and **Λ** is a diagonal of the associated variances (eigenvalues). Scores were calculated for baseline waveforms for the 54 participants in this study. These scores are weighting coefficients based on how much of the variability in a participant's waveform is explained by a particular PC. The scores were used in the statistical analyses. For this study, scores for KAMPC1 and KAMPC2, KFMPC2, HAAPC2, AFAPC3, AFMPC4, and ARMPC2 were retained for statistical analyses, as they were the patterns that showed significant differences between the TKA and no-TKA groups (Chapter 4).

6.2.6 Statistical Analysis

Assumptions of normality and equal variances were examined using the Kolmogorov-Smirnov and Levene's tests, respectively. Receiver operating characteristic (ROC) curve analyses were used to determine how well each baseline gait biomechanical feature discriminated progressors (i.e. TKA group) from non-progressors (no-TKA group). The area under the curve (AUC) was calculated and used to quantify the overall "diagnostic

accuracy" of each of the variables (McNeil and Hanley, 1984). Criterion values, the optimal cut-points that distinguished between the two groups (i.e. the value that maximized sensitivity and specificity), and the associated sensitivities (Equation 6.1) and specificities (Equation 6.2) of these cut-points were determined. Each gait variable was also entered separately into univariate linear discriminant models to determine how well they discriminated between the two groups in terms of correct classification rates.

$$\text{Sensitivity} = \frac{\text{Participants correctly classified in TKA group}}{\text{Total number of participants in TKA group}} \qquad \text{Equation 6.1}$$

$$\text{Specificity} = \frac{\text{Participants correctly classified in no-TKA group}}{\text{Total number of participants in no-TKA group}} \qquad \text{Equation 6.2}$$

Stepwise multivariate linear discrimination analyses between the TKA and no-TKA groups were performed with three combinations of baseline biomechanical gait features: i) a "discrete" model using KAM peak and impulse variables only, ii) a "PCA" model using scores for PCs found to be different between the TKA and no-TKA groups (Chapter 4), and iii) a "combined" model, using variables identified from models 1 and 2 that significantly discriminated between the two groups. Models were performed using moment data amplitude-normalized to body mass, and to body weight times height, making a total of 6 models. The relative importance of each term in the multivariate linear discriminant models was quantified with the magnitude of the coefficients in the discriminant model. Group separation was quantified with correct classification rates for all original cases, and model over-training was estimated with cross-validation (iterations of all cases except one) classification rates (Lachenbruch, 1975). The multivariate linear discriminant models were then used to calculate discriminant model scores for all participants. Standardized scores (z-scores) for the gait variables were used in the calculations, and were determined according to Equation 6.3. These discriminant function scores were used as input for additional ROC curve analyses to determine optimal cut-points that discriminated between the two groups (i.e. maximizing sensitivity and specificity), and the associated sensitivities and specificities. Finally, discriminant model

scores were entered into logistic regression models to determine the predictive ability of the multivariate linear discriminant models.

$$\text{Z Score} = \frac{x - \mu}{\theta} \qquad \text{Equation 6.3}$$

Where "x" is the participant's value for a given gait variable, μ is the sample mean, and θ is the sample standard deviation

The significance level (α) for all analyses was 0.05. The ROC curve analyses were performed using MedCalc software (Version 12.5.0, Mariakerke, Belgium), the discrimination analyses were completed using SPSS Statistics (Version 20.0.0, IBM Corporation, Armonk, NY), and logistic regression modelling was done using Minitab™ (Version 16, Minitab Inc, State College PA).

6.3 RESULTS

Demographic data for the TKA and no-TKA groups have previously been presented in Table 4.1, as have spatiotemporal gait characteristics and WOMAC scores. Means and standard deviations for each of the gait variables used in this study are presented in Table 6.1, along with the discrimination ability (AUC) of each, as determined from the ROC analyses. As seen in the table, the KAM impulse (amplitude-normalized to body mass, and to body weight times height) was best able to discriminate between participants in the TKA and no-TKA groups, with an AUC of 0.79 (both methods of normalization). Its associated criterion values were 0.26 (normalized to body mass, units of Nm/kg*s) and 1.41 (normalized to body weight times height, units of Nm/Nm*s and expressed as a percentage), indicating that an individual having a KAM impulse above these values would be classified as belonging to the TKA group, with sensitivities and specificities of 53.8 and 100.00 (normalized to body mass), and 61.5 and 88.9 (normalized to body weight times height).

In terms of variables extracted using PCA, the KAMPC1 scores were best able to discriminate between the groups, with AUCs of 0.77 (normalized to body mass) and 0.75 (normalized to body weight times height). These variables were also best able to correctly classify participants (correct classification rates of 72.2% and 74.1% when normalized to body mass and body weight times height, respectively). AUC values ranged from 0.50-0.79 for all gait variables. The KAM impulse and KAMPC1 (normalized to mass) were the most specific of the gait variables (100.0 and 89.3, respectively), and were able to correctly classify participants 71.7% and 72.2% of the time, respectively. AFAPC3 was the most sensitive of the gait variables (sensitivity of 96.2), but it had the second lowest specificity (32.1). While the sensitivity and specificity values changed depending on how the variables were amplitude-normalized, the AUC, and therefore the discrimination ability, remained consistent regardless of normalization method (except for ARMPC2).

In the stepwise multivariate linear discriminant models containing only discrete variables, only the KAM impulse emerged as a significant predictor, whereas multiple variables emerged in the PCA and combined models. The stepwise multivariate linear discriminant model that had the highest correct classification rate (74.1%) was the model including PCA variables, normalized to body mass (Table 6.2). This model had an odds ratio of approximately 5.72 (confidence interval 2.17-14.29) for predicting progression to TKA, the highest odds ratio for all of the discriminant models (Table 6.3). While it had the same correct classification rate as the univariate model containing KAMPC1 (normalized to body weight times height), the multivariate linear discriminant function was better able to discriminate between the two groups, with an AUC of 0.85 (Table 6.3), versus 0.75 for KAMPC1 scores alone (Table 6.1). KAMPC1 was the dominant variable in this multivariate linear discriminant model, with a coefficient of 0.849 (Table 6.2), followed by KFMPC2 (coefficient of -0.528) and AFMPC4 (coefficient of -0.477). KAMPC1 and KFMPC2 scores were significant predictors in both PCA multivariate linear discriminant models, but AFMPC4 was only a significant predictor in the PCA discriminant model that used waveforms normalized to body mass. The multivariate linear discriminant function containing only PCA variables (normalized to body mass) was also the only

multivariate model that was more sensitive than specific, and had the highest sensitivity (84.6) of all of the multivariate models. When the significant predictors from the discrete and PCA discriminant models were entered into additional combined models, one discrete variable (KAM impulse) and one PCA variable (KFMPC2) emerged as significant predictors, regardless of the method of amplitude-normalization (Table 6.2), however the classification ability (correct classification rate) and discrimination rate (AUC) did not improve from that of the multivariate linear discriminant model containing only PCA variables (normalized to body mass).

Table 6.1: Classification ability of gait characteristics for TKA and no-TKA groups, based on receiver operator curve (ROC) analyses. Group values presented as mean (standard deviation).

	TKA	No TKA	Area Under Curve	Criterion Value[¥]	Sensitivity[€]	Specificity[€]	Correct Classification Rate
KAM Peak (Nm/kg)	0.63 (0.19)	0.53 (0.15)	0.68[£]	> 0.62	61.5	75.0	63.0%
KAM Peak (Nm/Nm)%	3.67 (1.11)	3.10 (0.87)	0.67[£]	> 3.64	61.5	78.6	63.0%
KAM Impulse (Nm/kg)*s	0.26 (0.08)	0.18 (0.06)	0.79[£]	> 0.26	53.8	100.0	71.7%
KAM Impulse (Nm/Nm)*s%	1.51 (0.48)	1.06 (0.36)	0.79[£]	> 1.41	61.5	88.9	71.7%
KAMPC1 (normalized to mass)	3.21 (1.00)	2.38 (0.70)	0.77[£]	> 2.96	61.5	89.3	72.2%
KAMPC1 (normalized to weight*height)	0.19 (0.06)	0.14 (0.04)	0.75[£]	> 0.16	73.1	78.6	74.1%
KAMPC2 (normalized to mass)	0.14 (0.45)	0.44 (0.45)	0.69[£]	≤ 0.09	53.8	82.1	63.0%
KAMPC2 (normalized to weight*height)	0.01 (0.03)	0.03 (0.03)	0.67[£]	≤ 0.01	46.2	85.7	63.0%

	TKA	No TKA	Area Under Curve	Criterion Value[¥]	Sensitivity[€]	Specificity[€]	Correct Classification Rate
KFMPC2 (normalized to mass)	1.18 (0.86)	1.74 (1.01)	0.65	≤ 0.86	42.3	85.7	53.7%
KFMPC2 (normalized to weight*height)	0.07 (0.05)	0.10 (0.06)	0.65[£]	≤ 0.11	92.3	42.9	57.4%
HAAPC2	30.7 (14.0)	38.3 (12.4)	0.65[£]	≤ 42.2	92.3	42.9	61.1%
AFAPC3	35.1 (14.4)	43.9 (13.0)	0.66[£]	≤ 51.0	96.2	32.1	59.3%
AFMPC4 (normalized to mass)	-0.93 (0.19)	-0.75 (0.28)	0.68[£]	≤ -0.74	92.3	50.0	64.8%
AFMPC4 (normalized to weight*height)	-0.06 (0.01)	-0.05 (0.02)	0.67[£]	≤ -0.05	92.3	46.4	61.1%
ARMPC2 (normalized to mass)	0.12 (0.18)	0.23 (0.17)	0.50	> 0.11	53.8	28.6	64.8%
ARMPC2 (normalized to weight*height)	0.007 (0.011)	0.013 (0.010)	0.68[£]	≤ 0.01	65.4	75.0	64.8%

[¥] Indicates the cut-off value, above or below which an individual will be classified into the TKA group.
[€] Calculated based on criterion value. [£] Indicates that the gait variable was able to discriminate between groups ($p<0.05$)

Table 6.2: Multivariate linear discriminant functions to distinguish the TKA and no-TKA groups.

Model	Gait variables entered	Significant Predictors	Coefficients	Correct classification rate	Cross-validation correct classification rate[£]
Discrete (normalized to mass)	Peak KAM KAM Impulse	KAM Impulse	1.00	71.7%	71.2 (0.9) %
Discrete (normalized to weight*height)	Peak KAM KAM Impulse	KAM Impulse	1.00	71.7%	71.6 (0.9) %
PCA (normalized to mass)	KAMPC1 KAMPC2 KFMPC2 HAAPC2 AFAPC3 AFMPC4 ARMPC2	KAMPC1 KFMPC2 AFMPC4	0.849 -0.528 -0.477	74.1%	74.1 (0.8) %

Model	Gait variables entered	Significant Predictors	Coefficients	Correct classification rate	Cross-validation correct classification rate[£]
PCA (normalized to weight*height)	KAMPC1 KAMPC2 KFMPC2 HAAPC2 AFAPC3 AFMPC4 ARMPC2	KAMPC1 KFMPC2	0.907 -0.661	70.4%	71.0 (1.2) %
Combined (normalized to mass)	KAM Impulse KAMPC1 KFMPC2 AFMPC4	KAM Impulse KFMPC2	0.906 -0.664	69.8%	70.8 (1.4) %
Combined (normalized to weight*height)	KAM Impulse KAMPC1 KFMPC2	KAM Impulse KFMPC2	0.896 -0.643	71.7%	71.7 (0.0) %

[£] Cross-validation correct classification rate determined by calculating the correct classification for iterations of all subjects except one. Presented as mean (standard deviation).

Table 6.3: Discrimination ability of multivariate discriminant models[¥] for TKA and no-TKA groups, based on receiver operator curve (ROC) analyses.

Model	Area Under Curve	Criterion Value[£]	Sensitivity[€]	Specificity[€]	Odds Ratio[€]
Discrete (normalized to mass)	0.79	> 0.53	53.8	100.0	3.56
Discrete (normalized to weight*height)	0.79	> 0.27	61.5	88.9	3.45
PCA (normalized to mass)	0.85	> -0.24	84.6	71.4	5.72
PCA (normalized to weight*height)	0.80	> 0.46	61.5	92.9	4.00
Combined (normalized to mass)	0.83	> 0.53	65.4	96.3	4.97
Combined (normalized to weight*height)	0.84	> 0.42	65.4	96.3	4.71

[¥] Standardized scores for gait variables are used in linear discriminant models to calculate model scores.
[£] Indicates the cut-off value, above or below which an individual will be classified into the TKA group.
[€] Calculated based on criterion value.
[€] For one-unit increase in multivariate linear discriminant model score.

6.4 DISCUSSION

This study provides a comparison of prediction models for those with moderate knee OA who progress to TKA, based on gait biomechanical features found to differ between a group of participants with moderate medial compartment knee OA who progressed to TKA and a group that did not (Chapter 4 and 5). First, univariate models were developed to determine how well the gait biomechanical features that significantly differed between the two groups (Chapters 4 and 5) discriminated between the groups based on ROC and linear discriminate analyses. The univariate models found that, based on AUC values, the KAM impulse was best able to discriminate between the TKA and no-TKA groups, regardless of method of amplitude-normalization. Of the KAM gait variables, the peak had the lowest AUC, regardless of method of amplitude-normalization, although it was still able to significantly discriminate those in the TKA group when normalized to body mass or body weight times height, based on the AUC values. However, the correct classification rate was only 63.0% for the KAM peak, compared to 71.7% for the KAM impulse. The differential discrimination and classification abilities of the KAM impulse and peak are similar to the findings of Bennell et al (2011), who reported that the KAM impulse was a better predictor of structural progression than the peak, based on logistic regression modelling. Mechanistically, the KAM impulse may be a stronger predictor for structural progression, which is a component of progression to TKA (Gossec et al, 2011), than the KAM peak because it gives an indication of the overall magnitude of loading throughout the gait cycle, and therefore loading of different areas of cartilage as the position of the tibia relative to the femur changes. Conversely, the peak KAM only captures loading at one point in the gait cycle, and therefore only a focal area of cartilage. MRI findings support this theory; the peak KAM is associated with focal thinning in the tibia and femur, whereas the KAM impulse is related to total tibia and femur cartilage surface area (Maly et al, 2013). Additionally, the KAM impulse considers the duration of cartilage loading, whereas the KAM peak does not capture duration of loading.

In terms of gait patterns extracted using PCA, the overall shape and magnitude of the KAM (KAMPC1) were best able to discriminate between groups, with AUCs of 0.77 and

0.75 when amplitude-normalized to body mass and to body weight times height, respectively. The higher discriminatory ability of this variable compared to the other variables extracted using PCA is likely because, similar to the KAM impulse, it captures the overall magnitude of medial compartment loading throughout the gait cycle. Chapter 5 found that these two variables were highly correlated, with a correlation coefficient of 0.93, regardless of the method of amplitude-normalization. In the combined (discrete and PCA variables included) multivariate linear discriminant model the KAM impulse emerged as a significant discriminator, but KAMPC1 did not, a result partially explained by the high correlation between the two variables and the fact that, individually, the KAM impulse was better able to discriminate between groups. The slightly better discrimination performance of the KAM impulse (AUC of 0.79) compared to KAMPC1 (AUC of 0.75-0.77) could be because the KAM impulse captures the duration of knee loading, since it is calculated from non-time-normalized waveforms. KAMPC1 considers the shape and magnitude of the KAM throughout the gait cycle, but it is calculated from waveforms that are time-normalized.

The multivariate linear discriminant models containing only PCA variables and the combined multivariate linear discriminant models (discrete and PCA variables included) indicated that the KAM was not the only gait variable that was predictive of progression to TKA. While the overall KAM magnitude (either KAM impulse or KAMPC1, depending on the model) was the dominant variable in the multivariate linear discriminant models, a non-frontal plane factor, KFMPC2 emerged as well. This variable captured the difference between the early stance knee flexion and late stance knee extension moments, with the TKA group having lower scores (i.e. less of a difference between the flexion and extension moments, Chapter 4). This was interpreted as a "stiff gait", which combined with the lower KAMPC2 scores (i.e. decreased difference between the early and mid-stance KAM magnitudes) and decreased sagittal angles and moments at the ankle in the TKA group would indicate an inability to "unload" the joint or prolonged compressive cartilage loading (Chapter 4). Interestingly, the KFMPC2 had one of the lowest AUCs (0.65) when used individually to discriminate betwen the two groups.

The interaction between the KAM and the knee flexion moment has previously been documented in the literature. Walter et al (2010) found that a "medial thrust" gait modification reduced the peak KAM, but that the magnitude of medial compartment loading (measured using an instrumented knee prosthesis) remained the same because decreases in the peak KAM were offset by increases in the peak knee flexion moment. While the results of this study indicate that both the KAM and knee flexion moment play roles in progression to TKA, the relation may not be as simple as a trade off in magnitude between the peak of one and the peak of the other. In order to increase the multivariate PCA model and multivariate combined model scores (and therefore increase the odds of being in the TKA group), greater KAM magnitudes (KAM impulse or KAMPC1) and/or lower KFMPC2 scores would be required. Lower KFMPC2 scores would indicate less of a difference between the early stance knee flexion moment peak and late stance knee extension moment peak. Therefore, lower early stance knee flexion moment peaks could actually *increase* the odds of being in the TKA group, if found in combination with decreased late stance knee extension moment peaks. This highlights that the entire stance phase of the gait cycle is relevant to progression to TKA, not just what is occurring during one discrete point (i.e. weight acceptance in early stance), and provides a strong case for using pattern recognition techniques such as PCA which capture temporal waveform characteristics as well.

While the univariate KAMPC2 model had a higher AUC than the univariate KFMPC2 model, it did not come out as a significant predictor in the multivariate models, despite it capturing a unique aspect of the KAM (Chapter 5). This is likely because KAMPC2 captures the inability to effectively unload the knee during gait, therefore increasing the sustained compressive loading on the cartilage, and thus getting at the same progression mechanism that KFMPC2 would. Post hoc correlation analysis revealed that these two variables were significantly correlated, with correlation coefficients of 0.69 and 0.66 when amplitude-normalized to mass and to body weight times height, respectively. Both the KAM impulse and KAMPC1 capture the overall magnitude of medial compartment loading, but they do not indicate if the individual is able to effectively unload the medial compartment. So, the combination of the KAM impulse or KAMPC1 and KFMPC2 gets

at the overall magnitude of loading, but also the inability to unload the knee. Thus, the PCA and combined multivariate models suggest that it is not only higher overall cartilage loading that may be important for progression to TKA, but sustained cartilage loading as well. Sustained compressive load can lead to cartilage degradation (Chen et al, 1999) as well as upregulation of inflammatory chemicals (Wang et al, 2007) that have been found to be independent predictors of worsening knee pain over 5 years in those with knee OA (Stannus et al, 2013), thus this type of loading could play roles in structural and/or symptomatic progression.

While the multivariate linear discriminant model containing just PCA variables and the combined multivariate linear discriminant model (discrete and PCA variables) identified variables capturing the overall KAM magnitude and the inability to unload the knee, the best model (highest AUC, correct classification rate, and odds ratio for progression to TKA) was the multivariate model containing PCA variables normalized to body mass. In this model, in addition to KAMPC1 and KFMPC2, AFMPC4 emerged as a significant predictor. Lower AFMPC4 scores (i.e. lower dorsiflexion moments during stance) were associated with TKA group classification. This further supports a "stiff gait" mechanism of knee OA progression. Lower dorsiflexion moments could be the result of less dorsiflexion during stance, which was found in the TKA group (Chapter 4). Since during mid-stance the foot is in contact with the ground, and thus in a closed kinetic chain, less dorsiflexion would indicate a more posterior position of the tibia, and less knee flexion during mid-stance. The addition of AFMPC4 to the PCA multivariate prediction model increased the AUC because it was the variable with the second highest sensitivity (92.3), whereas the other terms in the model (KAMPC1 and KFMPC2) had higher specificities than sensitivities (based on the criterion values identified during the univariate ROC analysis). This model had an odds ratio of 5.72. The two previous prediction models for the structural progression of knee OA based on the peak KAM and KAM impulse had odds ratios of 6.46 (Miyazaki et al, 2002) and 1.80 (Bennell et al, 2011), respectively. The study populations in this study and that of Bennell et al were similar in age, BMI, and radiographic disease severity. The higher odds ratio for the prediction model in this study is likely because of the more comprehensive terms in the model, accounting for

overall knee load as well as sustained loading, and also because the follow-up period was longer: an average of 8 years in this study, versus one year in the Bennell et al study (Bennell et al, 2011). While the odds ratio for the prediction model based on the peak KAM in the Miyazaki et al study was higher than the model in this study, it is difficult to directly compare results because the study populations were dissimilar. The sample in the Miyazaki et al study was older (70 years old), and a healthy weight (BMI of 24.5 Nm/kg), whereas the sample in the present study was younger (approximately 60) and obese (BMI of 31 Nm/kg). Therefore, the mechanisms of progression may differ between the groups.

While it can be argued that performing PCA can be time-intensive, the results can be difficult to interpret, and the PCA multivariate linear discriminant model only improved the correct classification rate by 2% compared to the models including only discrete gait variables, a strength of the multivariate PCA discriminant model is that it contains objective gait characteristics that take two different aspects of loading into consideration: overall magnitude of loading (through KAMPC1) and the inability to unload (through KFMPC2 and AFMPC4). These different characteristics provide different conservative intervention targets that should be explored to reduce the risk of progression. For example, strategies that decrease the KAM magnitude, including weight loss, reduced walking speed, and other gait modifications such as toe out, trunk lean, and medial thrust, along with external devices such as heel wedges and unloader braces, should also ensure that the ability to unload the knee (i.e. *pattern* of knee loading) is addressed. Although no conservative intervention studies have looked at the pattern of knee loading as an outcome measures, it has been shown that there is more constant knee loading (less of a difference between the early and mid-stance KAM, and less of a difference between the early stance knee flexion and late stance knee extension moments) in obese individuals with knee OA (Harding et al, 2012). Thus, addressing obesity may alter both aspects of the PCA multivariate linear discriminant function: reducing overall joint loading through mass reduction, and reducing sustained loading. However, it is important to note that addressing obesity alone may not completely alter the discriminant model scores. The TKA and no-TKA groups were similar in mass; in fact, the no-TKA group was slightly

heavier. Yet, biomechanical differences were still found, indicating that mechanisms other than obesity (perhaps muscle co-activation) were causing the observed biomechanical differences that contributed to their increased risk of progression to TKA.

Another strength of PCA multivariate discriminant model is that it was the only multivariate model with higher sensitivity than specificity. When developing a prediction model for knee OA progression, sensitivity is a more desireable characteristic than specificity. A more specific model indicates who is *not* likely to progress to TKA, whereas a more sensitive model indicates who is *more likely* to progress to TKA. While a more sensitive model has the risk of false positives (i.e. putting patients in the TKA group who would not progress), the risk of intervening conservatively in this group is far less than the risk of *not* intervening. A more specific model runs the risk of false negatives, in which a patient would be classified as not likely to progress to TKA when they actually would progress. In this case, conservative interventions may not be used, and the patient may go on to undergo an unnecessary TKA. In this study, a one-unit increase in scores for the PCA multivariate linear discriminant model (normalized to mass) resulted in an almost six-fold increased risk of being in the TKA group. This model identifies potential targets for the development and evaluation of conservative interventions, but also allows the identification of those who would benefit most from these conservative interventions.

An important limitation of the prediction models is that only net external moments were entered as predictor variables. Other risk factors for knee OA progression have been identified in large epidemiological studies, such as obesity (Cooper et al, 2000; Yusuf et al, 2011), knee joint alignment (Sharma et al, 2010; Yusuf et al, 2011), previous anterior cruciate ligament injury (Lohmander et al, 2004; von Porat et al, 2004), quadriceps weakness (in women) (Segal et al, 2010), radiographic disease severity (Conaghan et al, 2010; Gossec et al, 2011; Riddle et al, 2009), and knee pain (Conaghan et al, 2010; Gossec et al, 2011). These factors were not included in the prediction models of the current study, as they do not provide an indication of the dynamic loading environment of the knee joint; furthermore, they were not different between groups. The research

question was to determine which dynamic biomechanical gait variables were most predictive of progression to TKA. Another limitation is that muscle forces can contribute to knee joint loading (Herzog et al, 2003), and muscle activation patterns have been found to be altered in those with knee OA (Hubley-Kozey et al, 2006). Future longitudinal research should encorporate electromyography, and include muscle activation patterns in multivariate prediction models, to determine if those are the variables that should be targeted to reduce joint loading.

In summary, this study provides longitudinal evidence that lower extremity kinetics during gait, specifically features from the KAM, knee flexion moment, and ankle flexion moment waveforms can predict progression to TKA. Importantly, it was not just the overall magnitude of the KAM that emerged as a predictor for progression to TKA, but also the inability to unload the knee (i.e. "stiff gait"). Together, these factors give a more comprehensive indication of the local, dynamic biomechanical environment of the knee during gait. Increasing our knowledge of mechanisms of knee OA progression is crucial when designing conservative interventions. The results of this study suggest that conservative interventions should take the overall KAM and relative unloading of the knee into consideration as potential targets. Future work should determine how the components of the multivariate discriminant function that best predicted progression to TKA (KAMPC1, KFMPC2, AFMPC4) can be altered conservatively, and what impact alterations have on the risk of progression to TKA.

CHAPTER 7 CONCLUSION

7.1 SUMMARY OF STUDY OBJECTIVES

The goal of this dissertation was to improve our understanding of the relation between three-dimensional lower extremity biomechanics and mechanisms of knee osteoarthritis (OA) progression. This information is beneficial to the development and evaluation of biomechanical targets for conservative management strategies, and illustrates that there are multidimensional consequences suggesting that one target alone is not appropriate. While gait biomechanics have been linked to knee OA structural progression, no studies have: i) included all three lower extremity joints to determine how the loads are distributed throughout the kinetic chain, ii) looked at non-frontal plane factors, even though sagittal plane features can affect medial compartment loading and transverse features can affect cartilage integrity, iii) looked at temporal patterns of knee loading, even though sustained compressive loads cause cartilage degeneration and increased expression of inflammatory chemicals that lead to worsening knee pain, iv) looked at the effect of various methods of amplitude-normalization on what biomechanical factors are related to knee OA progression, v) included multiple gait variables in prediction models for knee OA progression, and vi) looked at biomechanics and knee OA progression from a structural and/or symptomatic perspective (therefore capturing the "disease" and "illness" components of knee OA). This dissertation aimed to address these gaps in the literature. Total knee arthroplasty (TKA) was chosen as the measure of progression because it is a clear endpoint that includes both structural and symptomatic aspects of progression. In order to address the overall research question of the dissertation, there were three specific research objectives:

1) To determine if lower extremity (i.e. hip, knee, and ankle) amplitude and temporal biomechanical features during gait were different at baseline between those with moderate medial compartment knee OA who progressed to TKA versus those that did not at follow up. Two sub-objectives that helped address the primary objective were:

a) To determine the relation between measures of static frontal plane alignment calculated using motion capture data and calculated using full-leg radiographs.
b) To determine the relation between self-reported physical activity level and objectively measured physical activity level.

2) To determine how the knee adduction moment (KAM) features extracted using principal component analysis (PCA) compared to the discrete features already linked to structural progression (i.e. KAM peak and KAM impulse). Sub-objectives were:
   a) To determine whether discrete knee biomechanical gait variables previously associated with structural progression were associated with progression to TKA.
   b) To determine what effect amplitude normalization had on these features (i.e. would they still differ between the TKA and no-TKA groups using different methods of amplitude normalization).

3) To determine how well three-dimensional lower extremity biomechanical features identified as significantly different between the group who progressed to TKA and the group that did not (objectives 1 and 2) *predicted* progression to TKA. Sub-objectives were:
   a) To determine how well individual (univariate) three-dimensional biomechanical features during gait (KAM peak and KAM impulse, and features extracted using PCA) classified those who progressed to TKA versus those that did not.
   b) To determine if a multivariate model including multiple gait features improved the classification ability over univariate models.
   c) To determine how well the gait biomechanical features that best classified the two groups *predicted* progression to TKA.

Summaries of the results of the above research objectives are presented in the following three sections.

7.1.1 Summary of Chapter 4: Three-dimensional Biomechanical Gait Differences Associated with Knee Osteoarthritis Progression

The overall research question for this study was to determine whether a comprehensive understanding of the three-dimensional, dynamic biomechanical environment during gait would provide insight into mechanisms of knee OA progression, and whether this understanding would provide objective data on which to develop targeted biomechanical interventions. The specific objective was to determine if lower extremity (hip, knee, ankle joint) biomechanical gait features were different between those with moderate medial knee OA who progressed to TKA versus those that did not. Key findings from this chapter were:

- There were no significant differences in age, mass, body mass index, sex distribution, radiographic disease severity, frontal plane alignment, physical activity, spatiotemporal gait characteristics, or self-reported symptoms between the two groups at baseline, indicating the groups were similar in structural and symptomatic disease severity.
- The TKA group showed alterations in three-dimensional biomechanical gait patterns at baseline, including: i) an increased overall magnitude of the knee adduction moment (KAMPC1), indicating a higher magnitude of medial compartment (relative to total joint) loading, ii) less of a difference between the early and mid-stance KAM magnitudes (KAMPC2), indicating an inability to unload the knee during mid-stance, iii) decreased knee flexion and extension moments (KFMPC2), indicating a "stiff gait", iv) less of a difference between the stance and swing hip adduction angles (HAAPC2), indicating less hip range of motion, v) decreased stance ankle dorsiflexion angles (AFAPC3), vi) decreased stance ankle dorsiflexion moments (AFMPC4), and vii) less of a difference in ankle rotation moments between early and late stance (ARMPC2) compared to the no-TKA group.

The results of this study indicate that, with all clinical and radiographic disease features similar, biomechanical gait characteristics are associated with knee OA progression. The

increased overall magnitude of the KAM (KAMPC1) and the "stiff gait" (combination of lower KAMPC2 scores, lower KFMPC2 scores, and decreased AFAPC3 and AFMPC4 scores) seen at baseline in the TKA group suggest that this group was experiencing higher magnitudes of knee loads throughout the gait cycle at baseline, and also sustained compressive loading. Animal model work has indicated that increased compressive loads can lead to chondrocyte death (Horisberger et al, 2012; Horisberger et al, 2013), and sustained compressive loads can lead to reduced joint lubrication (Abusara et al, 2013), and cartilage degradation (Chen et al, 1999; Kim et al, 2012) by reducing biosynthetic activity (Arokoski et al, 2000; Wong et al, 1999) and disrupting covalent bonds between collagen molecules in the cartilage matrix (Chen et al, 1999). These mechanisms would lead to structural progression.

In terms of symptomatic progression, compressive load (both dynamic and static) has been shown to increase the expression of inflammatory chemicals, such as interleukin-1β and tumor necrosis factor-α in articular cartilage in animal models, although higher expression was seen in the static loading conditions (Wang et al, 2007). Baseline levels of these inflammatory chemicals have been found to be independent predictors of worsening knee pain over 5 years in those with knee OA (Stannus et al, 2013). While no pre-TKA self-reported pain and function scores were collected, the no-TKA group experienced no change in symptoms, or a decrease in symptoms at follow-up. The higher magnitude and sustained duration of loading seen in the TKA group at baseline could be an explanation for why they progressed to TKA.

While the results of this study indicated that gait biomechanics are factors in the progression to TKA, knowledge gaps remained. First, it was not known how the biomechanical differences found in the TKA group, specifically the KAM features, related to discrete gait biomechanical features previously associated with knee OA structural progression (i.e. KAM peak and KAM impulse). No studies have compared features extracted using PCA to discrete waveform measures. Furthermore, comparison of results between the few longitudinal studies is difficult, as the waveforms for this study were normalized to body mass, whereas the KAM waveforms in the two previous

longitudinal studies linking discrete KAM characteristics to knee OA structural progression were amplitude normalized to body weight times height. Different methods of amplitude normalization may affect between-group differences, particularly in amplitude measures, such as KAMPC1. It is also difficult to compare the results of this study to the other longitudinal studies since the progression outcome measure was different (i.e. progression to TKA versus structural progression). A strength of the study is that TKA captures both structural and symptomatic aspects of progression, but it is unknown whether the discrete KAM features associated with structural progression are also associated with progression to TKA. Finally, the overall goal of this dissertation was to identify potential targets for the development of conservative management strategies, but at this point it is unclear which of the gait biomechanical differences found in the TKA group are most important in predicting progression to TKA, thus providing effective targets for conservative interventions. Chapters 5 and 6 aimed to address these knowledge gaps.

7.1.2 Summary of Chapter 5: Relation Between Knee Adduction Moment Patterns Extracted Using Principal Component Analysis and the Knee Adduction Moment Peak and Impulse

The first aim of this study was to determine relations between KAM discrete measures and KAM features extracted using PCA, in order to facilitate comparisons between various biomechanical studies. The second aim was to determine whether baseline differences existed in KAM discrete measures (i.e. peak and impulse) between those with moderate medial knee OA who progressed to TKA and those that did not. The final aim was to examine the effects of different methods of KAM amplitude-normalization on the results of the first two aims. The key findings from this chapter were:

- The KAM peak was significantly higher at baseline in the group that progressed to TKA, compared to the group that did not progress, when amplitude-normalized to body weight times height.

- The KAM impulse was significantly higher at baseline in the group that progressed to TKA, compared to the group that did not progress, regardless of the method of amplitude-normalization.
- KAMPC1 (overall magnitude) was significantly correlated with the KAM peak (r = 0.88-0.90) and KAM impulse (r = 0.93). Higher correlations were found with the KAM impulse, and higher correlations were found when the KAM impulse was amplitude-normalized.
- KAMPC2 (difference between early and mid-stance magnitude) was not significantly correlated with the KAM impulse, and showed low correlations with the KAM peak (r = 0.27- 0.40).

Consistent with the only other two longitudinal studies relating KAM characteristics to knee OA progression (defined as structural progression), the results of this chapter found that the KAM peak and impulse are associated with progression to TKA. This was expected, as these variables had previously been associated with structural progression, and structural progression is a component in the surgical decision-making process. The first principal pattern from the PCA (KAMPC1), which captures the overall shape and magnitude of the KAM, was significantly related to both the KAM peak and KAM impulse, with correlation coefficients of over 0.88. The high correlation coefficients are likely because all three variables capture a magnitude component of the KAM, either in early stance (KAM peak), or throughout stance (KAM impulse and KAMPC1). The higher correlations between the KAM impulse and KAMPC1 reflect that both variables capture the KAM throughout the stance phase of gait.

KAMPC2, which captured the difference between the early and mid-stance magnitudes of the KAM, was not related to the KAM impulse, and had low correlation coefficients with the KAM peak, indicating that it captures a unique aspect of the KAM waveform. The weak relation between KAMPC2 and the peak KAM is likely because part of what KAMPC2 is capturing is the early stance KAM (i.e. first peak KAM), however the peak KAM is just a discrete part of the waveform, whereas KAMPC2 captures the shape of the entire waveform. The fact that KAMPC2 captures the shape of the waveform also

explains the lack of a relation between it and the KAM impulse. The KAM impulse captures the total exposure to load; the shape of the waveform is irrelevant. A high KAM impulse could occur with a variety of KAM waveform shapes, whereas a high KAMPC2 score would only be achieved with a specific KAM waveform shape: a high early stance magnitude and low mid-stance magnitude. Because it captures the difference between the early and mid-stance magnitudes, it is really getting at the relative unloading of the medial compartment during mid-stance, a unique feature that neither the KAM peak or impulse capture.

Between-group differences in the KAM impulse were consistent, regardless of how the data were normalized. However, between-group peak KAM differences were only significant when data were normalized to body weight times height (and approached significance, $p = 0.05$, when normalized to body mass), likely due to a reduction in between subject variability. The inconsistency in the KAM peak results when not amplitude-normalized supports amplitude-normalization. The higher correlation coefficients found for KAMPC1 scores and the KAM impulse when the data were amplitude-normalized also supports amplitude-normalization. Negligible differences in results were found whether the data were normalized to body mass, or to body weight times height, suggesting that either is an appropriate method of amplitude-normalization.

In summary, the results of this study showed that discrete KAM variables already linked to structural progression were linked to progression to TKA as well. The results also indicated that, when comparing between studies, the method of amplitude-normalization does not affect results, particularly for the KAM impulse and KAM variables extracted using PCA. Furthermore, KAMPC1 was highly correlated to the KAM impulse, as both capture the magnitude of the KAM throughout stance. However, KAMPC2 captured a unique aspect of the KAM waveform. The relative discriminative ability between the different aspects of the KAM was not known, nor was whether a combination of these variables (as well as the other gait variables linked to progression) best predicts progression to TKA. The last chapter of this dissertation aimed to address these remaining questions.

7.1.3 Summary of Chapter 6: Knee Biomechanics during Gait Predict Knee Osteoarthritis Progression

This study aimed to apply the results of Chapters 4 and 5 in order to gain insight into which gait biomechanical features were most predictive of progression to TKA, thus identifying potential biomechanical targets for conservative interventions. The purpose was three-fold: i) to determine how well individual (univariate) three-dimensional lower extremity biomechanical gait features discriminated between those who progressed to TKA versus those that did not, ii) to determine if a multivariate model including multiple gait features improved the discrimination ability over that of univariate models, and iii) to determine how well the gait biomechanical features that best discriminated between the two groups *predicted* knee OA progression. The key findings of this chapter were:

- The KAM impulse at baseline amplitude-normalized to either body mass or body weight times height was the best individual gait variable to discriminate between the two groups, with the highest area under the receiver operating characteristic (ROC) curve (AUC = 0.79). The KAM impulse normalized to body mass was the most specific of the gait variables (specificity of 100.0).
- The individual gait variable with the second highest area under the ROC curve was the KAMPC1 (AUC = 0.75-0.77).
- Multivariate models were better able to discriminate between the two groups than any univariate model, with AUCs of 0.80-0.85 and odds ratios of 4-6. All multivariate models (models derived from discrete variables, PCA variables, and a combination of discrete and PCA variables) indicated that the overall magnitude of the KAM (either the KAM impulse or KAMPC1) was the most dominant biomechanical variable for progression to TKA.
- KFMPC2 emerged as the second most dominant predictor variable in multivariate models including PCA and discrete variables, despite its low classification ability in univariate models, suggesting an interaction between the KAM and knee flexion moment, and indicating that three-dimensional gait

variables (specifically frontal and sagittal knee kinetics), *and not just frontal plane variables*, are important in progression to TKA.

- The multivariate model with the highest discrimination and correct classification ability (AUC = 0.85 and correct classification rate of 74.1%), and the only model that was more sensitive than specific, was a model containing PCA variables (amplitude-normalized to body mass): KAMPC1, KFMPC2, and AFMPC4. KAMPC1 and KFMPC2 had higher specificities than sensitivities, and AFMPC4 was more sensitive than specific. This model had an odds ratio of 5.72.
- The combination of KAMPC1, KFMPC2, and AFMPC4 in the multivariate models gets at the overall magnitude of loading (KAMPC1), but also the inability to unload the knee (KFMPC2 and AFMPC4), indicating that it is not only higher overall cartilage loading that is important for progression to TKA, but sustained cartilage loading as well.

This chapter provided insight as to how gait features identified as being different between a group of participants with moderate medial compartment knee OA who progressed to TKA and a group that did not play a role in structural and symptomatic progression. The multivariate linear discriminant model with the highest discrimination and classification abilities (AUC and correct classification rate) contained variables obtained using PCA, highlighting the importance of using pattern recognition techniques to capture temporal features of gait waveforms, rather than just amplitude features. The most dominant discriminatory factor in this model was KAMPC1, confirming the importance of the KAM in knee OA progression. However, KFMPC2 and AFMPC4 were the second and third most dominant predictors. KFMPC2 captures the difference between the early stance knee flexion moment and late stance knee extension moment, and AFMPC4 captures the mid-stance dorsiflexion moment. Low scores for these PCs were associated with progression, and indicate a "stiff gait" which would result in knee loading throughout stance, increasing the sustained duration of compressive load. Sustained loading can lead to cartilage degradation (Chen et al, 1999), reduced joint lubrication (Abusara et al, 2013), as well as an upregulation of inflammatory chemicals (Wang et al,

2007) that have been shown to increase knee pain over time (Stannus et al, 2013). Thus, this could provide mechanisms for both structural and symptomatic progression. The results of this chapter illustrate that not only frontal plane biomechanics are important in knee OA progression.

The different aspects of knee loading (overall magnitude as well as inability to unload) contained in the model provide different conservative intervention targets. The results of Chapter 6 indicate that interventions should aim not just to decrease the overall magnitude of load on the knee joint, but alter the pattern of knee loading. Specifically, interventions should aim to increase the unloading of the knee during mid-stance in order to reduce the damaging sustained compressive cartilage loads. This target has not previously been addressed in the development and evaluation of conservative interventions.

7.2 Clinical Implications and Future Directions for Research

This dissertation has increased knowledge related to biomechanical mechanisms of progression to TKA, and has identified potential targets for the future development and evaluation of conservative interventions for knee OA. While lower extremity gait biomechanics have previously been linked to knee OA structural progression, there were significant gaps in the literature, which this dissertation aimed to address. First, though studies have made links between hip and ankle gait biomechanics and knee OA structural progression, no studies have examined the *interrelation* among all three lower extremity joints. Second, previous longitudinal progression studies examined and interpreted results in the context of frontal plane biomechanics, even though non-frontal plane gait alterations are seen in those with knee OA. Third, previous longitudinal progression studies used discrete waveform features (i.e. peaks and impulses), which do not provide information about the temporal biomechanical patterns, including whether there is sustained loading during gait. Finally, all longitudinal studies have focused on structural progression. TKA was chosen as the measure of knee OA progression for this dissertation

because it is a clear endpoint that includes both structural and symptomatic aspects of knee OA progression (i.e. the "disease" and "illness" components of knee OA).

These gaps in the literature formed the basis for the three research objectives that were addressed in Chapters 4-6. Despite being similar in age, sex distribution, mass, body mass index, physical activity level, radiographic disease severity, frontal plane alignment, and symptom severity, there were significant lower extremity biomechanical differences between the two groups. Like the previous studies linking knee joint moments to structural progression (Bennell et al, 2011; Miyazaki et al, 2002), it was found that the KAM peak and KAM impulse were also related to progression to TKA (Chapter 5). In addition to the KAM peak and impulse, knee biomechanical gait features extracted using a pattern recognition technique were significantly different at baseline between the TKA and no-TKA groups. At the knee, KAMPC1, capturing the overall shape and magnitude of the KAM, KAMPC2, capturing the difference between the early and mid-stance KAM, and KFMPC2, capturing decreased early stance knee flexion and late stance knee extension moments were significantly different between the two groups at baseline (Chapter 4). The TKA group had a higher overall KAM magnitude, less of a difference between the early and mid-stance KAM, and decreased knee flexion and extension moments at baseline. The KAM gives an indication of medial compartment loading relative to loading of the whole joint (Zhao et al, 2007). Higher KAMPC1 scores indicate higher medial compartment loading in the TKA group. Low KAMPC2 scores indicate a relative inability to unload the medial compartment during mid-stance, and low KFMPC2 scores suggest a "stiff gait" which would also reduce knee unloading.

There were also significant differences in gait biomechanics at the hip and ankle. At the hip, the TKA group had less hip adduction range of motion at baseline (HAAPC2) than the no-TKA group. At the ankle, the TKA group had less ankle stance dorsiflexion (AFAPC3), lower stance dorsiflexion moments (AFMPC4), and lower rotation moments (ARMPC2) than the no-TKA group at baseline. These gait alterations, particularly the sagittal differences at the ankle, also support a "stiff gait" in the TKA group.

The best individual gait variables for discriminating between the two groups were the KAM impulse and KAMPC1, regardless of the method of amplitude-normalization (Chapter 6). This supports that frontal plane kinetics at the knee are the most dominant gait factors driving knee OA progression to TKA. KAMPC1 was significantly correlated with both the KAM peak and KAM impulse (Chapter 5), as all of these features capture the magnitude of the KAM, either in early stance (peak), or throughout stance (impulse and KAMPC1). These KAM features related to magnitude were more specific than sensitive (Chapter 6), indicating that low KAM peaks, impulses, and KAMPC1 scores were better able to correctly classify the no-TKA group. This is likely because low magnitudes of loading would be insufficient to initiate cartilage damage or the release of inflammatory chemicals that would increase knee pain. KAMPC2, capturing the relative unloading of the medial compartment during mid-stance, was not significantly correlated with the KAM impulse, and had low correlations with the KAM peak (Chapter 5), indicating that it captured a unique feature of the KAM.

Similar to the results of the univariate analysis, KAM variables related to magnitude (KAM impulse or KAMPC1) came out as the most dominant discriminators in the multivariate models (Chapter 6). However, two non-frontal plane gait variables (in addition to KAMPC1), KFMPC2, capturing the difference between the early stance knee flexion and late stance knee extension moment, and AFMPC4, capturing the mid-stance dorsiflexion moment, also came out as significant discriminators in the multivariate model with the highest classification ability, and highest odds ratio for prediction of progression to TKA. The combination of these gait variables suggests an interaction between frontal and sagittal plane biomechanics, and two different mechanisms for progression to TKA. An increased overall magnitude of the KAM (KAMPC1) suggests higher magnitudes of medial compartment (relative to total knee) loads throughout the gait cycle. Animal model work has indicated that increased compressive loads can lead to chondrocyte death (Horisberger et al, 2012; Horisberger et al, 2013). A “stiff gait” and reduced ability to unload the knee during gait (i.e. lower KFMPC2 and AFMPC4 scores) suggests sustained compressive loading. This can lead to structural progression due to reduced joint lubrication (Abusara et al, 2013), and cartilage degradation (Chen et al,

1999; Kim et al, 2012) due to reduced biosynthetic activity (Arokoski et al, 2000; Wong et al, 1999) and the disruption of covalent bonds between collagen molecules in the cartilage matrix (Chen et al, 1999). In terms of the symptomatic aspect of progression, compressive load (both dynamic and static) increases the expression of inflammatory chemicals that have been found to be independent predictors of worsening knee pain over 5 years in those with knee OA (Stannus et al, 2013; Wang et al, 2007).

The combination of these gait features in the multivariate model captures different aspects of knee loading and thus different potential targets for the development and evaluation of conservative interventions. Most conservative interventions, including orthotic devices, such as canes (Gross and Hillstrom, 2008), lateral wedge orthotics (Gross and Hillstrom, 2008; Radzimski et al, 2012), and unloader braces (Gaasbeek et al, 2007; Gross and Hillstrom, 2008; Lindenfeld et al, 1997; Pollo et al, 2002; Self et al, 2000), hip abductor strengthening exercise (Chang et al, 2005), gait modifications such as reduced walking speed (Mundermann et al, 2004), increased trunk lateral lean (Hunt et al, 2011; Simic et al, 2012), toe-ing out (Chang et al, 2007; Schache et al, 2008), and "medial thrust" (Schache et al, 2008; Fregly et al, 2007) target the KAM. The results of this dissertation suggest that reducing the magnitude of the KAM is not the only factor for reducing the risk of progression to TKA. Based on the multivariate model, focusing on interventions that reduce the total exposure to load as well as sustained compressive loading during gait may be more effective. Medial unloader braces have been found to be ineffective at lowering the peak KAM (Gaasbeek et al, 2007; Fantini Pagani et al, 2010), but have been shown to decrease the KAM impulse (Fantini Pagani et al, 2010). Since this variable is highly correlated to KAMPC1 (Chapter 5), they may be an effective clinical intervention for reducing the risk of progression, but longitudinal studies would be needed to confirm this speculation. Canes, crutches, walkers, or Nordic poles may also reduce the risk of progression, since they reduce the overall exposure to load by reducing the ground reaction force (Gross and Hillstrom, 2008). This would reduce the magnitude of the KAM, but may not have an effect on the KFMPC2 or AFMPC4, as it is a *pattern* of knee loading. Addressing obesity in some people with knee OA may be an effective way to alter the pattern of knee loading, since obesity has been associated with elevated

KAM throughout stance and less of a difference between the knee flexion and extension moments (Harding et al, 2012), two variables that emerged as important predictors in the multivariate linear discriminant model. However, while obesity reduction may work in some people, different biomechanical mechanisms causing the observed kinetic changes (i.e. muscle co-activation) may still be at work. It is important to note that there were no significant mass differences between the TKA and no-TKA groups in this study. In fact, the no-TKA group had a slightly higher mass. Thus, increased obesity did not cause the biomechanical differences observed in this study.

Another way to alter the pattern of loading during gait (i.e. increase unloading) may be through the use of gait or neuromuscular retraining. Most gait retraining thus far has focused on lowering the peak KAM. Barrios et al (2010) found that young adults with varus alignment could be taught, using visual feedback of the knee adduction angle during gait, to lower their peak KAM. However, there was a concomitant increase in the peak knee flexion angle during weight acceptance, which could increase the knee flexion moment in early stance and potentially negate any decreases in loading caused by the KAM changes. This tradeoff in loading between the KAM and knee flexion moments in early stance is supported with experimental evidence. Fregly et al (2009), using a patient with an instrumented knee prosthesis, found that a "medial thrust" gait that had previously been found to be effective in reducing the peak KAM (Fregly et al, 2007), resulted in minimal changes in tibial contact force during early stance. They noted that the "medial thrust" pattern required increased knee flexion in early stance. Another study found that decreases in the peak KAM due to the "medial thrust" pattern were offset by increases in the peak knee flexion moment to keep medial compartment loading the same (Walter et al, 2010). As stated above, focusing on the peak KAM during gait retraining may be ineffective in reducing the risk of knee OA progression, particularly due to the interaction between the KAM and knee flexion moments in early stance. This study has shown that both frontal and sagittal lower extremity kinetics need to be considered when developing and evaluating conservative interventions. Furthermore, this study has provided evidence that looking at peaks in any waveform is not sufficient to get a comprehensive indication of the loading environment of the knee joint. Temporal aspects

of the wavefrom *must be considered*. Future research could determine: i) if a gait retraining program is able to alter the biomechanical factors identified in this study as predictive of progression to TKA, and ii) if altering these factors results in a reduced risk of progression.

Because the changes that were seen in the TKA group compared to the no-TKA group are also associated with disease severity (Astephen et al, 2008; Astephen et al, 2008b; Mundermann et al, 2005; Thorp et al, 2006), it cannot be ruled out that the TKA group was more severe at baseline. There were no significant differences in radiographic severity, alignment, or self-reported symptoms between the two groups at baseline (Chapter 4), however these metrics may not be as sensitive as gait biomechanics in detecting changes in disease severity over time. There are known limitations of radiographs in assessing structural progression. There is a ceiling effect for those with KL4 grades, and a lot of structural change can occur within one grade (Felson et al, 2011). Self-reports are limited when assessing symptomatic knee OA severity as well, because scores can be influenced by a number of other factors, including sex (Elbaz et al, 2011), body mass index (Elbaz et al, 2011), short-term fluctuations in symptoms (Conner-Spady et al, 2004), co-morbidities (Dunbar et al, 2004), and coping style (Lane et al, 2011). If gait analysis were a more sensitive metric, it could be a useful clinical tool to monitor disease progression.

An additional limitation of this work is that the significance level of 0.05 was not adjusted based on the number of comparisons between the TKA and no-TKA groups in Chapter 4, which may have resulted in a Type I error. However, this was an exploratory study that provided preliminary data that were further used in multivariate analyses. The results of Chapter 6 provide evidence as to which of the variables play the biggest roles in the progression of knee OA to TKA.

TKA was used as the measure of progression as it captures both structural and symptomatic aspects of progression. Two potential factors that influence the need for surgery (in addition to structural severity) include a patient's pain and function (Gossec et

al, 2011). While pre-TKA WOMAC questionnaires were not administered to the TKA group, WOMAC questionnaires collected from the no-TKA group at their follow-up gait assessment indicated self-reported improvement or no change in symptoms in 20/28 participants. Perhaps increased inflammatory chemical release (Wang et al, 2007) due to the increased and sustained compressive joint loading at baseline in the TKA group caused increased pain over time (Stannus et al, 2013), which then lead to limitations in function. Rather than predicting progression to TKA, these biomechanical variables could be predicting progression of pain and functional limitations severe enough to warrant TKA, which does not diminish the clinical significance of the findings.

7.3 CONCLUSION

In summary, this dissertation aimed to improve our understanding of the relation between lower extremity biomechanics and mechanisms of progression to TKA, with the goal of identifying the best biomechanical targets for the development and evaluation of conservative interventions. It was found that multiple three-dimensional lower extremity biomechanical gait variables were significantly different in the group of participants with moderate, medial compartment knee OA that progressed to TKA, including frontal and sagittal knee moments, frontal hip angles, and sagittal and transverse ankle angles and moments. Discrete variables previously associated with structural progression (KAM peak and KAM impulse) were also found to be associated with progression to TKA. When the factors that were identified as different in the TKA group were entered into multivariate linear discriminant models, the model with the highest discrimination and classification abilities combined the overall exposure to medial compartment loading relative to total knee loading (KAMPC1) with a "stiff gait" (KFMPC2 and AFMPC4). Higher KAMPC1 scores and lower KFMPC2 and AFMPC4 scores were associated with an increased risk of being in the TKA group (odds ratio of 5.72).

The combination of these gait variables suggests two different mechanisms for progression to TKA. Higher KAMPC1 scores suggest higher magnitudes of medial compartment load throughout the gait cycle. Animal model work has indicated that

increased compressive loads can lead to cartilage degradation. Lower KFMPC2 and AFMPC4 scores, indicating a "stiff gait", suggest sustained compressive loading. This can lead to structural progression due to reduced joint lubrication and cartilage degradation, and symptom progression due to increased expression of inflammatory chemicals. Importantly, the results of these studies indicate, for the first time, the importance of non-frontal plane biomechanics in the progression of knee OA.

Clinically, the results of this dissertation suggest that biomechanical targets other than peak and impulse of the KAM should be the focus of conservative interventions. Developing interventions that reduce the total exposure to load as well as sustained compressive loading during gait may be effective in reducing the risk of progression to TKA. In order to alter the pattern of loading during gait (i.e. alter KFMPC2 and AFMPC4 scores), gait or neuromuscular retraining may be warranted. Future research should determine how the components of the multivariate linear discriminant model can be altered conservatively, and what impact alterations have on the risk of progression to TKA.

REFERENCES

Abusara Z, Krawetz R, Steele B, DuVall M, Schmidt T, Herzog W. Muscular loading of joints triggers cellular secretion of PRG4 into the joint fluid. J Biomech. 2013 Apr 26;46(7):1225-30.

Adams SA, Matthews CE, Ebbeling CB, Moore CG, Cunningham JE, Fulton J, et al. The effect of social desirability and social approval on self-reports of physical activity. Am J Epidemiol. 2005 Feb 15;161(4):389-98.

American College of Sports Medicine., Whaley MH, Brubaker PH, Otto RM, Armstrong LE. ACSM's guidelines for exercise testing and prescription. 7th ed. Philadelphia, Pa.: Lippincott Williams & Wilkins; 2006.

Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. classification of osteoarthritis of the knee. diagnostic and therapeutic criteria committee of the american rheumatism association. Arthritis Rheum. 1986 Aug;29(8):1039-49.

Altman RD, Fries JF, Bloch DA, Carstens J, Cooke TD, Genant H, et al. Radiographic assessment of progression in osteoarthritis. Arthritis Rheum. 1987 Nov;30(11):1214-25.

Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage. 2007;15 Suppl A:A1-56.

Anderson DD, Chubinskaya S, Guilak F, Martin JA, Oegema TR, Olson SA, et al. Post-traumatic osteoarthritis: Improved understanding and opportunities for early intervention. J Orthop Res. 2011 Jun;29(6):802-9.

Andriacchi TP, Briant PL, Bevill SL, Koo S. Rotational changes at the knee after ACL injury cause cartilage thinning. Clin Orthop Relat Res. 2006 Jan;442:39-44.

Andriacchi TP, Koo S, Scanlan SF. Gait mechanics influence healthy cartilage morphology and osteoarthritis of the knee. J Bone Joint Surg Am. 2009 Feb;91 Suppl 1:95-101.

Andriacchi TP, Mundermann A. The role of ambulatory mechanics in the initiation and progression of knee osteoarthritis. Curr Opin Rheumatol. 2006 Sep;18(5):514-8.

Andriacchi TP, Mundermann A, Smith RL, Alexander EJ, Dyrby CO, Koo S. A framework for the in vivo pathomechanics of osteoarthritis at the knee. Ann Biomed Eng. 2004 Mar;32(3):447-57.

Arokoski JP, Jurvelin JS, Vaatainen U, Helminen HJ. Normal and pathological adaptations of articular cartilage to joint loading. Scand J Med Sci Sports. 2000 Aug;10(4):186-98.

Arthritis Alliance of Canada. The impact of arthritis in Canada: Today and over the next 30 years. 2011.

Astephen JL, Deluzio KJ, Caldwell GE, Dunbar MJ, Hubley-Kozey CL. Gait and neuromuscular pattern changes are associated with differences in knee osteoarthritis severity levels. J Biomech. 2008;41(4):868-76.

Astephen JL, Deluzio KJ, Caldwell GE, Dunbar MJ. Biomechanical changes at the hip, knee, and ankle joints during gait are associated with knee osteoarthritis severity. J Orthop Res. 2008b Mar;26(3):332-41.

Astephen Wilson JL, Deluzio KJ, Dunbar MJ, Caldwell GE, Hubley-Kozey CL. The association between knee joint biomechanics and neuromuscular control and moderate knee osteoarthritis radiographic and pain severity. Osteoarthritis Cartilage. 2011 Feb;19(2):186-93.

Astephen Wilson JL, Wilson DA, Dunbar MJ, Deluzio KJ. Preoperative gait patterns and BMI are associated with tibial component migration. Acta Orthop. 2010 Aug;81(4):478-86.

Ayral X. Diagnostic and quantitative arthroscopy: Quantitative arthroscopy. Baillieres Clin Rheumatol. 1996 Aug;10(3):477-94.

Barker K, Lamb SE, Toye F, Jackson S, Barrington S. Association between radiographic joint space narrowing, function, pain and muscle power in severe osteoarthritis of the knee. Clin Rehabil. 2004 Nov;18(7):793-800.

Baliunas AJ, Hurwitz DE, Ryals AB, Karrar A, Case JP, Block JA, et al. Increased knee joint loads during walking are present in subjects with knee osteoarthritis. Osteoarthritis Cartilage. 2002 Jul;10(7):573-9.

Barrios JA, Crossley KM, Davis IS. Gait retraining to reduce the knee adduction moment through real-time visual feedback of dynamic knee alignment. J Biomech. 2010 Aug 10;43(11):2208-13.

Barrios JA, Royer TD, Davis IS. Dynamic versus radiographic alignment in relation to medial knee loading in symptomatic osteoarthritis. J Appl Biomech. 2012 Nov;28(5):551-9.

Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: A health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988 Dec;15(12):1833-40.

Bellamy N, Campbell J, Stevens J, Pilch L, Stewart C, Mahmood Z. Validation study of a computerized version of the western ontario and McMaster universities VA3.0 osteoarthritis index. J Rheumatol. 1997 Dec;24(12):2413-5.

Bennell KL, Bowles KA, Wang Y, Cicuttini F, Davies-Tuck M, Hinman RS. Higher dynamic medial knee load predicts greater cartilage loss over 12 months in medial knee osteoarthritis. Ann Rheum Dis. 2011 Oct;70(10):1770-4.

Bennell KL, Hunt MA, Wrigley TV, Hunter DJ, McManus FJ, Hodges PW, et al. Hip strengthening reduces symptoms but not knee load in people with medial knee osteoarthritis and varus malalignment: A randomised controlled trial. Osteoarthritis Cartilage. 2010 May;18(5):621-8.

Brandon SC, Deluzio KJ. Robust features of knee osteoarthritis in joint moments are independent of reference frame selection. Clin Biomech (Bristol, Avon). 2011 Jan;26(1):65-70.

Brandt KD, Radin EL, Dieppe PA, van de Putte L. Yet more evidence that osteoarthritis is not a cartilage disease. Ann Rheum Dis. 2006 Oct;65(10):1261-4.

Brandt KD, Mazzuca SA. Experience with a placebo-controlled randomized clinical trial of a disease-modifying drug for osteoarthritis: The doxycycline trial. Rheum Dis Clin North Am. 2006 Feb;32(1):217,34, xi-xii.

Brunner AM, Henn CM, Drewniak EI, Lesieur-Brooks AM, Crisco JJ, Ehrlich MG. The metabolic effects of high dietary fat and the development of osteoarthritis. Proceedings of the 56th Annual Meeting of the Orthopaedic Research Society. 2010.

Bruyere O, Genant H, Kothari M, Zaim S, White D, Peterfy C, et al. Longitudinal study of magnetic resonance imaging and standard X-rays to assess disease progression in osteoarthritis. Osteoarthritis Cartilage. 2007 Jan;15(1):98-103.

Buckwalter JA, Stanish WD, Rosier RN, Schenck RC,Jr, Dennis DA, Coutts RD. The increasing need for nonoperative treatment of patients with osteoarthritis. Clin Orthop Relat Res. 2001 Apr;(385)(385):36-45.

Buechel FF S, Buechel FF,Jr, Pappas MJ, D'Alessio J. Twenty-year evaluation of meniscal bearing and rotating platform knee replacements. Clin Orthop Relat Res. 2001 Jul;388:41-50.

Canadian Joint Registry. 2006 annual report: Hip and knee replacements in Canada. Canadian Institute for Health Information; 2006.

Challis JH. A procedure for determining rigid body transformation parameters. J Biomech. 1995 Jun;28(6):733-7.

Chang A, Hayes K, Dunlop D, Song J, Hurwitz D, Cahue S, et al. Hip abduction moment and protection against medial tibiofemoral osteoarthritis progression. Arthritis Rheum. 2005 Nov;52(11):3515-9.

Chang A, Hurwitz D, Dunlop D, Song J, Cahue S, Hayes K, et al. The relationship between toe-out angle during gait and progression of medial tibiofemoral osteoarthritis. Ann Rheum Dis. 2007 Oct;66(10):1271-5.

Chen CT, Burton-Wurster N, Lust G, Bank RA, Tekoppele JM. Compositional and metabolic changes in damaged cartilage are peak-stress, stress-rate, and loading-duration dependent. J Orthop Res. 1999 Nov;17(6):870-9.

Conaghan PG, D'Agostino MA, Le Bars M, Baron G, Schmidely N, Wakefield R, et al. Clinical and ultrasonographic predictors of joint replacement for knee osteoarthritis: Results from a large, 3-year, prospective EULAR study. Ann Rheum Dis. 2010 Apr;69(4):644-7.

Conn VS, Hafdahl AR, Minor MA, Nielsen PJ. Physical activity interventions among adults with arthritis: Meta-analysis of outcomes. Semin Arthritis Rheum. 2008 Apr;37(5):307-16.

Conner-Spady BL, Arnett G, McGurran JJ, Noseworthy TW, Steering Committee of the Western Canada Waiting List Project. Prioritization of patients on scheduled waiting lists: Validation of a scoring system for hip and knee arthroplasty. Can J Surg. 2004 Feb;47(1):39-46.

Cooper C, Snow S, McAlindon TE, Kellingray S, Stuart B, Coggon D, et al. Risk factors for the incidence and progression of radiographic knee osteoarthritis. Arthritis Rheum. 2000 May;43(5):995-1000.

Costigan PA, Wyss UP, Deluzio KJ, Li J. Semiautomatic three-dimensional knee motion assessment system. Med Biol Eng Comput. 1992 May;30(3):343-50.

Creamer P, Lethbridge-Cejku M, Hochberg MC. Factors associated with functional impairment in symptomatic knee osteoarthritis. Rheumatology (Oxford). 2000 May;39(5):490-6.

Deluzio KJ, Astephen JL. Biomechanical features of gait waveform data associated with knee osteoarthritis: An application of principal component analysis. Gait Posture. 2007 Jan;25(1):86-93.

DeLuzio KJ, Wyss UP, Li J, Costigan PA. A procedure to validate three-dimensional motion assessment systems. J Biomech. 1993 Jun;26(6):753-9.

Dillon CF, Rasch EK, Gu Q, Hirsch R. Prevalence of knee osteoarthritis in the united states: Arthritis data from the third national health and nutrition examination survey 1991-94. J Rheumatol. 2006 Nov;33(11):2271-9.

Dumond H, Presle N, Terlain B, Mainard D, Loeuille D, Netter P, et al. Evidence for a key role of leptin in osteoarthritis. Arthritis Rheum. 2003 Nov;48(11):3118-29.

Dunbar MJ, Robertsson O, Ryd L. What's all that noise? the effect of co-morbidity on health outcome questionnaire results after knee arthroplasty. Acta Orthop Scand. 2004 Apr;75(2):119-26.

Dunlop DD, Song J, Semanik PA, Sharma L, Chang RW. Physical activity levels and functional performance in the osteoarthritis initiative: A graded relationship. Arthritis Rheum. 2011 Jan;63(1):127-36.

Eckstein F, Wirth W. Quantitative cartilage imaging in knee osteoarthritis. Arthritis. 2011;2011:475684.

Elbaz A, Debbi EM, Segal G, Haim A, Halperin N, Agar G, et al. Sex and body mass index correlate with Western Ontario and McMaster Universities Osteoarthritis Index and quality of life scores in knee osteoarthritis. Arch Phys Med Rehabil. 2011 Oct;92(10):1618-23.

Escobar A, Quintana JM, Bilbao A, Arostegui I, Lafuente I, Vidaurreta I. Responsiveness and clinically important differences for the WOMAC and SF-36 after total knee replacement. Osteoarthritis Cartilage. 2007 Mar;15(3):273-80.

Ettinger WH,Jr, Burns R, Messier SP, Applegate W, Rejeski WJ, Morgan T, et al. A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis. the fitness arthritis and seniors trial (FAST). JAMA. 1997 Jan 1;277(1):25-31.

Fantini Pagani CH, Potthast W, Bruggemann GP. The effect of valgus bracing on the knee adduction moment during gait and running in male subjects with varus alignment. Clin Biomech (Bristol, Avon). 2010 Jan;25(1):70-6.

Felson DT, Nevitt MC, Yang M, Clancy M, Niu J, Torner JC, et al. A new approach yields high rates of radiographic progression in knee osteoarthritis. J Rheumatol. 2008 Oct;35(10):2047-54.

Felson DT, Niu J, Guermazi A, Sack B, Aliabadi P. Defining radiographic incidence and progression of knee osteoarthritis: Suggested modifications of the Kellgren and Lawrence scale. Ann Rheum Dis. 2011 Nov;70(11):1884-6.

Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. the framingham study. Ann Intern Med. 1992 Apr 1;116(7):535-9.

Fleiss JL. Statistical methods for rates and proportions. 2d ed. New York: Wiley; 1981.

Freedson PS, Melanson E, Sirard J. Calibration of the computer science and applications, inc. accelerometer. Med Sci Sports Exerc. 1998 May;30(5):777-81.

Fregly BJ, D'Lima DD, Colwell CW,Jr. Effective gait patterns for offloading the medial compartment of the knee. J Orthop Res. 2009 Aug;27(8):1016-21.

Fregly BJ, Reinbolt JA, Rooney KL, Mitchell KH, Chmielewski TL. Design of patient-specific gait modifications for knee osteoarthritis rehabilitation. IEEE Trans Biomed Eng. 2007 Sep;54(9):1687-95.

Frontera WR, Silver JK. Essentials of physical medicine and rehabilitation. Philadelphia: Hanley & Belfus; 2002.

Gaasbeek RD, Groen BE, Hampsink B, van Heerwaarden RJ, Duysens J. Valgus bracing in patients with medial compartment osteoarthritis of the knee. A gait analysis study of a new brace. Gait Posture. 2007 Jun;26(1):3-10.

Gaudreault N, Mezghani N, Turcot K, Hagemeister N, Boivin K, de Guise JA. Effects of physiotherapy treatment on knee osteoarthritis gait data using principal component analysis. Clin Biomech (Bristol, Avon). 2011 Mar;26(3):284-91.

Gelber AC, Hochberg MC, Mead LA, Wang NY, Wigley FM, Klag MJ. Body mass index in young men and the risk of subsequent knee and hip osteoarthritis. Am J Med. 1999 Dec;107(6):542-8.

Gossec L, Jordan JM, Mazzuca SA, Lam MA, Suarez-Almazor ME, Renner JB, et al. Comparative evaluation of three semi-quantitative radiographic grading techniques for knee osteoarthritis in terms of validity and reproducibility in 1759 X-rays: Report of the OARSI-OMERACT task force. Osteoarthritis Cartilage. 2008 Jul;16(7):742-8.

Gossec L, Paternotte S, Bingham CO,3rd, Clegg DO, Coste P, Conaghan PG, et al. OARSI/OMERACT initiative to define states of severity and indication for joint replacement in hip and knee osteoarthritis. an OMERACT 10 special interest group. J Rheumatol. 2011 Aug;38(8):1765-9.

Grood ES, Suntay WJ. A joint coordinate system for the clinical description of three-dimensional motions: Application to the knee. J Biomech Eng. 1983 May;105(2):136-44.

Gross KD, Hillstrom HJ. Noninvasive devices targeting the mechanics of osteoarthritis. Rheum Dis Clin North Am. 2008 Aug;34(3):755-76.

Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, Wilson PW, et al. The effects of specific medical conditions on the functional limitations of elders in the framingham study. Am J Public Health. 1994 Mar;84(3):351-8.

Gunther KP, Sun Y. Reliability of radiographic assessment in hip and knee osteoarthritis. Osteoarthritis Cartilage. 1999 Mar;7(2):239-46.

Haladik JA, Vasileff WK, Peltz CD, Lock TR, Bey MJ. Bracing improves clinical outcomes but does not affect the medial knee joint space in osteoarthritic patients during gait. Knee Surg Sports Traumatol Arthrosc. 2013 Jul 12 [Epub ahead of print].

Harding GT, Hubley-Kozey CL, Dunbar MJ, Stanish WD, Astephen Wilson JL. Body mass index affects knee joint mechanics during gait differently with and without moderate knee osteoarthritis. Osteoarthritis Cartilage. 2012 Nov;20(11):1234-42.

Hashimoto S, Nishiyama T, Hayashi S, Fujishiro T, Takebe K, Kanzaki N, et al. Role of p53 in human chondrocyte apoptosis in response to shear strain. Arthritis Rheum. 2009 Aug;60(8):2340-9.

Hatfield GL, Hubley-Kozey CL, Astephen Wilson JL, Dunbar MJ. The effect of total knee arthroplasty on knee joint kinematics and kinetics during gait. J Arthroplasty. 2011 Feb;26(2):309-18.

Hawker GA, Guan J, Croxford R, Coyte PC, Glazier RH, Harvey BJ, et al. A prospective population-based study of the predictors of undergoing total joint arthroplasty. Arthritis Rheum. 2006 Oct;54(10):3212-20.

Henriksen M, Aaboe J, Bliddal H. The relationship between pain and dynamic knee joint loading in knee osteoarthritis varies with radiographic disease severity. A cross sectional study. Knee. 2012 Aug;19(4):392-8.

Henriksen M, Simonsen EB, Alkjaer T, Lund H, Graven-Nielsen T, Danneskiold-Samsoe B, et al. Increased joint loads during walking--a consequence of pain relief in knee osteoarthritis. Knee. 2006 Dec;13(6):445-50.

Herzog W, Clark A, Wu J. Resultant and local loading in models of joint disease. Arthritis Rheum. 2003 Apr 15;49(2):239-47.

Holmberg S, Thelin A, Thelin N. Knee osteoarthritis and body mass index: A population-based case-control study. Scand J Rheumatol. 2005;34(1):59-64.

Hootman JM, Macera CA, Helmick CG, Blair SN. Influence of physical activity-related joint stress on the risk of self-reported hip/knee osteoarthritis: A new method to quantify physical activity. Prev Med. 2003 May;36(5):636-44.

Horisberger M, Fortuna R, Leonard TR, Valderrabano V, Herzog W. The influence of cyclic concentric and eccentric submaximal muscle loading on cell viability in the rabbit knee joint. Clin Biomech (Bristol, Avon). 2012 Mar;27(3):292-8.

Horisberger M, Fortuna R, Valderrabano V, Herzog W. Long-term repetitive mechanical loading of the knee joint by in vivo muscle stimulation accelerates cartilage degeneration and increases chondrocyte death in a rabbit model. Clin Biomech (Bristol, Avon). 2013 Jun;28(5):536-43.

Hubley-Kozey C, Deluzio K, Dunbar M. Muscle co-activation patterns during walking in those with severe knee osteoarthritis. Clin Biomech (Bristol, Avon). 2008 Jan;23(1):71-80.

Hubley-Kozey CL, Deluzio KJ, Landry SC, McNutt JS, Stanish WD. Neuromuscular alterations during walking in persons with moderate knee osteoarthritis. J Electromyogr Kinesiol. 2006 Aug;16(4):365-78.

Hui W, Litherland GJ, Elias MS, Kitson GI, Cawston TE, Rowan AD, et al. Leptin produced by joint white adipose tissue induces cartilage degradation via upregulation and activation of matrix metalloproteinases. Ann Rheum Dis. 2012 Mar;71(3):455-62.

Hunt MA, Simic M, Hinman RS, Bennell KL, Wrigley TV. Feasibility of a gait retraining strategy for reducing knee joint loading: Increased trunk lean guided by real-time biofeedback. J Biomech. 2011 Mar 15;44(5):943-7.

Hunter DJ, Felson DT. Osteoarthritis. BMJ. 2006 Mar 18;332(7542):639-42.

Iagnocco A. Imaging the joint in osteoarthritis: A place for ultrasound? Best Pract Res Clin Rheumatol. 2010 Feb;24(1):27-38.

Jackson JE. A user's guide to principal components. Hoboken, N.J.: Wiley-Interscience; 2003.

Jain NB, Higgins LD, Ozumba D, Guller U, Cronin M, Pietrobon R, et al. Trends in epidemiology of knee arthroplasty in the united states, 1990-2000. Arthritis Rheum. 2005 Dec;52(12):3928-33.

Jones G, Ding C, Glisson M, Hynes K, Ma D, Cicuttini F. Knee articular cartilage development in children: A longitudinal study of the effect of sex, growth, body composition, and physical activity. Pediatr Res. 2003 Aug;54(2):230-6.

Kaufman KR, Hughes C, Morrey BF, Morrey M, An KN. Gait characteristics of patients with knee osteoarthritis. J Biomech. 2001 Jul;34(7):907-15.

Kean CO, Hinman RS, Bowles KA, Cicuttini F, Davies-Tuck M, Bennell KL. Comparison of peak knee adduction moment and knee adduction moment impulse in distinguishing between severities of knee osteoarthritis. Clin Biomech (Bristol, Avon). 2012 Jun;27(5):520-3.

Kellgren JH, Lawrence JH. Radiological assessment of osteo-arthrosis. Ann Rheum Dis. 1957 Dec;16(4):494-502.

Kim W, Thambyah A, Broom N. Does prior sustained compression make cartilage-on-bone more vulnerable to trauma? Clin Biomech (Bristol, Avon). 2012 Aug;27(7):637-45.

Kuroyanagi Y, Nagura T, Kiriyama Y, Matsumoto H, Otani T, Toyama Y, et al. A quantitative assessment of varus thrust in patients with medial knee osteoarthritis. Knee. 2012 Mar;19(2):130-4.

Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the united states from 2005 to 2030. J Bone Joint Surg Am. 2007 Apr;89(4):780-5.

Laberge MA, Baum T, Virayavanich W, Nardo L, Nevitt MC, Lynch J, et al. Obesity increases the prevalence and severity of focal knee abnormalities diagnosed using 3T MRI in middle-aged subjects-data from the Osteoarthritis Initiative. Skeletal Radiol. 2012 Jun;41(6):633-41.

Lachenbruch PA. Discriminant analysis. New York: Hafner Press; 1975.

Lagace C, Perruccio A, DesMeules M, et al. Arthritis in canada: An ongoing challenge. In: Ottawa,ON: Health Canada; 2003. p. 7-30.

Landry SC, McKean KA, Hubley-Kozey CL, Stanish WD, Deluzio KJ. Knee biomechanics of moderate OA patients measured during gait at a self-selected and fast walking speed. J Biomech. 2007;40(8):1754-61.

Lane NE, Brandt K, Hawker G, Peeva E, Schreyer E, Tsuji W, et al. OARSI-FDA initiative: Defining the disease state of osteoarthritis. Osteoarthritis Cartilage. 2011 May;19(5):478-82.

Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the united states. part II. Arthritis Rheum. 2008 Jan;58(1):26-35.

Lindenfeld TN, Hewett TE, Andriacchi TP. Joint loading with valgus bracing in patients with varus gonarthrosis. Clin Orthop Relat Res. 1997 Nov;(344)(344):290-7.

Lewek MD, Rudolph KS, Snyder-Mackler L. Control of frontal plane knee laxity during gait in patients with medial compartment knee osteoarthritis. Osteoarthritis Cartilage. 2004 Sep;12(9):745-51.

Li J, Wyss UP, Costigan PA, Deluzio KJ. An integrated procedure to assess knee-joint kinematics and kinetics during gait using an optoelectric system and standardized X-rays. J Biomed Eng. 1993 Sep;15(5):392-400.

Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: Osteoarthritis. Am J Sports Med. 2007 Oct;35(10):1756-69.

Lohmander LS, Ostenberg A, Englund M, Roos H. High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. Arthritis Rheum. 2004 Oct;50(10):3145-52.

Malemud CJ. Cytokines as therapeutic targets for osteoarthritis. BioDrugs. 2004;18(1):23-35.

Maly MR, Acker SM, Calder KM, Totterman S, Tamez-Pena J. The peak knee adduction moment and adduction moment impulse at the knee relate to tibial and femoral cartilage morphology. Proceedings of the 2013 world congress on osteoarthritis; April 2013; Philadelphia, PA, USA. Osteoarthritis and Cartilage; 2013.

Maly MR, Robbins SM, Stratford PW, Birmingham TB, Callaghan JP. Cumulative knee adductor load distinguishes between healthy and osteoarthritic knees--a proof of principle study. Gait Posture. 2013 Mar;37(3):397-401.

McKean KA, Landry SC, Hubley-Kozey CL, Dunbar MJ, Stanish WD, Deluzio KJ. Gender differences exist in osteoarthritic gait. Clin Biomech (Bristol, Avon). 2007 May;22(4):400-9.

McNeil BJ, Hanley JA. Statistical approaches to the analysis of receiver operating characteristic (ROC) curves. Med Decis Making. 1984;4(2):137-50.

Messier SP, Legault C, Loeser RF, Van Arsdale SJ, Davis C, Ettinger WH, et al. Does high weight loss in older adults with knee osteoarthritis affect bone-on-bone joint loads and muscle forces during walking? Osteoarthritis Cartilage. 2011 Mar;19(3):272-80.

Messier SP, Loeser RF, Miller GD, Morgan TM, Rejeski WJ, Sevick MA, et al. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: The arthritis, diet, and activity promotion trial. Arthritis Rheum. 2004 May;50(5):1501-10.

Moisio KC, Sumner DR, Shott S, Hurwitz DE. Normalization of joint moments during gait: A comparison of two techniques. J Biomech. 2003 Apr;36(4):599-603.

Miyazaki T, Wada M, Kawahara H, Sato M, Baba H, Shimada S. Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. Ann Rheum Dis. 2002 Jul;61(7):617-22.

Mundermann A, Dyrby CO, Andriacchi TP. Secondary gait changes in patients with medial compartment knee osteoarthritis: Increased load at the ankle, knee, and hip during walking. Arthritis Rheum. 2005 Sep;52(9):2835-44.

Mundermann A, Dyrby CO, Hurwitz DE, Sharma L, Andriacchi TP. Potential strategies to reduce medial compartment loading in patients with knee osteoarthritis of varying severity: Reduced walking speed. Arthritis Rheum. 2004 Apr;50(4):1172-8.

Newell RS, Hubley-Kozey CL, Stanish WD, Deluzio KJ. Detecting differences between asymptomatic and osteoarthritic gait is influenced by changing the knee adduction moment model. Gait Posture. 2008 Apr;27(3):485-92.

Noyes FR, Stabler CL. A system for grading articular cartilage lesions at arthroscopy. Am J Sports Med. 1989 Jul-Aug;17(4):505-13.

O'Connor BL, Brandt KD. Neurogenic factors in the etiopathogenesis of osteoarthritis. Rheum Dis Clin North Am. 1993 Aug;19(3):581-605.

Ornetti P, Brandt K, Hellio-Le Graverand MP, Hochberg M, Hunter DJ, Kloppenburg M, et al. OARSI-OMERACT definition of relevant radiological progression in hip/knee osteoarthritis. Osteoarthritis Cartilage. 2009 Jul;17(7):856-63.

Osborne JW, Costello AB. Sample size and subject to item ratio in principal components analysis. Practical Assessment, Research & Evaluation. 2004;9(11).

Outerbridge RE. The etiology of chondromalacia patellae. J Bone Joint Surg Br. 1961 Nov;43-B:752-7.

Peterfy CG, Guermazi A, Zaim S, Tirman PF, Miaux Y, White D, et al. Whole-organ magnetic resonance imaging score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage. 2004 Mar;12(3):177-90.

Physical Activity Guidelines Advisory Committee. Activity guidelines advisory committee report. Washington, DC: Department of Health and Human Services; 2008.

Piazza SJ, Cavanagh PR. Measurement of the screw-home motion of the knee is sensitive to errors in axis alignment. J Biomech. 2000 Aug;33(8):1029-34.

Pierrynowski MR, Galea V. Enhancing the ability of gait analyses to differentiate between groups: Scaling gait data to body size. Gait Posture. 2001 May;13(3):193-201.

Plasqui G, Westerterp KR. Physical activity assessment with accelerometers: An evaluation against doubly labeled water. Obesity (Silver Spring). 2007 Oct;15(10):2371-9.

Pollo FE, Otis JC, Backus SI, Warren RF, Wickiewicz TL. Reduction of medial compartment loads with valgus bracing of the osteoarthritic knee. Am J Sports Med. 2002 May-Jun;30(3):414-21.

Pottie P, Presle N, Terlain B, Netter P, Mainard D, Berenbaum F. Obesity and osteoarthritis: More complex than predicted! Ann Rheum Dis. 2006 Nov;65(11):1403-5.

Racunica TL, Teichtahl AJ, Wang Y, Wluka AE, English DR, Giles GG, et al. Effect of physical activity on articular knee joint structures in community-based adults. Arthritis Rheum. 2007 Oct 15;57(7):1261-8.

Radin EL, Martin RB, Burr DB, Caterson B, Boyd RD, Goodwin C. Effects of mechanical loading on the tissues of the rabbit knee. J Orthop Res. 1984;2(3):221-34.

Radzimski AO, Mundermann A, Sole G. Effect of footwear on the external knee adduction moment - A systematic review. Knee. 2012 Jun;19(3):163-75.

Raynauld JP, Martel-Pelletier J, Berthiaume MJ, Beaudoin G, Choquette D, Haraoui B, et al. Long term evaluation of disease progression through the quantitative magnetic resonance imaging of symptomatic knee osteoarthritis patients: Correlation with clinical symptoms and radiographic changes. Arthritis Res Ther. 2006;8(1):R21.

Raynauld JP, Martel-Pelletier J, Berthiaume MJ, Labonte F, Beaudoin G, de Guise JA, et al. Quantitative magnetic resonance imaging evaluation of knee osteoarthritis progression over two years and correlation with clinical symptoms and radiologic changes. Arthritis Rheum. 2004 Feb;50(2):476-87.

Reijman M, Bierma-Zeinstra SM, Pols HA, Koes BW, Stricker BH, Hazes JM. Is there an association between the use of different types of nonsteroidal antiinflammatory drugs and radiologic progression of osteoarthritis? the rotterdam study. Arthritis Rheum. 2005 Oct;52(10):3137-42.

Riddle DL, Kong X, Jiranek WA. Two-year incidence and predictors of future knee arthroplasty in persons with symptomatic knee osteoarthritis: Preliminary analysis of longitudinal data from the osteoarthritis initiative. Knee. 2009 Dec;16(6):494-500.

Robbins SM, Astephen Wilson JL, Rutherford DJ, Hubley-Kozey CL. Reliability of principal components and discrete parameters of knee angle and moment gait waveforms in individuals with moderate knee osteoarthritis. Gait Posture. 2013 Jul;38(3):421-7.

Robbins SM, Birmingham TB, Callaghan JP, Jones GR, Chesworth BM, Maly MR. Frequency and magnitude of knee loading explain pain in knee osteoarthritis. Arthritis Care Res (Hoboken). 2011 Jul;63(7):991-7.

Robbins SM, Birmingham TB, Jones GR, Callaghan JP, Maly MR. Developing an estimate of daily cumulative loading for the knee: Examining test-retest reliability. Gait Posture. 2009 Nov;30(4):497-501.

Robbins SM, Birmingham TB, Maly MR, Chesworth BM, Giffin JR. Comparative diagnostic accuracy of knee adduction moments in knee osteoarthritis: A case for not normalizing to body size. J Biomech. 2011b Mar 15;44(5):968-71.

Robertsson O, Dunbar M, Pehrsson T, Knutson K, Lidgren L. Patient satisfaction after knee arthroplasty: A report on 27,372 knees operated on between 1981 and 1995 in sweden. Acta Orthop Scand. 2000 Jun;71(3):262-7.

Roebuck JA, Kroemer KHE, Thomason WG. Engineering anthopometry methods. New York: Wiley; 1975.

Rothney MP, Schaefer EV, Neumann MM, Choi L, Chen KY. Validity of physical activity intensity predictions by ActiGraph, actical, and RT3 accelerometers. Obesity (Silver Spring). 2008 Aug;16(8):1946-52.

Rudolph KS, Schmitt LC, Lewek MD. Age-related changes in strength, joint laxity, and walking patterns: Are they related to knee osteoarthritis? Phys Ther. 2007 Nov;87(11):1422-32.

Rutherford DJ, Hubley-Kozey C. Explaining the hip adduction moment variability during gait: Implications for hip abductor strengthening. Clin Biomech (Bristol, Avon). 2009 Mar;24(3):267-73.

Rutherford DJ, Hubley-Kozey CL, Deluzio KJ, Stanish WD, Dunbar M. Foot progression angle and the knee adduction moment: A cross-sectional investigation in knee osteoarthritis. Osteoarthritis Cartilage. 2008 Aug;16(8):883-9.

Schache AG, Fregly BJ, Crossley KM, Hinman RS, Pandy MG. The effect of gait modification on the external knee adduction moment is reference frame dependent. Clin Biomech (Bristol, Avon). 2008 Jun;23(5):601-8.

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

Segal NA, Glass NA, Torner J, Yang M, Felson DT, Sharma L, et al. Quadriceps weakness predicts risk for knee joint space narrowing in women in the MOST cohort. Osteoarthritis Cartilage. 2010 Jun;18(6):769-75.

Segal NA, Yack HJ, Khole P. Weight, rather than obesity distribution, explains peak external knee adduction moment during level gait. Am J Phys Med Rehabil. 2009 Mar;88(3):180,8; quiz 189-91, 246.

Self BP, Greenwald RM, Pflaster DS. A biomechanical analysis of a medial unloading brace for osteoarthritis in the knee. Arthritis Care Res. 2000 Aug;13(4):191-7.

Sharma L, Song J, Dunlop D, Felson D, Lewis CE, Segal N, et al. Varus and valgus alignment and incident and progressive knee osteoarthritis. Ann Rheum Dis. 2010 Nov;69(11):1940-5.

Simic M, Hinman RS, Wrigley TV, Bennell KL, Hunt MA. Gait modification strategies for altering medial knee joint load: a systematic review. Arthritis Care Res (Hoboken). 2011 Mar;63(3):405-26.

Simic M, Hunt MA, Bennell KL, Hinman RS, Wrigley TV. Trunk lean gait modification and knee joint load in people with medial knee osteoarthritis: The effect of varying trunk lean angles. Arthritis Care Res (Hoboken). 2012 Oct;64(10):1545-53.

Smith AJ, Lloyd DG, Wood DJ. Pre-surgery knee joint loading patterns during walking predict the presence and severity of anterior knee pain after total knee arthroplasty. J Orthop Res. 2004 Mar;22(2):260-6.

Song J, Semanik P, Sharma L, Chang RW, Hochberg MC, Mysiw WJ, et al. Assessing physical activity in persons with knee osteoarthritis using accelerometers: Data from the osteoarthritis initiative. Arthritis Care Res (Hoboken). 2010 Dec;62(12):1724-32.

Stannus OP, Jones G, Blizzard L, Cicuttini FM, Ding C. Associations between serum levels of inflammatory markers and change in knee pain over 5 years in older adults: A prospective cohort study. Ann Rheum Dis. 2013 Apr;72(4):535-40.

Thomas RH, Resnick D, Alazraki NP, Daniel D, Greenfield R. Compartmental evaluation of osteoarthritis of the knee. A comparative study of available diagnostic modalities. Radiology. 1975 Sep;116(3):585-94.

Thorp LE, Sumner DR, Block JA, Moisio KC, Shott S, Wimmer MA. Knee joint loading differs in individuals with mild compared with moderate medial knee osteoarthritis. Arthritis Rheum. 2006 Dec;54(12):3842-9.

Troiano RP. Large-scale applications of accelerometers: New frontiers and new questions. Med Sci Sports Exerc. 2007 Sep;39(9):1501.

Tudor-Locke C, Bassett DR,Jr. How many steps/day are enough? Preliminary pedometer indices for public health. Sports Med. 2004;34(1):1-8.

Valdes AM, Spector TD. The contribution of genes to osteoarthritis. Med Clin North Am. 2009 Jan;93(1):45,66

Vanwanseele B, Parker D, Coolican M. Frontal knee alignment: Three-dimensional marker positions and clinical assessment. Clin Orthop Relat Res. 2009 Feb;467(2):504-9.

Vaughan CL, Andrews JG, Hay JG. Selection of body segment parameters by optimization methods. J Biomech Eng. 1982 Feb;104(1):38-44.

Vaughan CL, Davis BL, O'Connor JC. Dynamics of human gait. Champaign, Ill. ; Windsor, ON: Human Kinetics Publishers; 1992.

von Porat A, Roos EM, Roos H. High prevalence of osteoarthritis 14 years after an anterior cruciate ligament tear in male soccer players: A study of radiographic and patient relevant outcomes. Ann Rheum Dis. 2004 Mar;63(3):269-73.

Waldman SD, Spiteri CG, Grynpas MD, Pilliar RM, Kandel RA. Long-term intermittent compressive stimulation improves the composition and mechanical properties of tissue-engineered cartilage. Tissue Eng. 2004 Sep-Oct;10(9-10):1323-31.

Waldman SD, Spiteri CG, Grynpas MD, Pilliar RM, Kandel RA. Long-term intermittent shear deformation improves the quality of cartilaginous tissue formed in vitro. J Orthop Res. 2003 Jul;21(4):590-6.

Walker ER, Boyd RD, Wu DD, Lukoschek M, Burr DB, Radin EL. Morphologic and morphometric changes in synovial membrane associated with mechanically induced osteoarthrosis. Arthritis Rheum. 1991 May;34(5):515-24.

Walter JP, D'Lima DD, Colwell CW,Jr, Fregly BJ. Decreased knee adduction moment does not guarantee decreased medial contact force during gait. J Orthop Res. 2010 Oct;28(10):1348-54.

Wang DL, Jiang SD, Dai LY. Biologic response of the intervertebral disc to static and dynamic compression in vitro. Spine (Phila Pa 1976). 2007 Nov 1;32(23):2521-8.

Wang Y, Simpson JA, Wluka AE, Teichtahl AJ, English DR, Giles GG, et al. Relationship between body adiposity measures and risk of primary knee and hip replacement for osteoarthritis: A prospective cohort study. Arthritis Res Ther. 2009;11(2):R31.

Weidow J, Tranberg R, Saari T, Karrholm J. Hip and knee joint rotations differ between patients with medial and lateral knee osteoarthritis: Gait analysis of 30 patients and 15 controls. J Orthop Res. 2006 Sep;24(9):1890-9.

Wilson DR, McWalter EJ, Johnston JD. The measurement of joint mechanics and their role in osteoarthritis genesis and progression. Med Clin North Am. 2009 Jan;93(1):67,82

Wilson W, van Rietbergen B, van Donkelaar CC, Huiskes R. Pathways of load-induced cartilage damage causing cartilage degeneration in the knee after meniscectomy. J Biomech. 2003 Jun;36(6):845-51.

Winter DA. Biomechanics of human movement. New York: Wiley; 1979.

Winter DA, Yack HJ. EMG profiles during normal human walking: Stride-to-stride and inter-subject variability. Electroencephalogr Clin Neurophysiol. 1987 Nov;67(5):402-11.

Wong M, Siegrist M, Cao X. Cyclic compression of articular cartilage explants is associated with progressive consolidation and altered expression pattern of extracellular matrix proteins. Matrix Biol. 1999 Aug;18(4):391-9.

Wong R, Davis AM, Badley EM, Grewal R, Mohammed M. Prevalence of arthritis and rheumatic diseases around the world. A growing burden and implications for health care needs. MOCA. 2010.

Yang NH, Nayeb-Hashemi H, Canavan PK, Vaziri A. Effect of frontal plane tibiofemoral angle on the stress and strain at the knee cartilage during the stance phase of gait. J Orthop Res. 2010 Dec;28(12):1539-47.

Yelin E, Murphy L, Cisternas MG, Foreman AJ, Pasta DJ, Helmick CG. Medical care expenditures and earnings losses among persons with arthritis and other rheumatic

conditions in 2003, and comparisons with 1997. Arthritis Rheum. 2007 May;56(5):1397-407.

Yusuf E, Bijsterbosch J, Slagboom PE, Rosendaal FR, Huizinga TW, Kloppenburg M. Body mass index and alignment and their interaction as risk factors for progression of knees with radiographic signs of osteoarthritis. Osteoarthritis Cartilage. 2011 Sept;19(9):1117-22.

Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis Cartilage. 2010 Apr;18(4):476-99.

Zernicke RF, Goulet GC, Cavanagh PR, Nigg BM, Ashton Miller JA, McKay HA, van den Bogert T. Impact of biomechanics research on society. *Kinesiology Review* 1: 5-16, 2012.

Zhao D, Banks SA, Mitchell KH, D'Lima DD, Colwell CW,Jr, Fregly BJ. Correlation between the knee adduction torque and medial contact force for a variety of gait patterns. J Orthop Res. 2007 Jun;25(6):789-97.

APPENDIX 1 LOWER LIMB ALIGNMENT CALCULATION

All of the participants in this study had predominantly medial compartment involvement (medial compartment joint space narrowing grade greater than lateral compartment joint space narrowing grade, based on the Scott Feature Based score system (Scott et al, 1993)), with similar radiographic disease severity grades at baseline between the two groups, but no gold-standard measure of frontal plane static alignment was obtained. Radiographs were standard anterior-posterior and lateral views, so the full lower extremity hip-knee-ankle (HKA) angle of alignment could not be determined. However, at the beginning of the data collection a standing calibration trial was conducted, which required the participant to stand quietly while the locations of the infrared emitting markers was recorded. Using marker position data from this trial, a measure of static alignment in the frontal plane was calculated.

In order to determine how to best capture static frontal plane alignment, correlations between each of three different methods and the HKA angle determined from full-leg standing radiographs were calculated for a sample of 35 participants (age 55 (6) years, mass 79.9 (17.0) kg, body mass index 28.1 (4.1) kg/m^2) from another study who had received standardized knee imaging (SKI) full-leg radiographs. The HKA angle was calculated from the SKI radiographs as the angle between the femoral mechanical axis (line from the centre of the femoral head to the femoral intercondylar notch) and the tibial mechanical axis (line from the midtibial eminence to the midmalleolar point). Angles were calculated with respect to neutral (0 degrees). Varus alignment was denoted by negative angles, and valgus alignment was denoted by positive angles.

Three different measures of static frontal plane alignment were calculated from the standing calibration trial:

1) HKA Angle: The HKA angle was calculated from the standing calibration trial marker data as the angle between the femoral mechanical axis (line from the hip joint centre to the knee joint centre (midpoint between the medial and lateral

epicondyles)) and the tibial mechanical axis (line from the knee joint centre to the ankle joint centre (midpoint between the medial and lateral malleoli)). A straight line between the femoral and tibial mechanical axes was 180 degrees. More varus alignment was denoted by larger angles (closer to 180 degrees), and more valgus alignment was denoted by smaller angles. The hip joint centre was calculated based on regression equations developed by Vaughan et al (Vaughan et al, 1992). These regression equations required the location of the greater trochanter, and the hip joint centre was calculated to be a certain distance medial to that landmark. Because the surface location of the marker over the greater trochanter would be more lateral to the actual bony landmark on participants with a high amount of adipose tissue, another method of calculating the femoral mechanical axis was used for Method 2.

2) Anterior superior iliac spine (ASIS)-knee-ankle angle: This method of calculating static frontal plane alignment was used in order to avoid the limitations of using the greater trochanter as a landmark to calculate the femoral mechanical axis. The ASIS-knee-ankle angle was calculated from the standing calibration trial marker data as the angle between the femoral mechanical axis (line from the ASIS to the knee joint centre) and the tibial mechanical axis (line from the knee joint centre to the ankle joint centre). A straight line between the femoral and tibial mechanical axes was 180 degrees. More varus alignment was denoted by larger angles (closer to 180 degrees), and more valgus alignment was denoted by smaller angles.

3) Tibial Angle: The tibial angle was calculated with respect to the vertical. The long axis of the tibia was defined as the line connecting the ankle joint centre to the knee joint centre. The angle of this line with respect to the vertical was then calculated. Tibial alignment with respect to the vertical (determined using an inclinometer) has previously been found to significantly correlate ($r=0.831$) with the lower limb mechanical axis obtained from standing full-leg radiographs (180).

Pearson product moment correlation coefficients were calculated between each measure of alignment calculated using data from the standing calibration trial and the gold-

standard measure of alignment obtained from the SKI radiographs. The correlation coefficients and p-values are shown in Table A1.1

Table A1.1 Relationships between static frontal plane lower limb alignment calculated from standing calibration trial data and alignment determined from full-leg radiographs.

	Hip-Knee-Ankle Angle from full-leg radiograph	
	Correlation co-efficient	p-value
Hip-Knee Ankle Angle	-0.676	<0.001
ASIS-Knee-Ankle Angle	-0.748	<0.001
Tibial Angle	-0.619	<0.001

Based on these results, the ASIS-knee-ankle angle correlated best with the HKA angle calculated from the SKI radiographs, although all three methods were significantly correlated with the measure of frontal plane alignment based on the radiographs. The best correlations were seen for the full lower extremity measures of alignment (the HKA and ASIS-knee-ankle angles). This was expected, as they consider the femoral and tibial mechanical axes, whereas the tibial angle only considers the tibial mechanical axis. The better correlation for the ASIS-knee-ankle angle compared to the HKA angle from the standing calibration trial data is likely due to the better landmarking of the ASIS compared to the greater trochanter. The ASIS was easier to palpate than the greater trochanter on all participants, and is less affected by excess adipose tissue than the greater trochanter. Based on the regression equation, larger ASIS-Knee-Ankle angles (i.e. closer to 180 degrees) were more varus, with approximately 175 degrees corresponding to a neutral HKA angle based on SKI radiographs.

Since the best correlation with frontal plane static alignment obtained from the full-leg radiographs was seen for the ASIS-knee-ankle angle, this method of calculating frontal plane alignment was used for the participants in the current progression study.

APPENDIX 2 RADIOGRAPH GRADING RELIABILITY

Since radiography is the most common way to assess knee osteoarthritis (OA) structural severity, and because worse radiographic severity is a predictor for total knee arthroplasty (TKA) (Gossec et al, 2011; Conaghan et al, 2010), baseline radiographs were obtained for the participants in this study. The radiographs were standard, weight-bearing anterior-posterior and lateral views. They were graded twice (once at the baseline time of recruitment into the study and once at follow-up 5-8 years later) by the same high-volume orthopaedic surgeon using the Kellgren and Lawrence (KL) scale for overall radiographic severity (Kellgren and Lawrence, 1957), and the Scott Feature Based score system for medial and lateral compartment joint space narrowing (Scott et al, 1993). As seen in the tables below, follow-up grading was only performed on 42/55 participants, due to the inability to locate the original baseline radiographs for 13 participants for re-grading.

This appendix contains the frequency tables for the two grading times for the: i) overall KL grade, ii) medial tibiofemoral compartment joint space narrowing grade, and iii) lateral tibiofemoral compartment joint space narrowing grade. These tables were used to calculate agreement between the two grading times in two ways: percent agreement and weighted Kappa coefficients.

Table A2.1: Frequency table for KL radiographic severity grade agreement.

		Original KL Grade					
		0	1	2	3	4	Total
Regraded	0	0	0	0	0	0	0
KL	1	0	3	0	0	0	3
Grade	2	0	0	16	0	0	16
	3	0	1	1	15	0	17
	4	0	0	0	0	6	6
	Total	0	4	17	15	6	42

Table A2.2: Frequency table for medial tibiofemoral compartment joint space narrowing (JSN) grade agreement.

		Original JSN Grade				
		0	1	2	3	Total
Rescored JSN Grade	0	3	0	0	0	3
	1	0	12	1	0	13
	2	0	0	17	0	17
	3	0	0	0	9	9
	Total	3	12	18	9	42

Table A2.3: Frequency table for lateral tibiofemoral compartment joint space narrowing (JSN) grade agreement.

		Original JSN Grade				
		0	1	2	3	Total
Regraded JSN Grade	0	30	0	0	0	30
	1	2	8	1	0	11
	2	0	0	0	0	0
	3	0	0	0	1	1
	Total	32	8	1	1	42

Based on these tables, the percent agreement between the two grading times was 95% for the overall KL grade and 98% and 93% for the medial and lateral joint space narrowing grades of the Scott Feature Based score system, respectively.

Weighted kappa coefficients of 0.91, 0.99, and 0.91 were found for the KL grade, and medial and lateral joint space narrowing grades, respectively. This suggests excellent agreement for all grades (Fleiss, 1981).

An additional consideration is that Scott et al found better agreement for lateral joint space narrowing grades compared to medial joint space narrowing grades. The opposite trend was found in this study. This is perhaps because all participants had predominantly medial compartment knee osteoarthritis (medial compartment joint space narrowing grade greater than lateral compartment joint space narrowing grade), with minimal lateral compartment involvement. Most lateral joint space narrowing grades were either 0 or 1: either normal joint space narrowing, or minimal joint space narrowing (Scott et al, 1993). Radiographic grading of knee OA is particularly hard in the early stages because of the ambiguity between what constitutes "normal", and what constitutes a "minimal" change. Difficulty distinguishing between "normal" and "minimal" joint space narrowing could account for the poorer agreement for lateral compartment grades.

APPENDIX 3 COMPARING SELF-REPORTED AND OBJECTIVE PHYSICAL ACTIVITY ASSESSMENTS IN ADULTS WITH KNEE OSTEOARTHRITIS

Joint loading plays a role in knee osteoarthritis (OA) progression (Bennell et al, 2011; Miyazaki et al, 2002). Daily physical activity can indicate the frequency of knee joint loading, but the role of physical activity in the OA process is unclear. Most studies use self-reports of physical activity rather than quantitative measures, which can suffer from social desirability bias (the tendency for individuals to portray themselves in keeping with perceived cultural norms (Adams et al, 2005)), resulting in an over-estimation of physical activity level. Accelerometers are the preferred method of objectively assessing physical activity, and have been shown to be valid, with activity counts correlating significantly with energy expenditure estimates obtained using the gold standard doubly labelled water technique (Plasqui and Westerterp, 2007, Rothney et al, 2008). However, at the time of baseline gait assessments of the participants in the current study, accelerometers were not available. At the time of follow-up testing, accelerometry had been incorporated into the standard gait analysis protocol. Therefore, the two aims of this appendix were: i) to examine the agreement between subjective and objective measures of physical activity for those with medial compartment knee OA, and ii) quantify differences in objective measures of physical activity between self-reported active and sedentary groups.

Twenty-five adults with moderate, medial compartment knee OA (66 years, 93 kg) wore accelerometers (Actigraph GT3X) for ≥ 10 waking hours/day for ≥ 4 days in a single week. ActiLife 5 software (Version 5.10.0, Actigraph, Pensacola, FL) was used to download the data and categorize the activity counts into different activity levels. When downloading the data, a valid day was defined as at least 10 hours of wear time, with a non-wear threshold of 60 minutes of zero-counts (with no more than 2 minutes of low activity counts) (Troiano, 2007). A dataset had to include at least four valid days (Song et al, 2010). The data were down-sampled to give an epoch length of 60 seconds in order to apply activity count cut-offs for classifying physical activity levels (Freedson et al, 1998;

Song et al, 2010). The cut-offs used were those recommended by Actigraph for use with their accelerometers, and were published by Freedson et al (1998). The cut-offs were originally determined by measuring metabolic equivalent (MET) values for a variety of tasks while participants were wearing accelerometers, and using regression equations to establish count ranges for different MET level categories. They are listed in Table A3.1.

Table A3.1: Accelerometer activity count cut-offs for classifying physical activity levels (Freedson et al, 1998).

Activity	MET level	Activity Count
Light	Equal to or less than 2.99	Equal to or less than 1951
Moderate	3.0-5.99	1952-5724
Hard	6.0-8.99	5725-9498
Very hard	Equal to or greater than 9.0	Equal to or greater than 9499

Participants were objectively classified as active or sedentary based on step count and activity count data. Based on step count data, participants were deemed active if they achieved an average of at least 10 000 steps per day (Tudor-Locke and Bassett, 2004). Based on activity counts, participants were deemed active if they achieved at least 150 minutes per week of moderate intensity physical activity (in bouts of at least 10 minutes) (Physical Activity Guidelines Advisory Committee, 2008). Participants were subjectively classified as active if they self-reported participating in physical activity causing sweating and rapid heart rate ≥ 3 days/week (American College of Sports Medicine guideline) (American College of Sports Medicine, 2006). Agreement between subjective and objective physical activity level were determined by calculating unweighted kappa coefficients and percent agreements. Unpaired Student's t-tests tested for differences in step count and minutes of moderate activity between the self-reported active and self-reported sedentary groups.

For objective classification 1 (≥ 10 000 steps/day), kappa coefficients and percent agreements were 0.08 and 52%. For classification 2 (≥150 minutes physical

activity/week), they were 0.08 and 52%. The mean step count and minutes of moderate activity in the subjective active and subjective sedentary groups are seen in Table A3.2.

Table A3.2 Objective physical activity measures in self-reported active and sedentary participants with moderate knee OA. Data are reported as mean (standard deviation).

Group	Valid Days	Wear Time (minutes/day)	Steps/day	Moderate activity (minutes/day)
Active	6 (1)	823 (55)	6414 (2566)	28 (15)*
Sedentary	6 (1)	850 (69)	5920 (2057)	11 (14)

* Indicates a significant between-group difference ($p<0.05$)

There was no significant between-group difference for the mean daily step count, however the self-reported active participants spent significantly more time in moderate activity than the self-reported sedentary participants.

This validation study confirms that self-report in those with moderate knee OA is able to significantly distinguish between objectively-measured active and sedentary physical activity levels in terms of minutes spent in moderate activity, but did not accurately reflect physical activity level in terms of step count. This may be due to the overall low levels of steps within the OA group, which led to overlap between the self-reported active and sedentary OA categories.

APPENDIX 4 WAVEFORM RECONSTRUCTION

Principal component analysis (PCA) was used to extract amplitude and temporal information from the three-dimensional hip, knee, and ankle gait waveforms. In order to increase the robustness of the PCs extracted (Osborne and Costello, 2004), the matrices used for PCA were constructed from a larger dataset of 149 baseline and follow-up waveforms for asymptomatic and moderate knee OA participants in the follow-up study. Therefore, the matrices for each variable were 149x101. PCs that accounted for a total of 90% of the variance (but did not contribute less than 1% of the variance) were retained for statistical hypothesis testing, which typically meant 3 or 4 PCs were retained for each gait variable. In order to ensure that retained PCs accurately represented original waveforms, waveforms were reconstructed by the linear combination of the PCs multiplied by the corresponding PC scores. Original waveforms and reconstructed waveforms were then compared and the root mean squared error was calculated.

This appendix contains mean original and mean reconstructed waveforms for the three-dimensional hip, knee, and ankle angle and moments for the 54 participants included in this dissertation. The average root mean squared error for each reconstruction is also provided in Table A4.1.

As seen in the figures, the reconstructions were better for the moments than for the angles, for all of the joints. Non-sagittal plane angle reconstruction was considerably worse than sagittal reconstruction. The poor reconstruction in the adduction and rotation angles may have been due to the increased variability in these measures, perhaps due to kinematic crosstalk, particularly in the swing phase of gait. The moment reconstruction appeared to be particularly good for the stance phase of gait, which is most important, since that is where the majority of joint loading takes place.

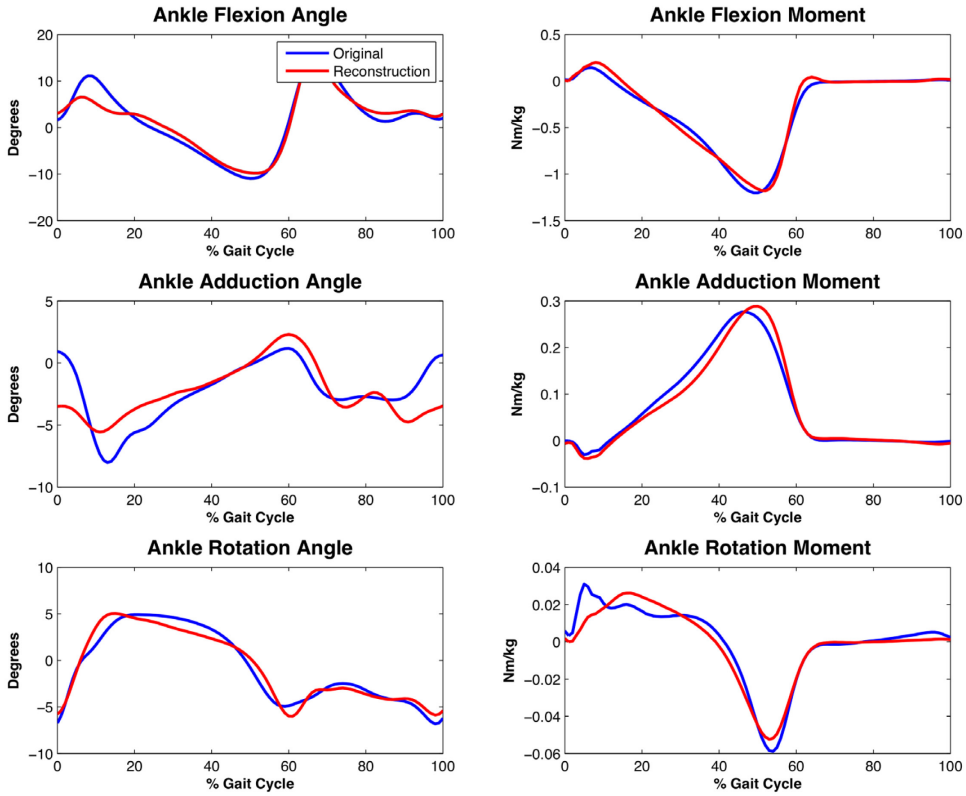

Figure A4.1: Original (blue) and reconstructed (red) three-dimensional ankle angle and moment waveforms for the 54 participants in the present study. Reconstructed waveforms were created based on the number of extracted PCs explaining at least 90% of the variance in the larger dataset (n=149) used for PCA.

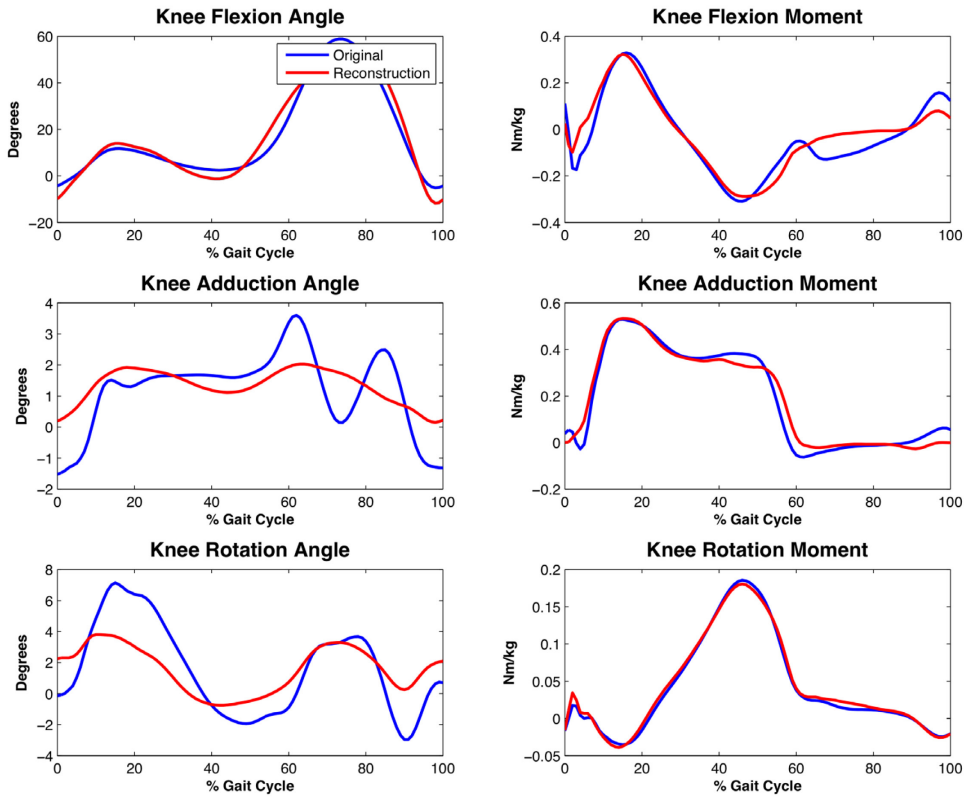

Figure A4.2: Original (blue) and reconstructed (red) three-dimensional knee angle and moment waveforms for the 54 participants in the present study. Reconstructed waveforms were created based on the number of extracted PCs explaining at least 90% of the variance in the larger dataset (n=149) used for PCA.

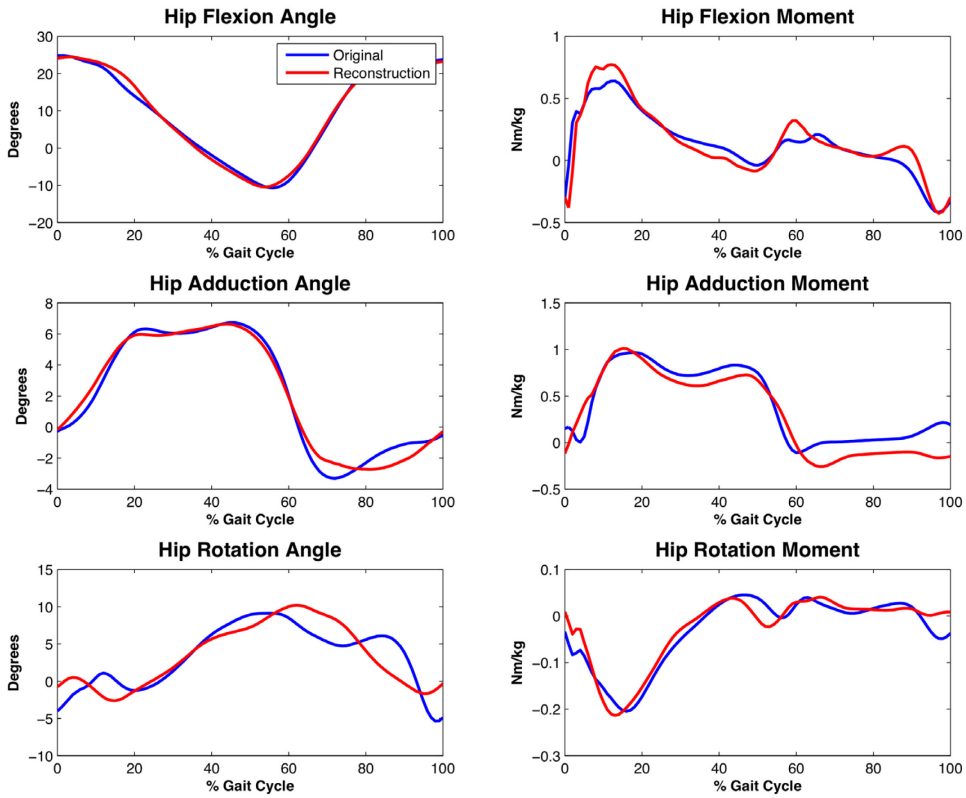

Figure A4.3: Original (blue) and reconstructed (red) three-dimensional hip angle and moment waveforms for the 54 participants in the present study. Reconstructed waveforms were created based on the number of extracted PCs explaining at least 90% of the variance in the larger dataset (n=149) used for PCA.

Table A4.1: Root mean squared error for the waveform reconstructions based on PCs extracted from PCA. Data presented as mean (standard deviation).

Joint	Motion	Angle	Moment
Ankle	Flexion	3.53 (1.04)	0.08 (0.03)
	Adduction	3.27 (0.94)	0.04 (0.02)
	Rotation	1.98 (0.63)	0.01 (0.01)
Knee	Flexion	7.13 (1.04)	0.09 (0.02)
	Adduction	2.00 (0.88)	0.08 (0.02)
	Rotation	4.46 (1.54)	0.02 (0.01)
Hip	Flexion	2.37 (1.03)	0.17 (0.04)
	Adduction	1.49 (0.50)	0.25 (0.03)
	Rotation	4.72 (1.89)	0.05 (0.02)

APPENDIX 5 ANALYZED PRINCIPAL COMPONENTS

Principal component analysis (PCA) was used to extract amplitude and temporal information from the three-dimensional hip, knee, and ankle gait waveforms. In order to increase the robustness of the PCs extracted, the matrices used for PCA were constructed from a larger dataset of 149 baseline and follow-up waveforms for asymptomatic and moderate knee OA participants in the follow-up study. Therefore, the matrices for each variable were 149x101. PCs that accounted for a total of 90% of the variance in this large dataset (but did not contribute less than 1% of the variance) were retained for statistical hypothesis testing, which typically meant only 3 or 4 PCs were retained for each gait variable. This appendix depicts the extracted PCs for each gait variable.

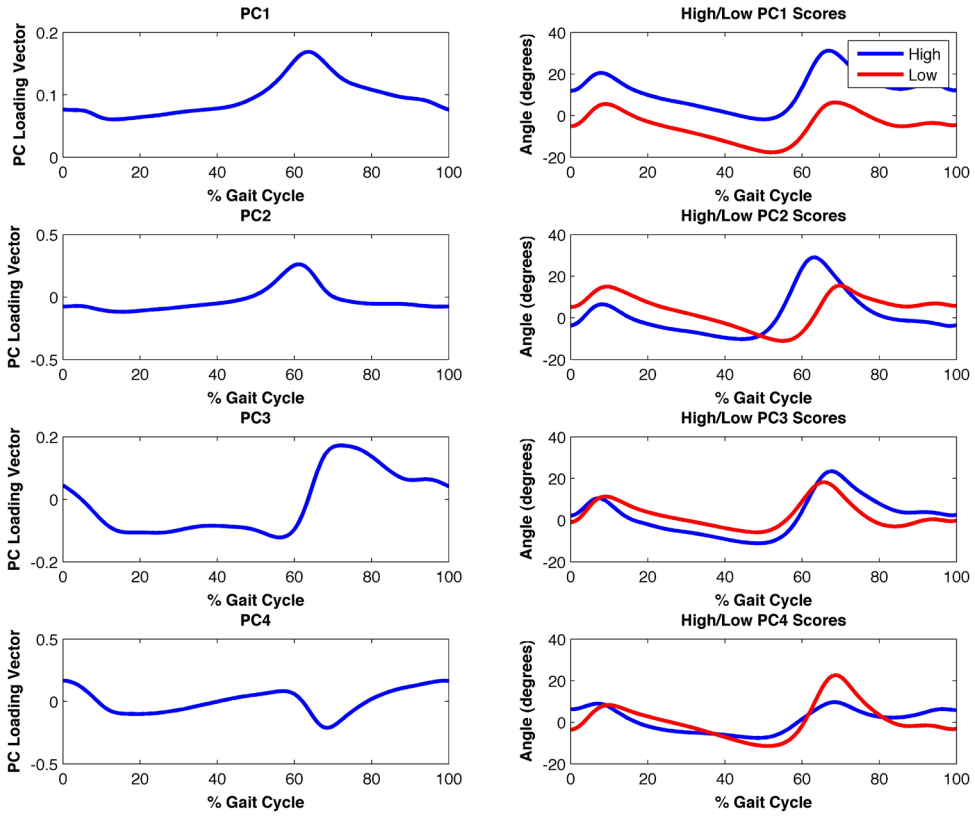

Figure A5.1: Extracted principal components (PCs) for the ankle flexion angle (left column), and mean waveforms for the five original waveforms scoring highest (blue) and lowest (red) for a particular PC (right column). Four PCs were required to account for 91.8% of the variability in the larger dataset (n=149). From top to bottom, PCs 1-4 accounted for 55.5%, 23.3%, 7.7%, and 5.4% of the variability, respectively.

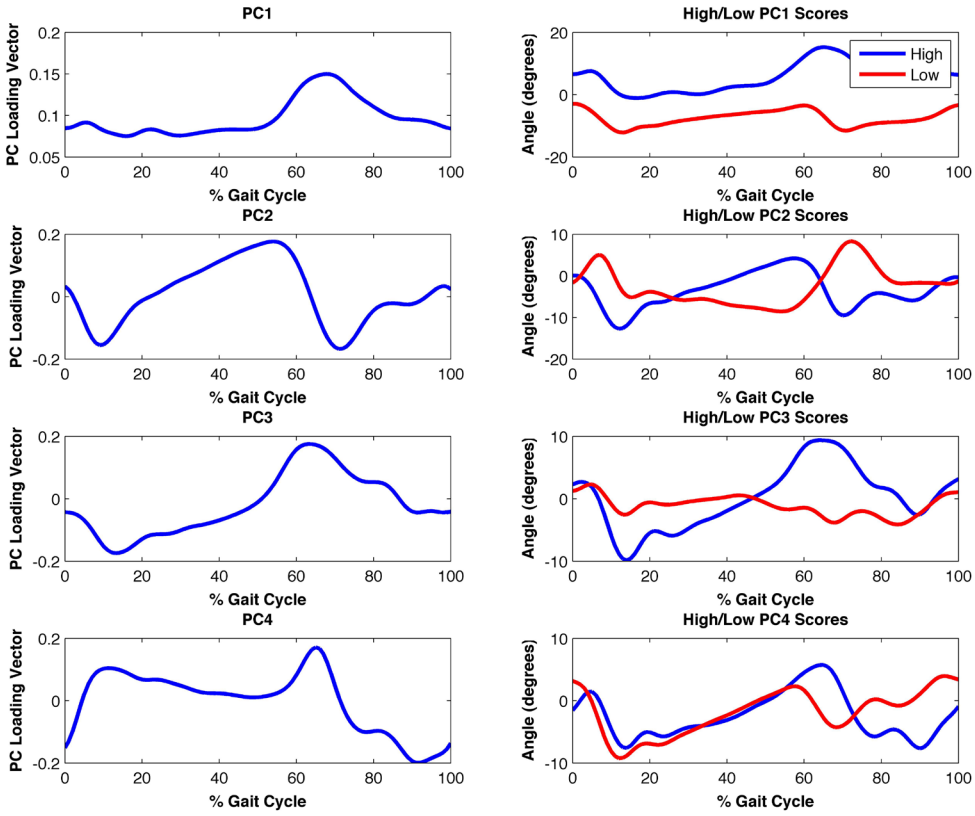

Figure A5.2: Extracted principal components (PCs) for the ankle adduction angle (left column), and mean waveforms for the five original waveforms scoring highest (blue) and lowest (red) for a particular PC (right column). Four PCs were required to account for 87.3% of the variability in the larger dataset (n=149). From top to bottom, PCs 1-4 accounted for 58.2%, 17.4%, 7.3%, and 4.4% of the variability, respectively.

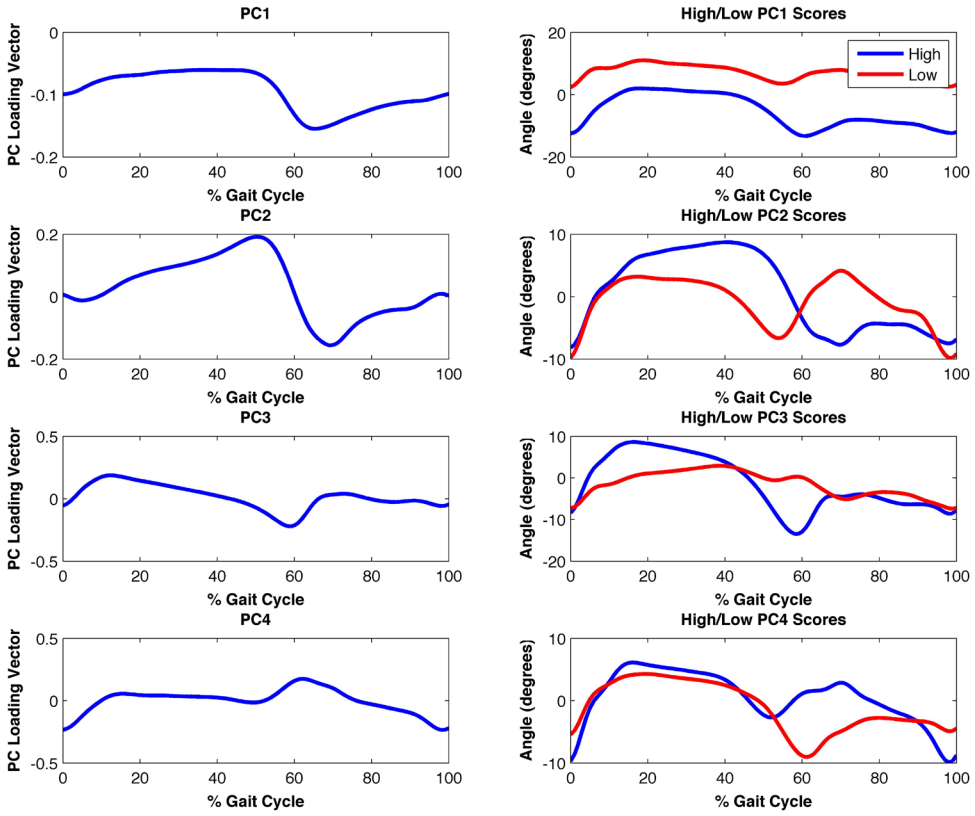

Figure A5.3: Extracted principal components (PCs) for the ankle rotation angle (left column), and mean waveforms for the five original waveforms scoring highest (blue) and lowest (red) for a particular PC (right column). Four PCs were required to account for 92.1% of the variability in the larger dataset (n=149). From top to bottom, PCs 1-4 accounted for 66.6%, 12.5%, 8.5%, and 4.5% of the variability, respectively.

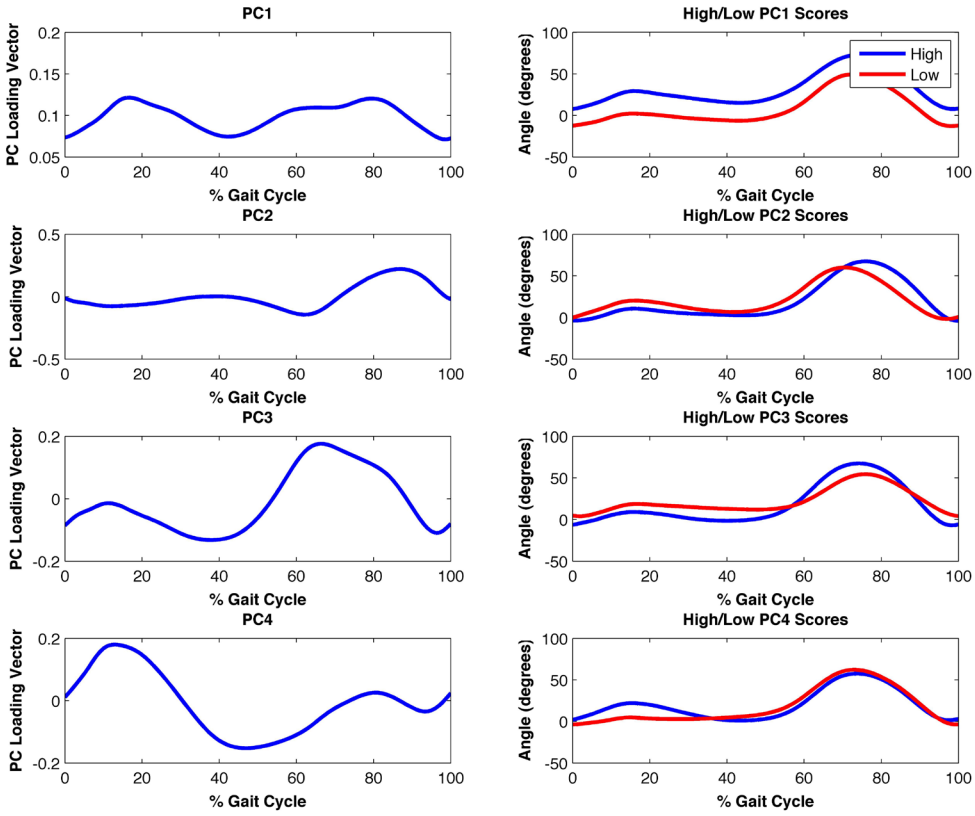

Figure A5.4: Extracted principal components (PCs) for the knee flexion angle (left column), and mean waveforms for the five original waveforms scoring highest (blue) and lowest (red) for a particular PC (right column). Four PCs were required to account for 94.6% of the variability in the larger dataset (n=149). From top to bottom, PCs 1-4 accounted for 62.8%, 14.7%, 10.4%, and 6.5% of the variability, respectively.

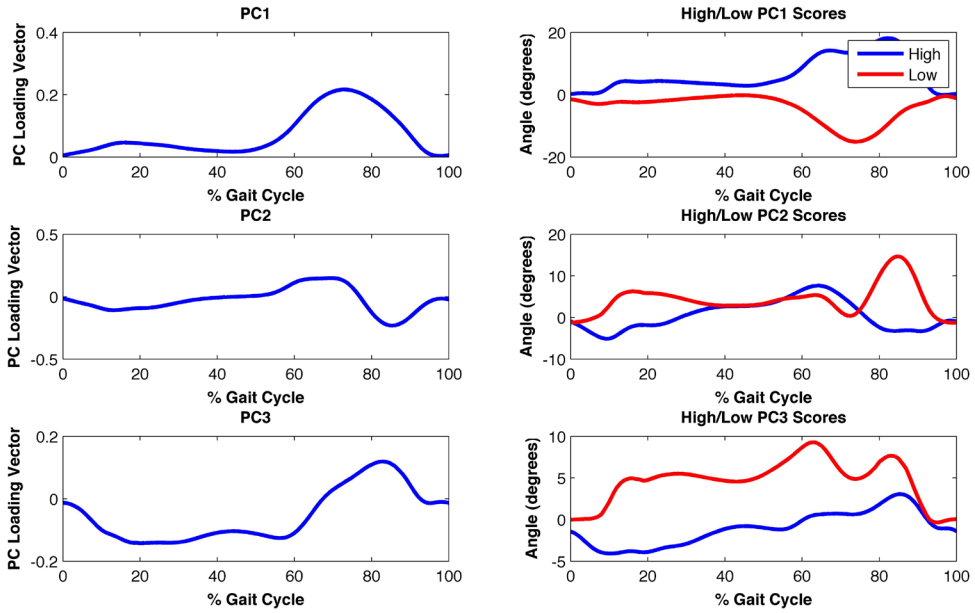

Figure A5.5: Extracted principal components (PCs) for the knee adduction angle (left column), and mean waveforms for the five original waveforms scoring highest (blue) and lowest (red) for a particular PC (right column). Three PCs were required to account for 90.2% of the variability in the larger dataset (n=149). From top to bottom, PCs 1-3 accounted for 73.5%, 9.9%, and 6.7% of the variability, respectively.

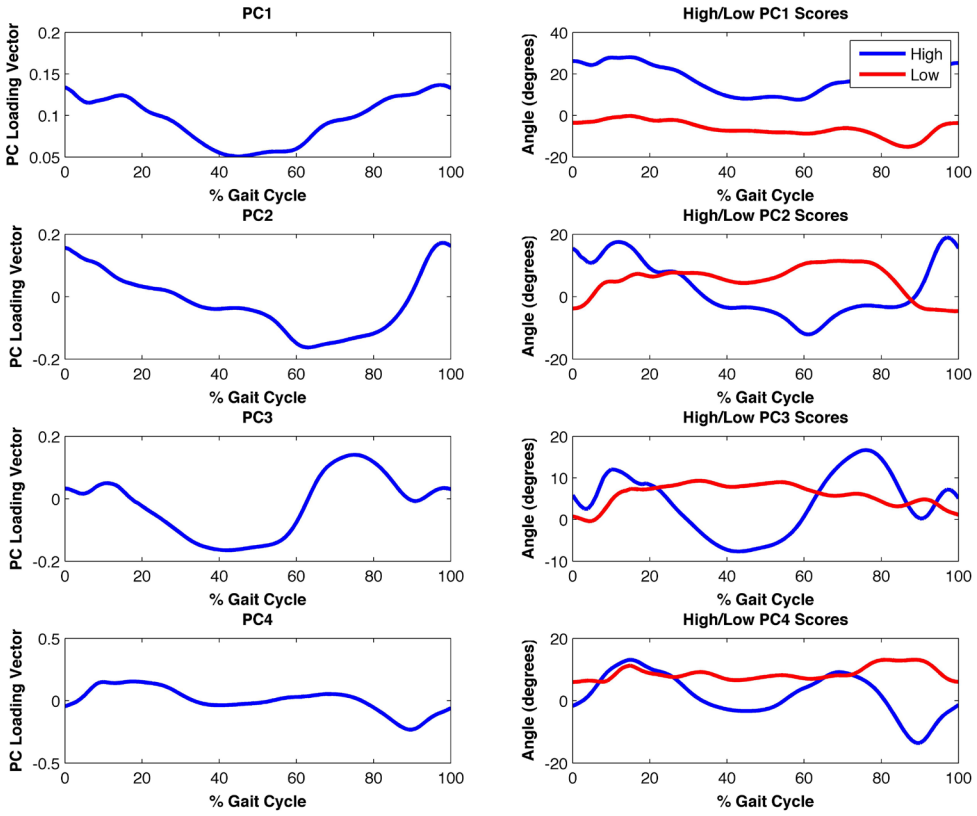

Figure A5.6: Extracted principal components (PCs) for the knee rotation angle (left column), and mean waveforms for the five original waveforms scoring highest (blue) and lowest (red) for a particular PC (right column). Four PCs were required to account for 88.5% of the variability in the larger dataset (n=149). From top to bottom, PCs 1-4 accounted for 54.5%, 22.2%, 8.1%, and 3.7% of the variability, respectively.

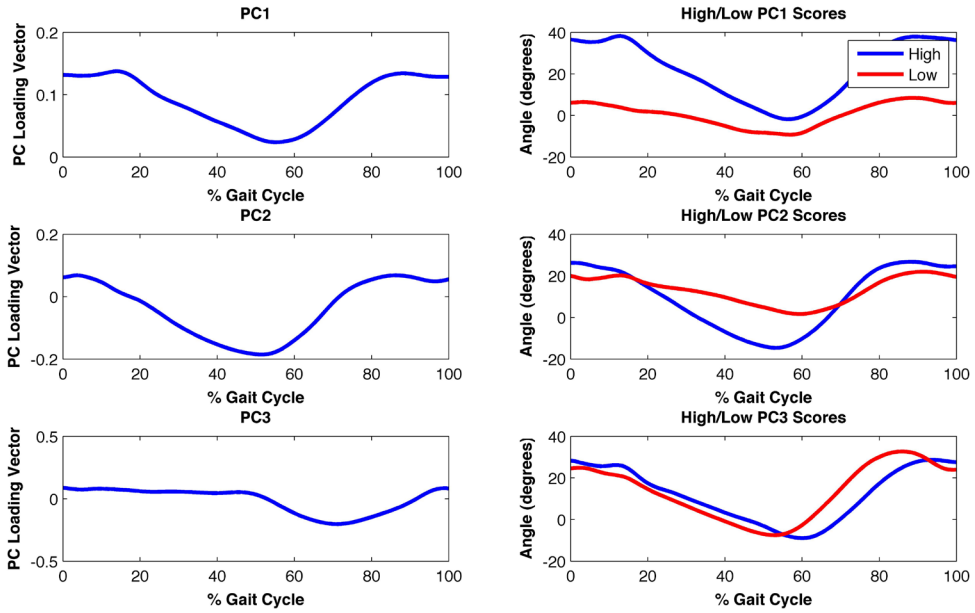

Figure A5.7: Extracted principal components (PCs) for the hip flexion angle (left column), and mean waveforms for the five original waveforms scoring highest (blue) and lowest (red) for a particular PC (right column). Three PCs were required to account for 92.8% of the variability in the larger dataset (n=149). From top to bottom, PCs 1-3 accounted for 70.3%, 15.0%, and 7.4% of the variability, respectively.

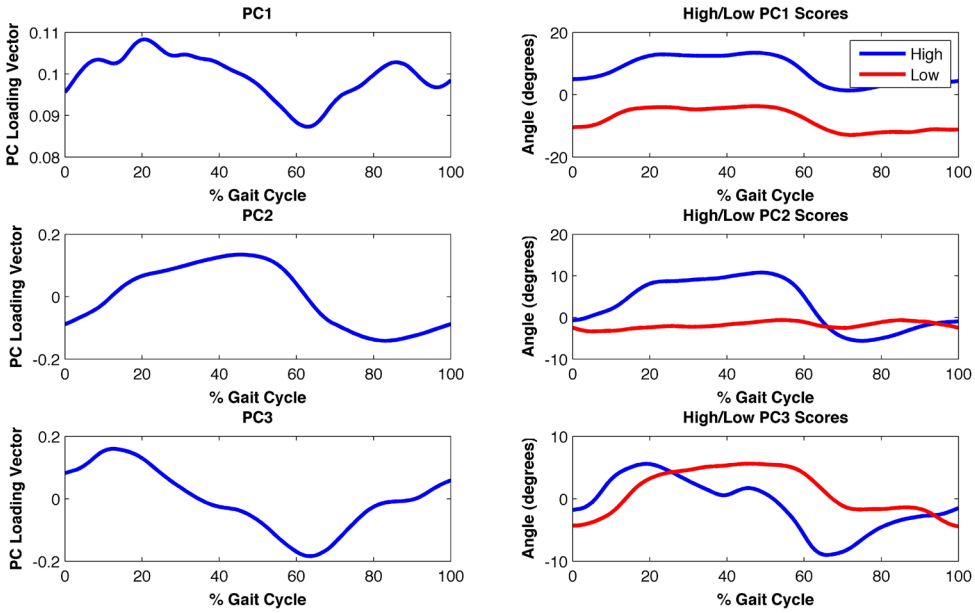

Figure A5.8: Extracted principal components (PCs) for the hip adduction angle (left column), and mean waveforms for the five original waveforms scoring highest (blue) and lowest (red) for a particular PC (right column). Three PCs were required to account for 94.2% of the variability in the larger dataset (n=149). From top to bottom, PCs 1-3 accounted for 77.7%, 10.3%, and 6.2% of the variability, respectively.

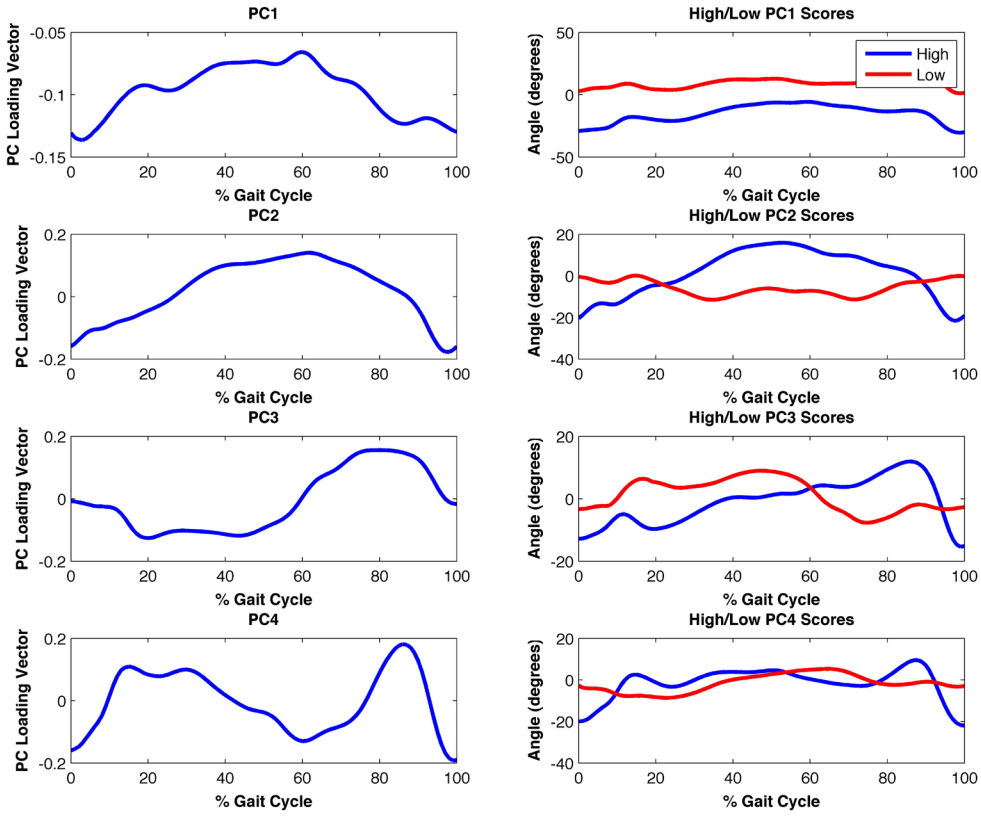

Figure A5.9: Extracted principal components (PCs) for the hip rotation angle (left column), and mean waveforms for the five original waveforms scoring highest (blue) and lowest (red) for a particular PC (right column). Four PCs were required to account for 91.0% of the variability in the larger dataset (n=149). From top to bottom, PCs 1-4 accounted for 62.4%, 18.2%, 6.0%, and 4.4% of the variability, respectively.

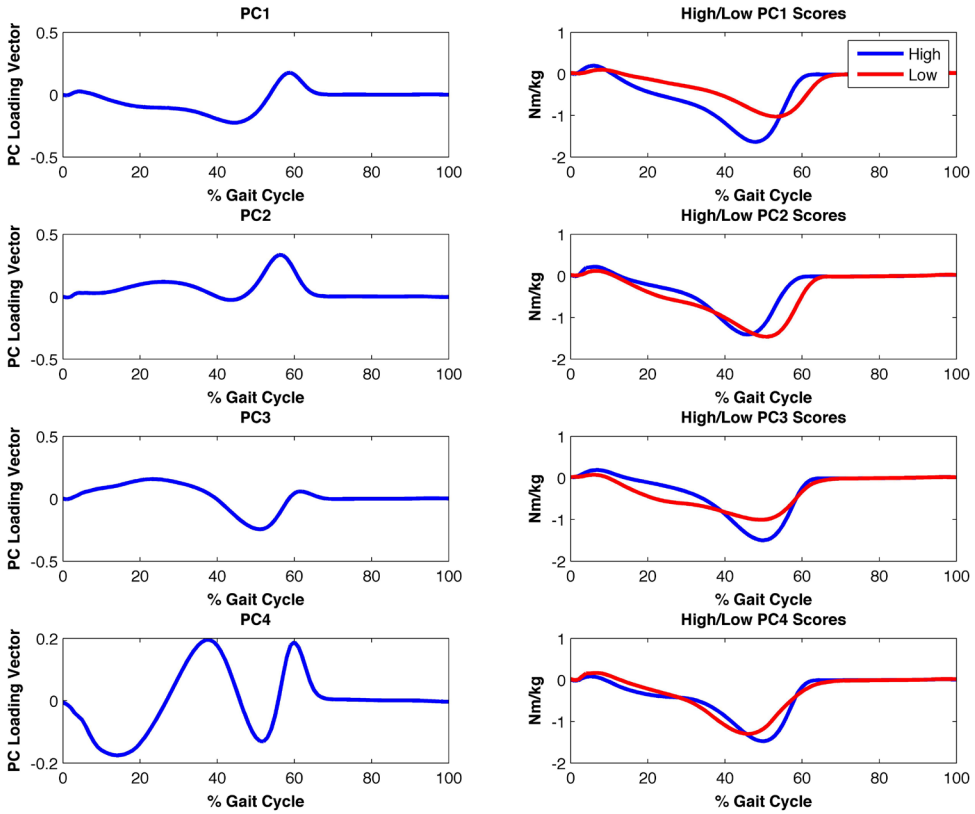

Figure A5.10: Extracted principal components (PCs) for the ankle flexion moment (left column), and mean waveforms for the five original waveforms scoring highest (blue) and lowest (red) for a particular PC (right column). Four PCs were required to account for 94.8% of the variability in the larger dataset (n=149). From top to bottom, PCs 1-4 accounted for 48.2%, 24.1%, 16.7%, and 5.8% of the variability, respectively.

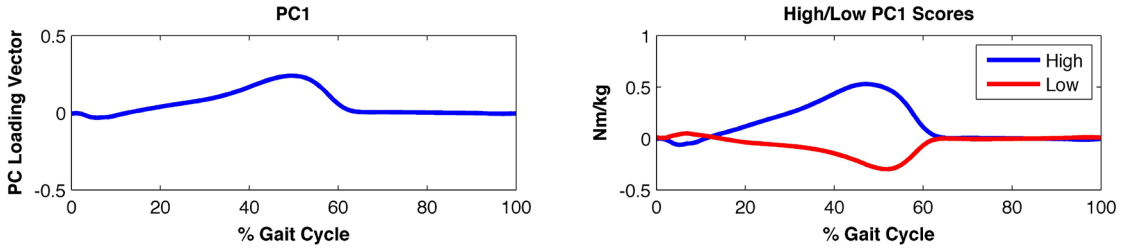

Figure A5.11: Extracted principal component (PC) for the ankle adduction moment (left), and mean waveforms for the five original waveforms scoring highest (blue) and lowest (red) for PC1 (right). One PC was required to account for 93.9% of the variability in the larger dataset (n=149).

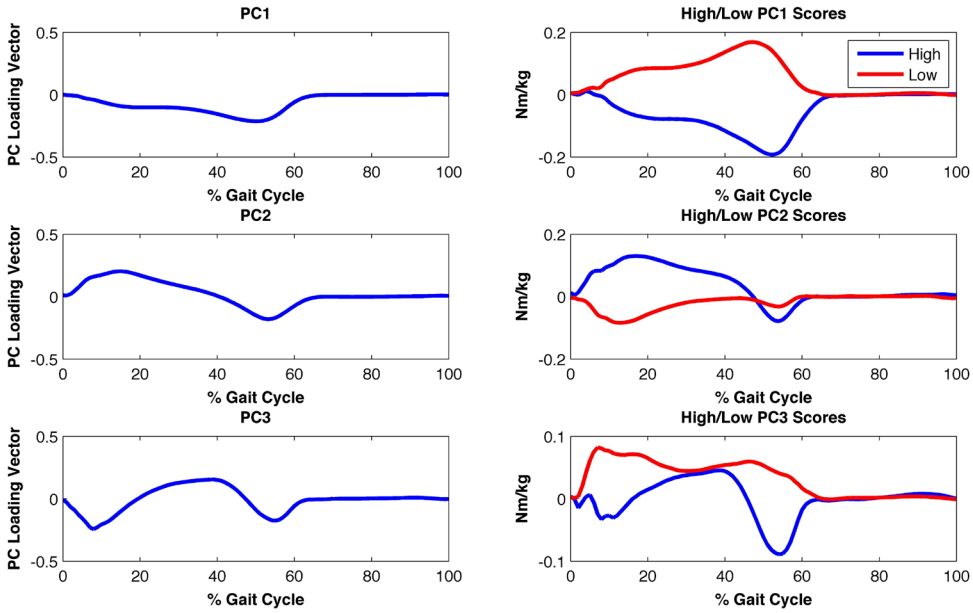

Figure A5.12: Extracted principal components (PCs) for the ankle rotation moment (left column), and mean waveforms for the five original waveforms scoring highest (blue) and lowest (red) for a particular PC (right column). Three PCs were required to account for 94.4% of the variability in the larger dataset (n=149). From top to bottom, PCs 1-3 accounted for 75.3%, 14.5%, and 4.6% of the variability, respectively.

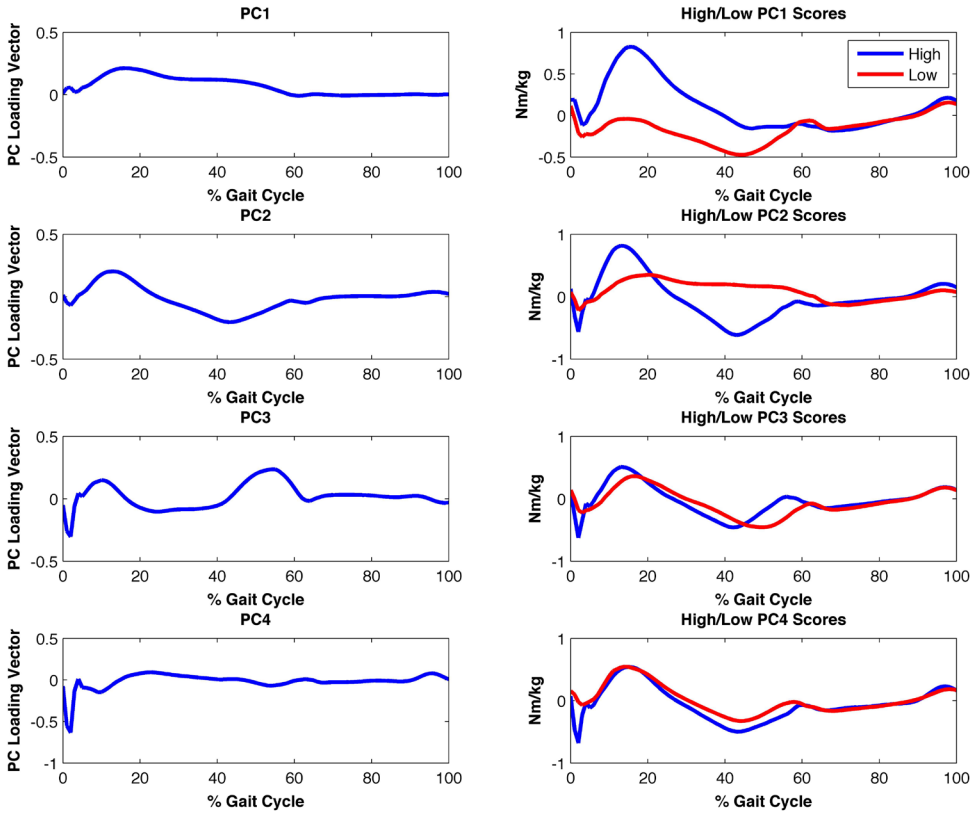

Figure A5.13: Extracted principal components (PCs) for the knee flexion moment (left column), and mean waveforms for the five original waveforms scoring highest (blue) and lowest (red) for a particular PC (right column). Four PCs were required to account for 91.5% of the variability in the larger dataset (n=149). From top to bottom, PCs 1-4 accounted for 44.1%, 37.9%, 7.1%, and 2.4% of the variability, respectively.

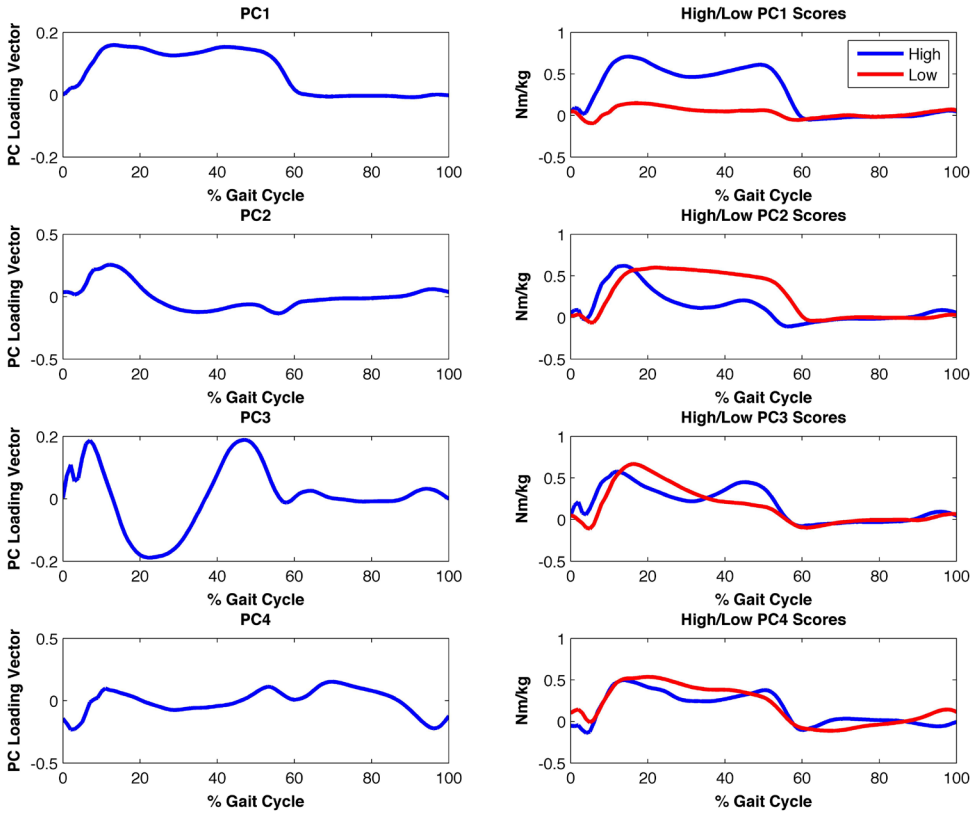

Figure A5.14: Extracted principal components (PCs) for the knee adduction moment (left column), and mean waveforms for the five original waveforms scoring highest (blue) and lowest (red) for a particular PC (right column). Four PCs were required to account for 90.4% of the variability in the larger dataset (n=149). From top to bottom, PCs 1-4 accounted for 63.7%, 15.9%, 7.0%, and 3.7% of the variability, respectively.

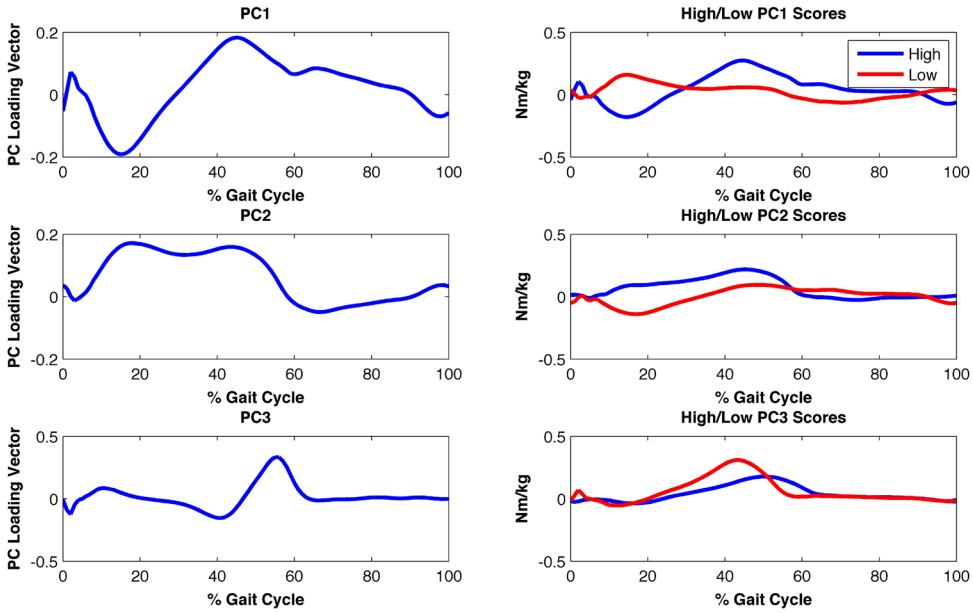

Figure A5.15: Extracted principal components (PCs) for the knee rotation moment (left column), and mean waveforms for the five original waveforms scoring highest (blue) and lowest (red) for a particular PC (right column). Three PCs were required to account for 92.1% of the variability in the larger dataset (n=149). From top to bottom, PCs 1-3 accounted for 52.4%, 34.2%, and 5.5% of the variability, respectively.

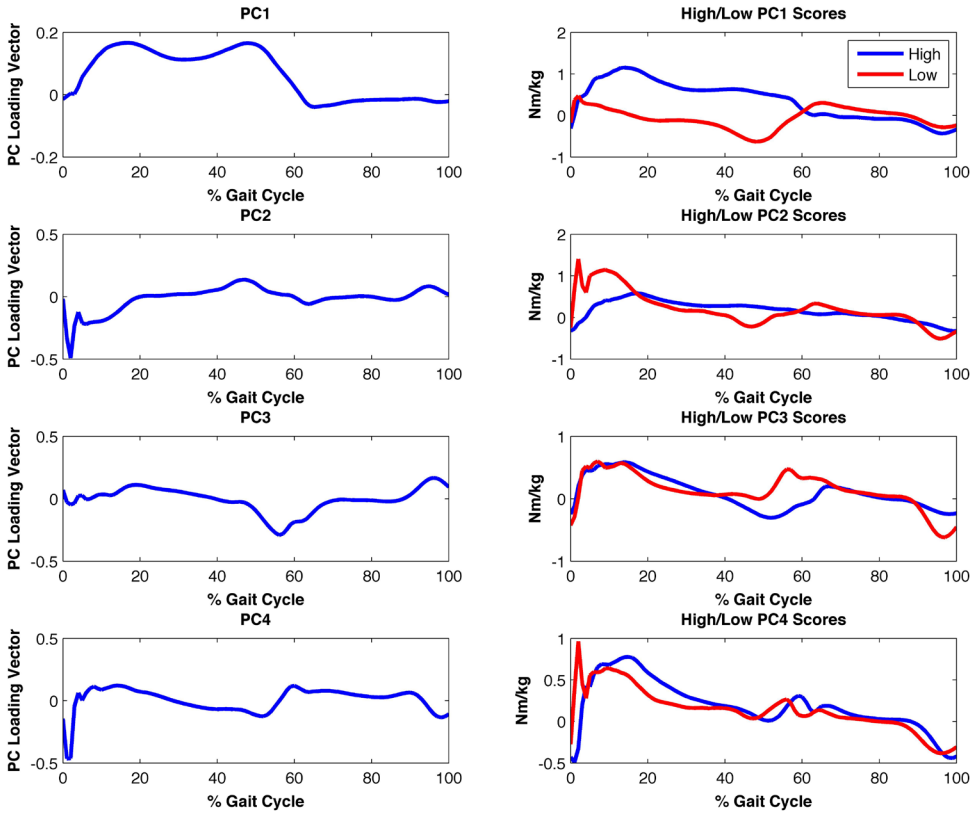

Figure A5.16: Extracted principal components (PCs) for the hip flexion moment (left column), and mean waveforms for the five original waveforms scoring highest (blue) and lowest (red) for a particular PC (right column). Four PCs were required to account for 85.4% of the variability in the larger dataset (n=149). From top to bottom, PCs 1-4 accounted for 60.3%, 12.0%, 7.7%, and 5.3% of the variability, respectively.

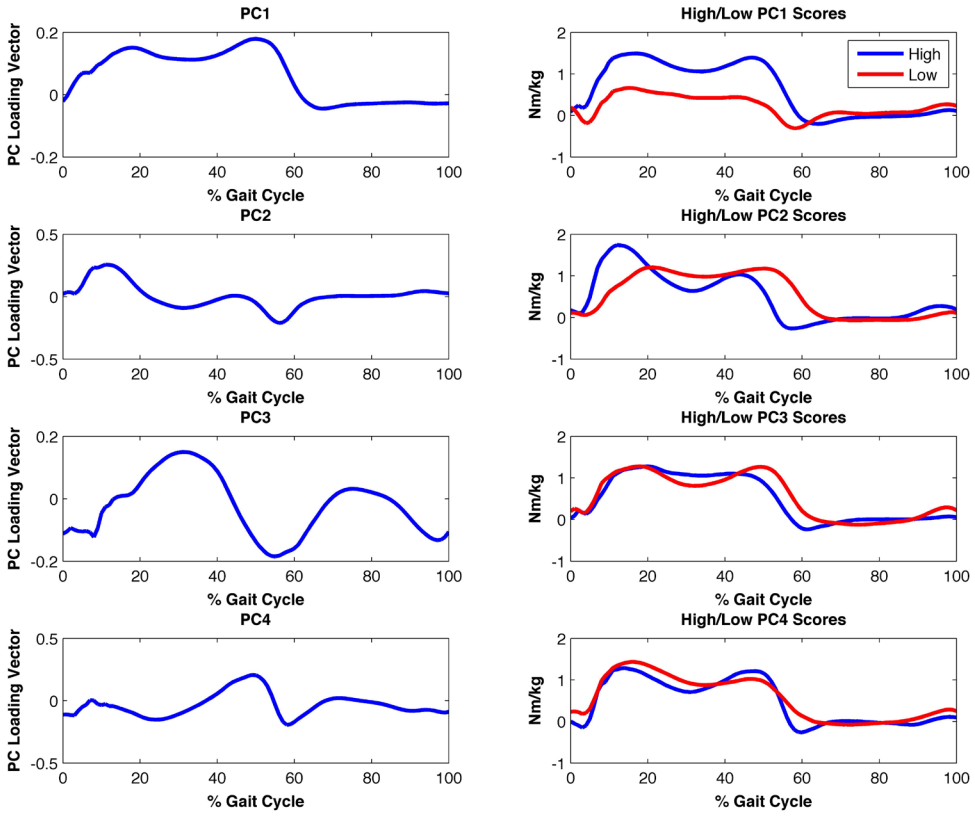

Figure A5.17: Extracted principal components (PCs) for the hip adduction moment (left column), and mean waveforms for the five original waveforms scoring highest (blue) and lowest (red) for a particular PC (right column). Four PCs were required to account for 88.7% of the variability in the larger dataset (n=149). From top to bottom, PCs 1-4 accounted for 57.5%, 22.2%, 5.4%, and 3.6% of the variability, respectively.

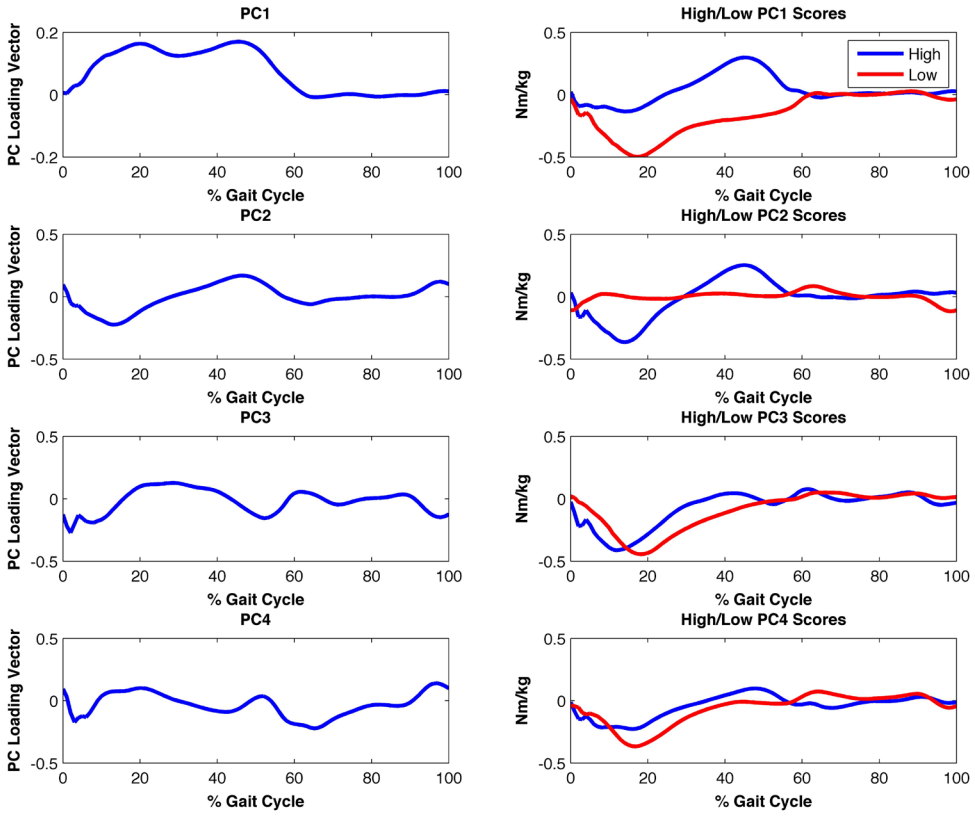

Figure A5.18: Extracted principal components (PCs) for the hip rotation moment. Four PCs were required to account for 88.7% of the variability in the larger dataset (n=149). From top to bottom, PCs 1-4 accounted for 57.9%, 21.2%, 5.6%, and 4.0% of the variability, respectively.