KNEE MECHANICS OF HEALTHY AND OSTEOARTHRITIC JOINTS

by

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Dedicated to Jasper

Table of Contents

List of Tables ..... *vii*

List of Figures ..... *ix*

Abstract ..... *xi*

List of Symbols and Abbreviations ..... *xii*

Acknowledgements ..... *xv*

CHAPTER 1 Introduction *1*

1.1 Motivation 1

1.2 Thesis Aims and Objectives 2

1.3 Format of Thesis 6

CHAPTER 2 Background *8*

2.1 Knee OA: A Biomechanics Problem 8

2.2 The Knee Joint Organ 10

2.3 Force Sharing Across the Knee Joint 11

2.4 Resultant Joint Moments as a Model of Joint Loading in Humans 12

2.5 The Effect of Abnormal Forces: Knee OA and its Progression 16

2.6 Characterizing Abnormal Forces 20

2.7 Sport Participation: An Overload Model of Knee OA Initiation 23

2.8 Joint Moments, Muscle Activation and Knee OA 25

2.9 Joint mechanics, Muscle Activation and Knee OA Progression 29

2.10 Summary 31

CHAPTER 3 Methods *32*

3.1 Participant Datasets 32

3.1.1 Three-Year Progression Study 32

3.1.2 Longitudinal Study on Adolescent Biomechanics 33

3.1.3 Collegiate Athlete Knee Joint Health Study 34

3.2 Biomechanics Data Collection Protocols 35
3.2.1 Three-Year Progression Study 35
3.2.2 Longitudinal Study on Adolescent Biomechanics 37
3.2.3 Collegiate Athlete Joint Health Study 38
3.3 Data Processing 38
3.3.1 Three-Year Progression Study 38
3.3.1 Adolescent Biomechanics and Collegiate Athlete Joint Health Studies 40
3.4 Principal Component Analyses 41
3.4.2 PC Scores 42
3.5 Imaging 42
3.2.1 Three-Year Progression Study 42
3.2.2 Collegiate Athlete Joint Health Study 44
CHAPTER 4 Longitudinal Evidence Links Joint Level Mechanics and Muscle Activation Patterns to Three-Year Medial Joint Space Narrowing *46*
4.1 Background 46
4.2 Methods 48
4.3 Results 51
4.4 Discussion 56
4.5 Conclusion 60
CHAPTER 5 Three-Year Changes in Knee Moments and Muscle Activation Patterns With and Without Knee Osteoarthritis Clinical Diagnosis and Structural Progression *62*
5.1 Introduction 62
5.2 Methods 64
5.3 Results 66
5.4 Discussion 73
5.6 Conclusion 76

CHAPTER 6 Sex and Puberty Dependent and Independent Features of Knee Joint Moments During Over-Ground Walking and Running *77*

6.1 Background 77

6.2 Methods 79

6.2.1 Participants 79

6.2.2 Data Collection 79

6.2.3 Data Analysis 80

6.2.4 Statistical Analysis 81

6.3 Results 82

6.3.1 Walking Results 82

6.3.2 Running Results 87

6.3.3 Linear Discriminant Analysis (LDA) 91

6.4 Discussion 93

6.5 Conclusion 98

CHAPTER 7 The Effect of Sport Type and Knee Mechanics on the MRI Detected Changes in the Knees of Female Collegiate Athletes *99*

7.1 Background 99

7.2 Methods 102

7.2.1 Participants 102

7.2.2 MRI Acquisition 103

7.2.3 MRI Scoring 103

7.2.4 Definition of Worsening OA Features 104

7.2.5 Motion Analysis Data Collection 104

7.2.6 Data Analysis 105

7.3 Results 106

7.4 Discussion 110

7.5 Conclusion 114

CHAPTER 8 Conclusion *116*

Conclusion *116*

8.1 Summary of Findings **116**
8.1.1 Three-Year Progression Study 116
8.1.2 Three-Year Changes in Gait 118
8.1.3 Puberty and Gait 118
8.1.4 Female Athlete Joint Health Study 119
8.2 Research Limitations and Future Directions **120**
8.3 Final Thoughts **123**
References ***124***
APPENDIX A Description and Figures of Principal Components ***151***
APPENDIX B Linear Discriminant Function – MRI Study ***171***
APPENDIX C Copyright Permission ***173***
APPENDIX D Acknowledgements Word Search Key ***177***

List of Tables

Table 3. 1 Demographics of Asymptomatic (Asym) and Moderate OA (Mod-OA) Subjects in the Asym-Mod-OA PC Model 33

Table 3. 2 Demographics of the Three-Year Progression Study (Chapters 4 and 5) Asym and Mod-OA 33

Table 3. 3 Demographics of the Longitudinal Study on Adolescent Biomechanics Subjects 34

Table 3. 4 Demographics of Collegiate Athlete Knee Joint Health Study Subjects 35

Table 3. 5 Magnetic Resonance Imaging Parameters 44

Table 4. 1 Participant Baseline Demographics 52

Table 4. 2 Baseline Gait Variables that are Significantly Different Between the Progression (PG) and Non-Progression (NPG) Groups 53

Table 5. 1 Baseline Group Demographics 67

Table 5. 2 Pair-wise comparisons for demographic variables with significant group differences baseline 68

Table 5. 3 Variables with a Significant Interaction Effect or Main Effect of Group or Time 71

Table 6. 1 Distribution of Primary Sport Participation 79

Table 6. 2 Participant Data 82

Table 6. 3 Analysis of Variance Results for Knee Joint Moment PC Features During Overground Walking 83

Table 6. 4 Post Hoc Analysis for PC Features with Significant Interactions 85

Table 6. 5 Post Hoc Analysis for PC Features with Significant Main Effect of Puberty 85

Table 6. 6 Analysis of Variance Results for Knee Joint Moment PC Features During Overground Running 88

Table 6. 7 Discriminant Function Standardized Canonical Coefficients and Classification Rates for each LDA 92

Table 7. 1 Subject characteristics 103

Table 7. 2 Subject characteristics of the worsening and non-worsening groups 106

Table 7. 3 Baseline MRI findings for XC and BB 107

Table 7. 4 Generalized Estimating Equations Results for Knee Joint Moment Features..... 108

List of Figures

Figure 2. 1 Illustration of Simplified External KAM Calculation 13

Figure 3. 1 Marker Position for Three-Year Progression Study 36

Figure 3. 2 Marker Positions for the Longitudinal Study on Adolescent Biomechanics and the Collegiate Athlete Joint Health Study 37

Figure 3. 3 Segment Anatomical Coordinate Systems and the Joint Coordinate System Used for the Three-Year Progression Study 39

Figure 3. 4 Segment Anatomical Coordinate Systems and the Joint Coordinate System Used for the Adolescent Biomechanics and Collegiate Athlete Studies 40

Figure 3. 5 Standard Examples of KL Grades 43

Figure 3. 6 Atlas Images Showing Medial Compartment Narrowing 43

Figure 3. 7 Regional Subdivisions for MOAKS 45

Figure 4. 1 Ensemble Averaged External Knee Joint Moment Waveforms for PG (Red) and NPG (Black). 54

Figure 4. 2 Ensemble Averaged Quadriceps EMG Waveforms for PG (Red) and NPG (Black) (Left Column) 55

Figure 4. 3 Ensemble Averaged Gastrocnemius and Hamstring EMG Waveforms for PG (Red) and NPG (Black) 56

Figure 5. 1 Change in WOMAC Scores from Baseline to Follow-Up 68

Figure 5. 2 Knee Joint Moment Waveforms for Baseline (Solid) and Follow-Up (Dashed) for the Three Groups 69

Figure 5. 3 Three-Year Change for KAM Impulse (Left), KAM PC1 (Middle) and KAM Peak Two (Right) for ASYM (Black), OA (Blue) and PG (Red) 70

Figure 5. 4 Ensemble Average EMG waveforms for LG, MH and VL at Baseline (solid) and Follow-up (dashed) for ASYM (Black), OA (Blue) and PG (Red). 70

Figure 5. 5 Three-Year Change for KFM PC1 (Left), KFM PC2 (Middle) and KRM PC2 (Right) for ASYM (Black), OA (Blue) and PG (Red) 72

Figure 5. 6 Three-Year Change for LG PC1 (Left), VL PC1 (Middle) and MH PC2 (Right) for ASYM (Black), OA (Blue) and PG (Red) 72

Figure 6. 1 KAM Mean Waveforms for Each Puberty Category (Top Left), Ensemble Average Waveforms for Each Sex (Top Right), and KAM PC1 Scores (Bottom) 84

Figure 6. 2 KAM Mean Waveforms for Each Puberty Category for Females (Top Left) and Males (Top Right), and KAM PC1-3 Scores (Bottom) 86

Figure 6. 3 Puberty Mean KRM Waveforms (Top Left) and Sex Mean Waveforms (Top Right) and KRM PC1 Scores (Bottom Left) and KRM PC2 Scores (Bottom Right) 87

Figure 6. 4 Running KAM Mean Waveforms for Each Puberty Category for Females (Top Left) and Males (Top Right), and KAM PC1-3 Scores (Bottom) 89

Figure 6. 5 Puberty Ensemble Average Running KFM Waveforms (Left) and PC1 Scores For Each Puberty Stage (Right) 90

Figure 6. 6 Puberty Mean Running KRM Waveforms (Top Left) and Sex Mean Waveforms (Top Right) and KRM PC1 Scores (Bottom Left) and KRM PC2 Scores (Bottom Right) 91

Figure 6. 7 Scatter plot of Pre-Early-Mid (Red) and Late-Post (Green) Walking and Running Discriminant Scores 93

Figure 7. 1 Mean Knee Joint Moment Waveforms during Walking (Left) and Running (Right) for MRI-Worsening and Non-Worsening Groups 109

Figure 7. 2 Mean Knee Joint Moment Waveforms during Walking (Left) and Running (Right) for BB and XC Groups 110

Abstract

Objective: Knee Osteoarthritis (OA) can be the result of both mechanical and biological events that interfere with normal joint function. The aims of this thesis were to (1) quantify the biomechanical factors that differentiated structural OA progression, (2) determine if knee biomechanics changed over time in response to structural changes, (3) identify sex and puberty specific differences that may mechanically predispose females to OA, and (4) determine the response of healthy knee joints to a high dose of sport to assess the contribution of knee mechanics to tissue damage.

Methods: A three-year prospective study of knee OA progression addressed Aim 1 by measuring principal components (PCs) of knee moments and muscle activation patterns that differentiated the progression group, and for Aim 2, identified PC scores that changed with and without knee OA diagnosis and progression. A cross-sectional comparison of PCs between sex and puberty cohorts addressed Aim 3. A five-month prospective study of female varsity athletes addressed aim 4, where the knee joint response to one season of sport was measured with MRI.

Results: (1) The peak KAM was higher prior to structural progression confirming previous findings however greater lateral muscle activity with progression was contradictory. (2) Knee joint moment and muscle activation patterns changed over the three years, with the greatest magnitude of difference occurring in the progression group. (3) Later puberty stages had higher frontal and transverse plane moments when walking and altered patterns of frontal and transverse plane moments when running. (4) The athletes that had worsening of MRI features had different features of knee joint moments characterizing lower magnitude joint loading.

Conclusions: Higher frontal and altered transverse plane knee moments in the OA progression group highlights the sensitivity of the osteoarthritic knee joint to altered mechanical load. The change in mechanics over time reinforces the dynamic mechanical environment with OA and the sensitivity of gait to this changing structure. The lack of congruence of MRI changes of asymptomatic knees with mechanical features related to knee OA suggests that longer prospective studies are needed to trace mechanical factors in young adulthood to knee OA initiation.

List of Symbols and Abbreviations

3D	Three-Dimensional
$\vec{a}$	Acceleration
ACL	Anterior Cruciate Ligament
ACR	American College of Rheumatology
ACS	Anatomical Coordinate System
ANOVA	Analysis of Variance
ASIS	Anterior Superior Iliac Spine
ASYM	Asymptomatic
BB	Basketball
BME	Bone Marrow Edema
BMI	Body Mass Index
BML	Bone Marrow Lesion
CCI	Co-contraction Index
DOHM	Dynamics of Human Motion Laboratory
EARLY	Early-Puberty
EMG	Electromyography
F	Female
$\vec{F}$	Force
GEE	Generalized Estimating Equations
GRF	Ground Reaction Force
Hz	Hertz
IMU	Inertial Measurement Unit
IRED	Infrared Light Emitting Diode
JCS	Joint Coordinate System
JNS	Joint Space Narrowing
k	Stiffness
KAM	Knee Adduction Moment
KE	Knee Extension
KEM	Knee Extension Moment
KF	Knee Flexion
KFM	Knee Flexion Moment
kg	Kilogram
KL	Kellgren-Lawrence

KRM	Knee Rotation Moment
LATE	Late-Puberty
LDF	Linear Discriminant Function
LG	Lateral Gastrocnemius
LH	Lateral Hamstrings
M	Male
m	Mass
m/s	Meters Per Second
m2	Meters Squared
MCID	Minimum Clinically Important Difference
MCL	Medial Collateral Ligament
MG	Medial Gastrocnemius
MH	Medial Hamstrings
MID	Mid-Puberty
mLAB	Motion Laboratory of Applied Biomechanics
MOAKS	MRI Osteoarthritis Knee Score
Mod-OA	Moderate Osteoarthritis
MRI	Magnetic Resonance Image
ms	Millisecond
MVIC	Maximum Voluntary Isometric Contraction
Nm	Newton Meters
NPG	Non-Progression
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatology
PC	Principal Component
PCA	Principal Component Analysis
PF	Plantarflexion
PG	Progression
POST	Post-Puberty
PRE	Pre-Puberty
PSIS	Posterior Superior Iliac Spine
RF	Rectus Femoris
TE	Echo Time
TKA	Total Knee Arthroscopy

TR	Repetition Time
VL	Vastus Lateralis
VM	Vastus Medialis
vs	Versus
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WORMS	Whole Organ Magnetic Resonance Imaging Score
$\vec{x}$	Deformation
XC	Cross-Country

Acknowledgements

O S F M F M A C A D I A B A S K E T B A L L W H Q J V Q B X
Y S S N A I R D A C A D I A U N I V E R S I T Y H D T O L G
G U R M O E N N S T A R B U C K S C O F F E E W G G K H U E
M E T O A M T T J B S D R S I Y J F V V A F K D L Q S I U T
K S M Y S I T C R C N X I E D T X R W Q K B O X L O Z M W L
G C K V W I L L I A M S T A N I S H F W I M H E A K Z J X R
B W T R M A V L S T H L J N C S A S F O Y Q Q N G G H I W F
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N S I G V X Q X I M Y B V H W N T W B B Q B G D M S X R P L

CHAPTER 1
Introduction

1.1 Motivation

Knee Osteoarthritis (OA) is a prevalent degenerative joint disease that involves all tissues of the synovial joint and can be the result of both mechanical and biological events that interfere with normal joint function of the knee (Brandt et al., 2008). Knee OA is the 11th highest contributor to global disability (Cross et al., 2014) and the most common cause of functional limitations in older adults (Guccione et al., 1994), affecting women at a disproportionally higher rate (Buckwalter and Lappin, 2000). The disease starts at the molecular level with abnormal joint tissue metabolism and progresses to physical disorders characterized by cartilage degradation, osteophyte formation, joint inflammation and loss of normal joint function (Hochberg et al., 2008). The illness – what the patient feels (Helman, 1981) – is characterized by joint pain, swelling and stiffness. As symptoms progress, physical activity is subsequently limited, and this ultimately leads to loss of independence and reduced quality of life.

When knee OA is considered as a biomechanical problem, walking gait has been the predominant model used to study the loading environment of the joint, as daily walking is the most common type of unstructured physical activity in older adults (Mota and Esculcas, 2002). The tibia is typically chosen as the system of interest due to the high prevalence of medial compartment tibiofemoral knee OA (Wise et al., 2012), with predominant damage occurring on the medial tibial plateau. Abnormal macroscale mechanical forces associated with an individual's joint mechanics are translated into nanoscale forces at the level of the extracellular matrix and cell membranes (Erdemir et al., 2015). This can lead to mechanical failure at the molecular level, which may eventually lead to joint-level pathology. This mechanically centric framework is associated with the general hypothesis that knee OA is the result of abnormal loading of the knee joint and the subsequent scientific pursuit of identifying "normal" and "abnormal" patterns of joint loading. Due to the difficulty of determining *in vivo* joint contact forces, indirect measures are commonly used in research, such as the calculation

of resultant joint moments: a generalized measure of joint loading not associated with specific anatomical structures.

Freund (1939) proposed that the load-response of articular cartilage follows a U-shape relationship: that an optimal range of loading exists which is conducive to articular cartilage health, above and below which the tissue integrity is compromised. This theoretical model is still used today to describe two distinct failure modes of articular cartilage and potential pathways to knee OA, specifically underuse and overuse; however, specific knowledge of a generalized safe upper limit for knee joint load exposure does not exist for healthy or osteoarthritic joints. This is in part due to a lack of understanding of the transfer of macroscale forces to nanoscale forces in the human knee joint (i.e. the distribution problem/force sharing), the heterogeneity of knee OA, and the tolerance (or necessitation) for load variance across knee joint structures in diseased and non-diseased states. While there is indirect support for the role of abnormal knee mechanics in progression of knee OA (Miyazaki et al., 2002, Bennell et al., 2011, Chang et al., 2015), a clear connection between altered joint mechanics and detrimental changes in the knee joint loading environment has not been well established.

This thesis is centered on the theory that overloading the knee joint, quantified through *in vivo* joint mechanics and high magnitude or sustained loading features, triggers the onset of knee OA. This theory is extended to the progression of the disease, where an increased rate of progression may also be associated with joint overloading. The motivation for this thesis is to add to the knowledge related to the full scope of disease process of knee OA which necessarily includes the adaptation and deterioration of healthy joint tissue as underlying mechanisms of disease progression.

1.2 Thesis Aims and Objectives

AIM 1: To compare the knee joint moments and muscle activation patterns during overground walking between participants who had an increase in medial joint space narrowing score at three-years and those who did not.

Rationale: It is currently not known if there are different mechanical factors involved in accelerated rates of knee osteoarthritis structural progression. Data regarding the role of

the transverse plane moment along with the contributions to joint loading from muscle activity, a primary contributor to the joint loading environment, is not well represented in the current literature on knee OA radiographic progression. The objective of this study was to understand if a three-year end point corroborates what has been shown for longer term radiographic progression or provides more insight into factors that may be implicated in more accelerated radiographic progression than those shown previously.

Hypothesis 1: The external knee adduction moment will be higher at baseline for subjects with medial joint space narrowing after three years, confirming the results of previous longer-term radiographic progression studies (Miyazaki et al., 2002) and results of studies using MRI defined features of progression of medial compartment knee OA (Chang et al., 2015, Bennell et al., 2011).

AIM 2: To compare three-year changes in knee joint mechanics and muscle activation patterns during gait in individuals with and without knee osteoarthritis diagnosis and structural progression.

Rationale: Longitudinal changes in gait may reflect a shift away from optimal joint mechanics and mark the start of a decline in general knee joint function, either triggering the OA process or accelerating an existing process. The motivation for understanding the stability of knee joint loading over time in an asymptomatic adult population is to strengthen the ability to associate longitudinal changes in the progression and osteoarthritic groups to the presence of knee OA and structural progression, and not part of the normal aging process.

Hypothesis 2: The gait of the knee OA progression group will deteriorate from baseline to three years towards gait patterns consistent with more severe radiographic knee OA, specifically with increases in the knee adduction moment magnitude (Mundermann et al., 2004) and decreases in knee flexion and extension moment magnitudes and ranges over the gait cycle (Astephen et al., 2008a). Without changes in symptoms or joint structure, the asymptomatic and knee OA (without progression) groups will not have significant

deviations in gait mechanics, and therefore will display a "stable" gait pattern over three years.

AIM 3: To examine the effect of sex and maturation (puberty) on pattern and magnitude features of knee joint moments during walking and running gait in healthy adolescent athletes.

Rationale: Abnormal frontal plane knee biomechanics have been associated with the sex disparity of joint injuries (Sutter et al., 2015) and identified as risk factors for the later development of musculoskeletal disorders, including knee OA (Lynn et al., 2007). Describing the change in relative magnitude and patterns of load acting at the knee joint as a function of puberty stage and sex may provide insight into the role of joint mechanics during critical stages of joint adaptation and development, and how these may differ for the female and male joints. If walking gait results in the same sex and puberty differences, walking may be used as a sub-maximal assessment of joint function in athletes.

Hypothesis 3a: There will be significant interaction effects (sex, puberty stages) in knee joint biomechanics during walking and running gait, where significant sex differences in the dynamic pattern of joint moments will become evident after puberty (late-puberty, post-puberty).

Hypothesis 3b: Later puberty stages will be associated with greater magnitudes of knee joint moments.

Hypothesis 3c: Sex and puberty have the same effect on knee joint mechanics during walking and running gait, where the sex, puberty and interaction effects of knee joint moments during running will be the same as those identified during walking.

AIM 4a: To compare the incidence of MRI-defined joint structural changes using the MRI Osteoarthritis Knee Score (MOAKS) after one season of varsity-level basketball and cross-country running for young healthy adult females.

Rationale: One season of varsity sport participation represents a high dose of joint loading and therefore stresses the knee joint. Both long-term repetitive loading and instantaneous overload can theoretically result in micro-injury to the joint tissues (Gardiner et al., 2016). Basketball athletes experience high impact (short-term) loads in a stochastic manner, which are hypothesized to damage cartilage at the cellular and structural level, and damage subchondral bone (Gardiner et al., 2016). The difference in the type of load exposure between basketball and cross-country athletes facilitates research into the separate roles of joint mechanics and physical activity type on joint damage. By contrasting the knee joint response in basketball and cross-country athletes, the effect of load-type can be studied, while person-specific joint load patterns can be used to explore the contribution of joint mechanics within each load type to knee joint tissue injury.

Hypothesis 4a: The response in the knee joint will be specific to the type of load, where one season of basketball participation will result in greater signal changes, measured with MOAKS, than one season of cross-country running. Due to the high external abduction moment incurred during basketball-specific movements (Hewett et al., 2005), and high patellar-femoral forces during jumping, it is further hypothesized that there will be greater lateral-tibial and patellofemoral signal changes in basketball athletes.

AIM 4b: To compare the knee joint moment magnitude and features during walking and running gait between those athletes who show any worsening change in components of the MOAKS score compared to those who did not show change over one season.

Hypothesis 4b: Knee joint moment magnitude and pattern features during walking and running gait will differ between those athletes who show any worsening (change in components of the MOAKS) compared to those who did not show change over one season.

1.3 Format of Thesis

This thesis comprises three studies which address the four aims of this thesis by exploring the link between joint mechanics and the changing structure of tissues in the knee. Chapters four to seven are written in manuscript format, addressing the separate aims of the thesis. The background and literature review in the second chapter frames knee OA as a biomechanics problem, and summarizes the current literature regarding the characterization of abnormal forces related to knee OA and its progression. Although each manuscript-style chapter contains methods, the third chapter is a detailed overview of the methods used, including a description of the principal component analysis (PCA) of two large datasets of gait data that was performed to extract stable features of knee joint kinetics and muscle activation specific to each population (adults with and without OA, adolescent athletes).

Chapters four and five address aims one and two of the thesis respectively and are focused on the adult knee joint and the mechanical factors linked to the three-year progression of medial compartment knee OA. Three-years represents an accelerated timeline for structural progression that has not previously been investigated as a viable alternative to longer term assessments of progression. Chapter four was written for, and has been published in Clinical Biomechanics (Davis et al., 2019). Chapter five explores the differences in longitudinal stability of biomechanical features of knee joint loading and muscle activation patterns during gait with and without knee OA diagnosis and structural progression.

While there is utility in identifying modifiable mechanical factors in knee OA progression, the prevention of knee OA requires research into young, healthy joints and the mechanical response of these joints to abnormal loading. Chapters six and seven shift the attention to the developing knee joint and the earliest signs of knee joint tissue change as a result of participation in sport in answering aims three and four of the thesis. Chapter

six details the differences in knee joint kinetics during overground walking and running gait at each puberty stage, addressing aim three. Chapter 7 is a pilot study that was designed to address aim four, and to test the ascending portion of the load-dose response of knee joint tissue and the potential for overloading of healthy female knee joints due to participation in elite level sport using the MRI osteoarthritis knee score (MOAKS). The thesis is summarized in Chapter 8 along with a look to the future of this research topic.

CHAPTER 2
Background

2.1 Knee OA: A Biomechanics Problem

For centuries, scientists across multiple disciplines have been looking for a good explanation for knee osteoarthritis (OA) in order to make progress towards a fundamental understanding of the pathology and within that understanding, find a cure. This pursuit has appeared stagnant at times, as there remains no cure, no effective non-surgical treatment to stop the progression of the disease, and little hope for those who are not surgical candidates. There has been, however, a steady increase in the knowledge of the disease and the factors related to its pathogenesis, including biomechanics. The function of synovial joints is to facilitate motion and transfer forces (Nigg and Herzog, 2007) and the role of the knee joint is to permit flexion, extension and a small amount of internal and external rotation of the lower leg relative to the thigh while supporting the body (Grood et al., 1988). The knee, therefore, has a predominant role in most movements of the lower extremity, including walking, running and jumping. The knee sustains relatively high forces and moments as it is situated between the two longest levers in the body: the femur and tibia. It is mechanically and biologically complex and intrinsically unstable, factors that contribute to the high injury rates (Ingram et al., 2008) and common occurrence of OA (Buckwalter and Lappin, 2000).

When viewed as a biomechanics problem, knee OA can be described as the effect of abnormal forces acting on the knee joint (Herzog et al., 2004). Many years of research have been devoted to describing the magnitudes and patterns of forces (or their surrogates) that act on the joint during various activities to determine what is normal and what is abnormal joint loading in the context of knee OA. A time-varying force can be described by its overall magnitude, orientation, rate of increase, duration and frequency and therefore can be normal or abnormal in any of those dimensions. The most common view of abnormal loading in reference to the pathomechanics of knee OA is abnormally high forces and the respective overload-theory of knee OA initiation and progression (Arendt et al., 2014, Radin, 1982, Felson, 2004, Felson, 2013). Within this operational

theory, the knee joint can be viewed as a structure that has a specific capacity for load, above which, damage occurs (Gardiner et al., 2016). Failure can occur when a local stress of a component tissue exceeds the ultimate stress, such as excessive impact loading (Gardiner et al., 2016), or it can fail chronically, as a product of interfacial problems or fatigue failure (Nigg and Herzog, 2007).

Women have a 1.5-4 times greater risk for knee OA than men (Tsai and Lui, 1992; Buckwalter and Lappin, 2000) with disease of the medial compartment being four times more common than lateral OA (Ledingham et al., 1993). The differential risk could be attributed to sex specific difference in the forces acting on the joint, different system of interest (sex specific geometry or mechanical properties of the knee joint), or a different biological or mechanical response to abnormal loads. Sex specific differences in the knee joint anatomy emerge during periods of adolescent development (Jones et al., 2000; Jones et al., 2003). Females have significantly less knee articular cartilage than males (Jones et al., 2000) where the sex disparity is greatest in the medial compartment. Male adolescents have been shown to accrue articular cartilage at a faster rate than females (Citcuttini et al., 1999; Jones et al., 2003), and males and females that engage in higher intensity physical activity accrue twice as much cartilage at the tibia (Jones et al., 2003). Females and males have differences in strength (Cureton et al., 1988), joint laxity (Bridges et al., 1992) and muscle activation patterns (White et al., 2003), which have been identified as risk factors for knee OA (Culvenor et al., 2017).

The knee is “loaded” constantly throughout the day. The most common dynamic task performed daily is walking, a fundamental aspect of independent living, and is the most studied movement with respect to the pathomechanics of knee OA in humans. The knee is subjected to large loads during walking, with peak loads well above body weight (Anderson and Pandy, 2001, Glitsch and Baumann, 1997, Heinlein et al., 2009). The repetitive impulsive loading of the knee joint during walking is thought to provoke the changes within the joint necessary to initiate the OA process in knees that are at risk, based on abnormal joint alignment and abnormal movement patterns and muscular control (Andriacchi et al., 2004). Shifting the pattern of joint contact from regions well-adapted to specific loading patterns to regions poorly suited for such loads is a proposed mechanism of initiation for idiopathic knee OA (Andriacchi et al., 2009, Andriacchi et

al., 2004, Chaudhari et al., 2008). Repetition of abnormal loading is thought to eventually damage the collagen matrix and initiate OA development (Anderst and Tashman, 2009, Andriacchi and Mundermann, 2006, Carter et al., 2004, Setton et al., 1999).

2.2 The Knee Joint Organ

In a healthy knee joint, bones, ligaments, muscles, cartilage, and other joint tissues function as a biomechanical organ system that supports the body and maintains proper movement of the tibia relative to the femur. Articular cartilage, bone and synovial fluid comprise the parenchyma of the knee joint – providing the physical requirements for the articulation of the femur with the tibia and the required properties for smooth motion and the transfer of forces. The remaining components (ligaments, capsule, muscles, tendons, nerves, etc.) comprise the stroma and serve to maintain the knee's structure and stability.

The majority of physical maturation of the knee occurs within the first year of life (Clark and Ogden, 1981), however the knee is a dynamic system that continuously evolves through processes of tissue remodeling (Carter et al., 2004). Children gain articular cartilage during periods of skeletal growth, and there is evidence of a load-dose relationship for accrual rates (Jones et al., 2003). In addition to conditioning cartilage as it develops, loading of the knee joint is critical for maintaining its biological balance. Articular cartilage is avascular and alymphatic and the transport of nutrients to the cells and removal of waste products occurs through pumping synovial fluid in and out of the joint with motion (O'Hara et al., 1990).

The knee joint is passively stabilized by ligaments and actively stabilized by surrounding muscles. Two collateral ligaments outside the joint capsule and two cruciate ligaments inside the joint capsule maintain joint alignment and stabilize the knee. The medial knee compartment is referred to as the "stable knee compartment" (Hirschmann and Müller, 2015). There is less rotation excursion on the medial side of the joint because the axis of internal-external rotation typically stays in the medial compartment (Müller, 1982). The lateral compartment is more mobile because there is no ligament directly connecting the tibial and the femur in the lateral compartment. Two fibrocartilaginous menisci are positioned between the medial and lateral femoral condyles and the tibia,

which accommodate changes in the articular surfaces during activity. Lateral menisci are more mobile than the medial menisci, which may contribute to the higher rate of medial side injuries (Hirschmann and Müller, 2015) as fixed menisci are less able to compensate for joint forces and rotations during movement. The medial menisci receive a greater blood supply than lateral menisci and consequently, injuries involving the lateral menisci require longer rehabilitation. Injury to the lateral meniscus, although less common, leads to more rapid development of osteoarthritis (Haviv et al., 2016).

The primary function of muscles surrounding the knee is to produce and control knee motion. The anterior compartment consists of the quadriceps muscles: rectus femoris, vastus lateralis, vastus medialis, and vastus intermedius. The primary function of these muscles is to extend the tibia relative to the femur and provide active stiffness to stabilize the joint. Each muscle in the quadriceps group has a unique origin and common insertion (tibial tuberosity via quadriceps tendon) and innervation (posterior division of femoral nerve). The rectus femoris is biarticular and has a role in hip flexion in addition to knee extension, while the vastii muscles are responsible for knee extension.

The posterior compartment consists of the hamstring muscle group: biceps femoris, semitendinosus and semimembranosus. These muscles have a common origin (ischial tuberosity) and innervation (tibial portion of the sciatic nerve) but unique insertion points. The biceps femoris inserts into the fibular head (lateral), semitendinosus the medial surface of the tibia and semimembranosus inserts on the horizonal groove on the posterior-medial surface of the medial tibial condyle. These three muscles have a dual role in hip extension in addition to knee flexion. The medial and lateral heads of the gastrocnemius muscle are also part of the posterior musculature of the knee. These muscles act primarily as plantar flexors and secondarily as knee flexors. The line of action of these muscles enable active contribution to frontal and transverse plane torque, which may serve a critical role in balancing the external adduction and rotation moments at the knee joint.

2.3 Force Sharing Across the Knee Joint

The mechanically defined knee joint is a complex modified hinge joint and has six degrees of freedom (three rotations and three translations): flexion–extension,

internal–external rotation, adduction-abduction, anterior–posterior translation, medial–lateral translation, compression and distraction. The ten major muscles, four major ligaments and two primary contact areas in the knee joint all contribute to the total net force and moment at the joint. Muscles are primary producers of moments about a joint and therefore movement of the skeleton, however deciphering the precise force generated by each muscle is not trivial. Modeling the knee joint as a mechanical structure results in a greater number of scalar unknowns than the number of system equations. This theoretical problem of relating the global measures of joint loading to the specific loading of joint structures (including ligaments, articular cartilage, muscle/tendons) is referred to as the "general distribution problem in biomechanics" (Crowninshield and Brand, 1981). In human studies, instrumented knee implants that measure the internal forces acting on the replaced joint have provided general estimates of contact forces and helped to improve models (Fregly et al., 2012, for example), however direct measurement of healthy internal joint contact forces is impractical. This barrier is one of the largest limiting factors in studying the load-dose response to the human knee joint.

2.4 Resultant Joint Moments as a Model of Joint Loading in Humans

Net forces and moments acting on the joint, surrogate measures for internal joint forces, are calculated indirectly using sensible approximations, mechanical laws and experimental measurements (Nigg and Herzog, 2007). These net joint forces and moments are not often resolved further into the force and moment contributions of each individual structure due to the aforementioned underdetermined problem when studying knee joint biomechanics (Crowninshield and Brand, 1981). There are two ways to quantify joint moments. The first is a quick approximation by relating the resultant ground reaction force vector to the perpendicular distance from the rotation center of a joint (Nigg and Herzog, 2007). For example, a simplified equation for the external knee adduction moment (KAM) works under the assumptions that the ground reaction force and the lever arm from the knee joint center to the ground reaction force are the primary variables contributing to the KAM magnitude (Lewinson et al., 2015):

$$KAM_Y = r_z GRF_x + r_x GRF_z \quad (1)$$

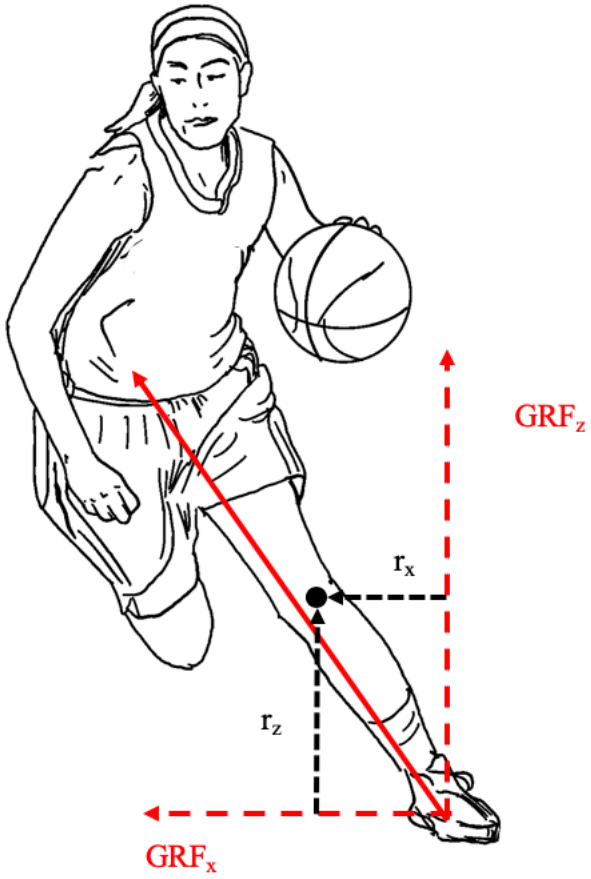


Figure 2. 1 Illustration of Simplified External KAM Calculation

In this equation, GRF_x is the mediolateral ground reaction force, GRF_z is the vertical ground reaction force, r_x is the mediolateral distance from the ground reaction force center of pressure to the knee joint center, and r_z is the vertical distance from the ground reaction force center of pressure to the knee joint center. This method does not take into account the angular acceleration and/or the mass moment of inertia of the segments. It does not consider local segment coordinate systems, and therefore the orientation of the segment, and assumes the lower leg and foot act as one rigid body. Many of these assumptions are violated when studying overground walking (Lewinson et al., 2015). In addition, the method is limited to timepoints when the foot is in contact with the ground (for example, the stance phase of walking), and errors increase at the more proximal joints. Alternatively, inverse dynamics is a mechanical analysis of a system that

determines forces from kinematics (Nigg and Herzog, 2007). In this approach, equations of motion are solved algebraically using experimentally collected external ground reaction forces and body positions to determine net resultant joint forces and moments. Position data is double differentiated to obtain segment linear and angular accelerations which are used in conjunction with the external force, estimated mass and inertial properties of each segment (Vaughan and Davis, 1992). The body is modeled as a series of rigid linked segments, and one segment is considered at a time, starting distally and working proximally until the joint or segment of interest is reached.

The advantages of the inverse dynamics method are the ease of use (relative to more complex forward dynamic models) and ability to understand the implication of and account for a few assumptions (Gordon et al., 2004). Inverse dynamics derives the minimum forces and moments for a given movement. It is the net effect of all bony contact regions, and soft tissue forces (ligaments and muscle-tendons) that produce forces and moments across the joint. Nothing about the details of the internal environment can be inferred from these quantities. The biggest limitations with this method stem from the amplification of noise in marker position data when it is differentiated, and the inaccuracy of scaled segment properties (Buchanan et al., 2004). The most inappropriate use of this method is estimating muscle contributions from net joint moments as there is no way to account for the relative contribution of individual structures within the joint. The internal net joint moment and force can be interpreted as an external joint moment and force by multiplying the inverse dynamics output by negative one.

Anatomical landmarks are used to construct coordinate systems that are anatomically relevant (Cappozzo et al., 1995, Lucchetti et al., 1998). For example, the half way point between femoral epicondyles, easily palpable anatomical locations, provides a good estimation of the knee joint center (although the actual center of rotation may vary depending on the movement (Koo and Andriacchi, 2008)), and the line that passes through these two points, a good approximation for the axis of tibial flexion and extension relative to the thigh. Net resultant moments can be projected onto these anatomical joint coordinate systems (Grood and Suntay, 1983), for example) and normalized to body weight to aid in the interpretation and comparison. Imprecise location of anatomical landmarks and therefore mis-location of the anatomical coordinate systems

and subsequent joint centres, propagates to errors in reported joint kinematics and kinetics (Holden and Stanhope, 1998, Della Croce et al., 1999, Stagni et al., 2000). This has been noted as the greatest source of error in motion analysis, compared to instrument error or skin movement artefact (Cappozzo et al., 1997).

Surface electromyography (EMG) data compliments joint kinetic analysis as it provides insight into muscle activation and, by extension, muscle contributions to load and loading patterns (Soderberg and Knutson, 2000). This information helps to address the shortcomings of net joint moments when activation of antagonistic muscles (commonly referred to as muscle co-activation) is present. EMG is not a direct analog to muscle force, but rather represents the relative activation of the underlying muscle. As resultant joint moments underestimate the joint load when muscle co-contraction is present, EMG has been used to contextualize net joint moment differences when co-activation during gait is present (Childs et al., 2004). Co-contraction indices (CCI) for a variety of muscle pairs (Childs et al., 2004) or a comparison of the relative magnitude and timing of muscle activation (Hubley-Kozey et al., 2008, Hubley-Kozey et al., 2015, Hubley-Kozey et al., 2006) have been used for this purpose.

The result of joint kinetic and muscle activation analysis during gait are time-varying signals, requiring both feature extraction and dimensionality reduction to be able to statistically compare groups or interventions. Features can be selected based on *a priori* clinical or mechanical relevance, or without previous knowledge through the use of pattern recognition techniques. In addition to extracting discrete features that have previously been published, this thesis uses principal component analysis (PCA) as a feature extraction and dimensionality reduction tool. PCA is a common statistical procedure, to convert measured observations into a set of uncorrelated variables called principal components (PCs) (Jackson, 1991). The transformation is defined so the first principal component has the largest possible variance, and each succeeding component is orthogonal with the next highest variance possible. This can be thought of as a rotation matrix that rotates data so that the projection with greatest variance is along the first axis. The PCs are linear combinations of the original variables but differs from linear regression in that PCA minimizes the distance between a data point and the principal component, whereas linear regression minimizes the distance between the response

variable and its predicted value. By retaining the first few PCs that explain the majority of variance within the data for analysis, dimensionality reduction is achieved.

2.5 The Effect of Abnormal Forces: Knee OA and its Progression

A biological system can react to forces biologically, mechanically, or both (Nigg and Herzog, 2007). Mechanical reactions can be deformations (Hooke's Law: $\vec{F} = k\vec{x}$) or accelerations (Newton's Second Law: $\vec{F} = m\vec{a}$). Biological reactions can be anabolic (strengthening, repair), or catabolic (breaking down, weakening). Knee OA is partly a mechanical reaction and partly a biological reaction to abnormal forces acting on the knee joint, characterized by an imbalance in the anabolic and catabolic reactions in the joint tissue and mechanical failure of the joint structure. Bone tissue enters unregulated anabolism, evident by hyper vascularization of the subchondral bone, bone stiffening, and osteophyte formation, while articular cartilage undergoes progressive deterioration (Chang et al., 2005). For example, subchondral bone turnover appears to be increased 20-fold with OA compared to normal bone turnover (Bailey et al., 2004). The disease state is realized when environmental conditions stress the biological system (organ, tissue, cell) beyond its repair capabilities, resulting in mechanical failure (Gardiner et al., 2016). In knee OA, the disease includes focal damage of cartilage and menisci, loss of articular cartilage, abnormal remodeling and attrition of subchondral bone, osteophytes, ligamentous laxity, weakening of muscles and inflammation (Arden and Nevitt, 2006). The strongest person-level risk factors for osteoarthritis include age, sex, family history and obesity, while joint level risk factors include injury and joint loading (Allen and Golightly 2015).

The structural changes that characterize OA at the joint level have been distinguished from the patients' experience of OA as the 'disease' and 'illness', respectively (Lane et al., 2011). Clinical progression, the worsening of the illness, is marked by a change in both the structural severity and expression of symptoms. Examples of clinical progression include the initial diagnosis of OA by an orthopaedic surgeon, following the American College of Rheumatology (ACR) diagnostic criteria (Altman et al., 1986). A second example is the recommendation for total knee joint

arthroplasty (TKA) (Maillefert and Dougados, 2003). The severity of self-reported symptoms are monitored using scales, such as the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index (Bellamy et al., 1988). Both the disease and the illness create a change to the biological system and therefore affect the subsequent biological or mechanical reactions to external forces, however the biomechanical effects of both are not well correlated (Barker et al., 2004).

Structural damage scales, either using radiographic images (Kellgren and Lawrence, 1952, Scott et al., 1993) or magnetic resonance images (MRI) (Peterfy et al., 1999) are used to measure the relative severity of the disease in the joint. Radiographs remain the gold standard imaging tool to aid in the diagnosis of knee OA following the American College of Rheumatology (ACR) Classification Criteria (Altman et al., 1986), and to measure the severity of structural abnormalities (Kellgren et al., 1953, Scott et al., 1993) although much effort is being placed on reaching a consensus on the use of MRI (Hunter et al., 2015, Roemer et al., 2019). The American College of Rheumatology (ACR) Classification Criteria for osteoarthritis, uses the presence of osteophytes as radiographic criteria for clinical diagnosis (Altman et al., 1986). An osteophyte is "a fibrocartilage-capped bony outgrowth" and can be the source of pain and loss of function (van der Kraan and van den Berg, 2007) and early studies of knee OA found that osteophytes increased with increasing degradation of the joint space (Ahlbäck, 1968).

Distilling the image into a useable numeric score for research or clinical purposes requires the extraction of relevant features. One of the most common tools used to do this is the Kellgren-Lawrence (KL) grading scale: a five point (0-4) global composite radiographic OA score which captures a progression of joint level changes associated with worsening of the disease including the presence of osteophytes, reduced joint space between the femur and tibia, and bone deformations (Kellgren et al., 1953). A KL score of two, corresponding to definite osteophytes, is therefore used as a threshold for radiographic osteoarthritis, or in conjunction with symptoms required for clinical diagnosis, as it aligns to the ACR criteria (Altman et al., 1995). The overall KL grade has been evaluated with good within-observer reproducibility, in addition to the independent use of joint space and osteophytes scoring (Spector et al., 1993).

Joint space narrowing, the reduction in space between the femur and tibia, can be measured in millimeters or scored using an atlas on a standard radiograph (Scott et al., 1993). Joint space narrowing scores have been used to confirm the presence of predominantly medial compartment tibiofemoral osteoarthritis and to monitor radiographic progression of OA (Davis et al., 2017). In 2004, OARSI and OMERACT (Outcome Measures in Rheumatology) established criteria that would reflect structural damage that could be used to delineate disease progression in clinical trials and recommended the use of a dichotomous factor (progression versus no-progression) over using the average change in joint space width (Ornetti et al., 2009a).

The idea to use magnetic resonance imaging (MRI) to monitor knee osteoarthritis structural progression was published shortly after Altman's radiographic atlas (Brandt et al., 1991) in response to the lack of sensitivity of radiography to detect subtle changes in bone and inability to directly image articular cartilage. There is a high prevalence of osteoarthritis-related features detected using MRI in people without clinical symptoms or radiographic abnormalities (Guermazi et al., 2012). MRI is currently not used clinically to measure the disease, however research into the creation of a composite MRI based OA severity score for the purpose of diagnosis and quantification of severity is ongoing (Hunter et al., 2011a).

Semi-quantitative scoring of knee osteoarthritis through MRI provides a method for a multi-feature joint assessment (Hunter et al., 2011b), similar to those applied to a radiograph. These scores incorporate features that are either relevant to the functional integrity of the knee or are potentially involved in the pathophysiology of osteoarthritis (Hunter et al., 2011a). Features used in semi-quantitative MRI scoring of knee osteoarthritis include: articular cartilage morphology, subchondral bone marrow lesions (BML) and cysts, osteophytes, the menisci, the anterior and posterior cruciate ligaments, the collateral ligaments, synovitis, joint effusion, bone attrition, intraarticular loose bodies, and periarticular cysts/bursitis (Hunter et al., 2011a). The comprehensive feature set reflect the more modern definition of osteoarthritis that is centered around a disease of the whole joint (Peterfy et al., 1999), and the heightened importance of characterizing all tissues and structures in the knee joint.

In 2004, Peterfy and colleagues published the first MRI-based semi-quantitative scoring system for knee osteoarthritis with a "whole joint" approach: the Whole-Organ Magnetic Resonance Imaging Score (WORMS) (Peterfy et al., 2004). This score included aspects of cartilage and subchondral bone, similar to radiographic scores, but also included lesions around the knee joint (Peterfy et al., 2004). WORMS uses a sub-regional approach to scoring cartilage, dividing the knee joint into thirteen sub-regions: the femur and tibia are divided into anterior, central, and posterior sub-regions, with the femur and tibia further divided into medial and lateral sub-regions. The MRI Osteoarthritis Knee Score (MOAKS) was designed in an effort to evolve scoring methods based on limitations of existing tools (Hunter et al., 2011b). The refinement of the scoring of bone marrow lesions and meniscal morphology was attempted by adding a sub-spinous region and removing some redundancy in bone marrow lesion and cartilage scoring. For this method, the knee is divided into 14 sub-regions for scoring articular cartilage and 15 regions for scoring BMLs. Recently, Roemer et al. (2019) published a new and simplified MRI screening tool: Rapid Osteoarthritis MRI Eligibility Score (ROAMES) targeted for use in disease modifying osteoarthritis drug clinical trials. This is not proposed as a method to measure progression but rather screen potential patients into difference structural phenotypes.

Raynauld et al. (2004) compared cartilage volume loss (MRI) to joint space narrowing (radiograph) and clinical symptoms using 6-month intervals. Almost all participants (27/31) had some MRI calculated volume of cartilage loss over the two years, while only approximately 50 percent of the participants showed a decrease in radiographic joint space width. Similarly, Amin et al. (2005), reported a loss of medial cartilage on MRI in almost half of 224 knees, with only approximately 16 percent of participants showing radiographic progression of the medial compartment based on joint space narrowing. Only 70 percent of those who progressed radiographically also had cartilage loss in at least one of the five regions in the medial tibiofemoral compartment on the MRI. The remaining 30 percent were described as "False Positive" radiographs, which could potentially be explained by meniscal involvement, however meniscal tears and extrusion may be a signal of early OA. The disconnect between radiographic and MRI OA features underscores the increased sensitivity of MRI but potentially the

decreased specificity to disease progression and highlights the need for thresholding some minimum meaningful change for cartilage volume loss with OA.

2.6 Characterizing Abnormal Forces

The upper and lower limits of physiological loading that mark the dose regions of adverse effects (Calabrese and Baldwin, 2001) resulting in knee OA initiation have not been identified. A large barrier to defining this is the lack of understanding of the load-dose response of tissues in the knee joint (Herzog et al., 2004), as current technology does not allow for the accurate measurement of *in vivo* tissue stress-strain states and the corresponding adaptive or degenerative responses. Furthermore, the optimal bandwidth for load is most likely person specific, due to the natural variability of human articular cartilage (Kurkijarvi et al., 2004), and a moving target throughout one's life due to mechanically stimulated biological adaptation of joint tissue (Guilak, 2011). Although the thresholds are not well understood, there is general consensus supporting Freund's (Freund, 1939) U-shaped hypothesis: that articular cartilage and load have a hormetic relationship where above and below some person-specific threshold, tissue integrity is compromised and the cascade of OA initiates.

The biological response of articular cartilage to load occurs within the chondrocytes. These cells sense and respond to physical signals through the integrated actions of ion channels, integrin-mediated connections to the extracellular matrix (ECM), and through deformation of the nuclei (Ramage et al., 2009, Finan et al., 2011, Guilak, 1995). The consensus of multiple studies is that static compression suppresses while cyclic and intermittent loading stimulates chondrocyte metabolism (e.g. (Bonassar et al., 2000, Gray et al., 1988, Guilak et al., 1994). For example, cyclic compression or tension has been shown to upregulate the expression of the cartilage oligomeric matrix protein (COMP) gene, a marker of cartilage turnover, at different frequencies and magnitudes of stress *in vitro* (Wong et al., 1999).

The mechanical response of articular cartilage to load is the result of a combined action of the solid and fluid phases of the tissue. Articular cartilage stiffens non-linearly with increasing strain and strain rate (Langelier and Buschmann, 2003, Li and Herzog, 2004), due to the compaction of the solid matrix, density of proteoglycans and the fixed

charge density which reduces the permeability of the tissue (Mansour and Mow, 1976). The elastic modulus of normal cartilage extracellular matrix alone is well below typical joint stresses by an order of magnitude (Arokoski et al., 1999, Mow et al., 1984, Jurvelin et al., 1987), however dynamic cartilage stiffness can be 10 times higher than the modulus of the extracellular matrix (Jurvelin et al., 1990, Jurvelin et al., 1997) due to interstitial fluid pressurization. This pressurization provides a shielding mechanism for the collagen matrix against mechanical failure (Soltz and Ateshian, 1998). Increases in proteoglycan content resulting from a history of high compressive stress increases the hydration and swelling pressure, enabling it to withstand higher compressional forces (Yanagishita, 1993), while there is rapid loss of proteoglycans in joints that are immobilised or in disuse (Guilak, 2011).

The link between disuse and OA was supported by the early observations of Müller (Müller, 1929), who hypothesized that a pumping mechanism was necessary for cartilage nutrient transport and therefore a minimum amount of intermittent pressure was essential to maintain articular cartilage health. By studying the joints of cadavers, Harrison et al. (Harrison et al., 1953) proposed the idea of the "unused arc" as the catalyst for OA development in the hip – suggesting that it was the areas that did not receive enough load that were most vulnerable to OA initiation. The underload theory for OA initiation was further supported by Videman (1987) via evidence from animal experiments that showed immobilization initiated osteoarthritic changes in the joint. Alexander (2004) proposed a need to return to the unused arc paradigm of Harrison et al. (1953) and suggested that it was the lack of synovial clearance that perpetuated a joint environment conducive to OA. Alexander (2004) believed this could separate idiopathic OA from post-traumatic OA.

Despite this relationship to underuse, the ascending portion of the load-dose response has garnered more attention. OA has historically been referred to as a "wear and tear" disease due to the prevalence of OA in individuals who appear to have overloaded their joints (Kellgren and Lawrence, 1952, Kellgren et al., 1953). A field survey published in 1952 found that miners suffered more disability from knee pain than the general population (Kellgren and Lawrence, 1952). The follow-up to this study was a radiographic and clinical study of workers between the ages of 40 and 50, including

office workers (clerks and administrative staff), manual workers (blacksmiths, machinists, carpenters, painters, and general labourers), and miners (Kellgren and Lawrence, 1952). Of those included in the study, seven percent of miners and manual workers had physical signs and symptoms of knee arthritis (clinical knee OA), compared to two percent of office workers. Forty percent of miners had slight or severe radiographic evidence of knee OA, compared to only 22 percent of manual workers and 10 percent of office workers.

While it was presumed from these early studies that abnormally high repetitions of the back and forth motion wore out the joint, the discovery of the low friction environment of the knee joint (Radin et al., 1970) led Radin et al. (1972) to dismiss this idea of frictional wear and propose a theory that impulsive loading was responsible for OA initiation. The theory followed that impulsive loading could lead to microfracture of trabecular bone, stimulating bone remodeling according to Wolff's law (Wolff, 1892). The remodeling would result in stiffening of the bone, and less shock attenuation capacity, thereby increasing the stress on articular cartilage. It was hypothesized that this would cause cartilage breakdown and the joint to degenerate. Experiments using animal models have displayed damage to articular cartilage and subchondral bone when subjected to repeated acute (50 ms, onset to peak) impulsive loading of the knee, whereas loads of similar or greater magnitude were not detrimental if applied over a longer period (500ms) (Radin, 1985). The fatigue life (number of loading cycles until failure) of articular cartilage decreases exponentially as the peak stress per loading cycle increases (Weightman et al., 1978 1978), providing evidence that impulsive loading may damage the micro-structure of articular cartilage extracellular matrix (Miller, 2017).

Radin et al. (1982) theorized that long term exposure to impacts with hard ground could lead to degenerative changes in the subchondral bone and articular cartilage based on a study of the effect of walking on concrete to the knees of sheep. Voloshin (1988) described a similar mechanism where impact loading could cause fractures of the subchondral bone, which eventually would lead to thickening and stiffening of the bone, subjecting cartilage to increase stresses from normal activities. This theory is only loosely supported by studies on humans, where subjects with knee pain have "harder" heel-strike (Radin et al., 1991b), and a decreased ability to attenuate impacts following meniscectomy

(Voloshin and Wosk, 1983). The reliance on the ground to stop the motion of the foot during walking varies between individuals (Whittle, 1999), and can result in high variations in the resulting impact force acting on body, and therefore articular cartilage and subchondral bone. More recent studies have contradicting results where some have shown OA individuals to have a distinct heel strike transient (Liikavainio et al., 2007), while others failed to measure differences in impact loading between OA and control subjects (Kean et al., 2017).

2.7 Sport Participation: An Overload Model of Knee OA Initiation

Participating in sport can subject the knee joint to extremely high magnitude loads (Buckwalter and Lane, 1997b) at extremely high volumes. If abnormal mechanical loading is a cause of OA (Saxby and Lloyd, 2017), and if sport participation involves abnormal joint loading, then it is logical to question whether sport participation leads to higher rates of knee OA. Whether or not sport involves physiologically abnormal joint loading is not well understood as there is a lack of prospective data on the changes in joint tissue health following a bout of intense sport participation. Sport is associated with increased rates of knee injuries, with female athletes sustaining more injuries than male athletes (Arendt and Dick, 1995; Powell et al., 2000). Knee osteoarthritis is initiated by micro- and macro-injuries to the joints (Kraus et al., 2015), and while there is information on the relative rates of sport induced macro-injuries, less information is available on micro-damage to the knee joint. Sport participation is a broad category that includes many forms, intensities, and durations of physical activity and therefore is associated with many types of joint load histories and a range of potential risk for knee OA initiation.

Sports that involve twisting, turning, and jumping impart high biomechanical forces to the knee joint, and have been associated with joint degeneration that would likely lead to OA (Radin et al., 1991a, Felson et al., 2000, Muthuri et al., 2011). Athletes who practice sports including rapid acceleration and deceleration or continuous training with high impact on joints, or who compete at elite levels for prolonged periods of time, present greater likelihood of developing OA even without incurring a major knee injury (Kujala et al., 1994, Saxon et al., 1999, Kujala et al., 1995, Spector et al., 1996,

Buckwalter and Lane, 1997b). This finding has been repeated in studies that have shown a higher incidence of OA in knees and ankles of former professional soccer, volleyball and basketball players than in those of the normal population (Drawer and Fuller, 2001). Compared with unexposed persons, participants in soccer, competitive weightlifting, and wrestling had a three to seven times higher prevalence of knee OA (Driban et al., 2017). Studies focused on the occurrence of knee OA (diagnosis based on arthroscopy or self-report) among former elite athletes from various team sports (ice hockey, basketball, handball), presented prevalence rates between 16 and 95 percent (Kettunen et al., 2001, Nebelung and Wuschech, 2005, Tveit et al., 2012).

Unrecognized joint injuries (micro-injuries) may be a risk factor for OA and confound the retrospective study of idiopathic OA. This may be of particular importance in individuals engaged in sports associated with high levels of impacts and torsional loading (Buckwalter, 2003). Similar to the discordance between OA structural disease and the manifesting illness (Barker et al., 2004), positive MRI findings of joint micro-damage are not always symptomatic, especially among athletic populations (Brunner et al., 1989, Connor et al., 2003, Major, 2006). Previous studies of asymptomatic knees of collegiate and professional basketball players have shown rates of one or more abnormalities in up to 89% of knees imaged, including high rates of articular cartilage lesions (41%–50%), meniscal lesions (20%–54%), bone marrow edema (lesions) (BME) (25%– 41%), joint effusion (29%–35%), and patellar tendinopathy (24%–39%) (Kaplan et al., 2005, Major and Helms, 2002, Walczak et al., 2008, Pappas et al., 2016). It is not known if these incidences are related to the future development of knee OA. Only a few studies have measured the effect of sex on the occurrence of MRI signal changes. No significant differences were found in overall prevalence or severity of any knee MRI feature between male and female volleyball players (Boeth et al., 2017) or long-distance runners (Schueller-Weidekamm et al. 2006).

There is conflicting evidence as to whether participation in running is linked to an increased risk of knee OA (Spector et al., 1996, Kujala et al., 1999, Driban et al., 2017, Lo et al., 2017), with an abundance of studies suggesting no association between running and knee OA (Lane et al., 1986, Leech et al., 2015, Miller, 2017). The lack of OA in runners is seemingly in direct conflict with the overload theory of knee OA initiation as

peak loads during running can be up to three times higher than walking (Pandy, 2010, Sasaki and Neptune, 2010). Miller (Miller, 2017) suggested that either running conditions knee articular cartilage, raising its intrinsic threshold to handle high loads, or that peak contact force or surrogates of the peak are not the most important loading feature in relation to knee OA. While Miller (2017) argued that the per-unit-distance load is not greater for running than for walking, his argument failed to account for the longer distances traversed by runners compared to walkers. Epidemiological data indicate that long-distance runners are at high risk for OA if they have a pre-existing joint injury, or if athletes participate at the most competitive level (Lequesne et al., 1997). Prospective research found a dose-response for increased risk (Wang et al., 2011) and elite-level long-distance running has been associated with increased risk for knee OA (Driban et al., 2017). It is therefore likely that at a sufficiently large volume, the knee loading associated with running can be detrimental to joint health.

The conditioning hypothesis of running (Miller, 2017) is supported by cadaveric studies that found a correlation between the prevalent stresses arising during locomotion in different joint areas and the cartilage properties in the corresponding areas (Swann and Seedhom, 1993, Yao and Seedhom, 1993, Shepherd and Seedhom, 1999). Articular cartilage which is regularly subjected to high levels of stress has a higher content of proteoglycans (Slowman and Brandt, 1986, Kiviranta et al., 1987) and is stiffer (Swann and Seedhom, 1993) than a cartilage exposed to low stress levels. Knee cartilage glycosaminoglycan content, which affects lubrication and shock absorption, was greater in recreationally active individuals than in sedentary individuals, and greater in high-volume runners than in recreationally active individuals (Tiderius et al., 2004).

2.8 Joint Moments, Muscle Activation and Knee OA

Due to the long duration of disease progression and the silent nature of idiopathic disease initiation, most biomechanics research on humans have been limited to comparing the mechanics of those with established (clinically diagnosed) knee OA to those without (Landry et al., 2007a) for example), or comparing those with radiographic features of knee OA at varying levels of severity (Astephen et al., 2008b) for example). This cross-sectional approach to understanding the role of mechanics impairs the

separation of abnormal forces that cause knee OA and its progression, from abnormal forces that result from OA. The only longitudinal study to date on joint loading and the initiation of symptomatic knee OA found that older adults who developed knee pain had greater peak knee adduction moments during activities of daily living at baseline (Amin et al., 2004). Regardless of mechanism of initiation, the presence of knee OA changes the way individuals move and load their joint, where the severity level of OA (how compromised the structure and how severe the symptoms are) has been associated with different patterns of joint kinetics, and muscle activation (Astephen et al., 2008a, Creaby et al., 2010, Foroughi et al., 2009, Heiden et al., 2009, Hubley-Kozey et al., 2009). Identifying consistent trends in the biomechanical features that separate knee OA from asymptomatic joints may lead to a strengthened understanding of the progression of functional deficits with the disease.

Higher than typical external knee adduction moments (KAM) during walking gait have been implicated as a mechanical factor related to knee OA by overloading the medial compartment of the knee joint (Schipplein and Andriacchi, 1991). There are four main magnitude features that are extracted from the KAM waveform: the first peak (and often maximum value) occurring during weight acceptance, the mid-stance minimum, the second (late stance) peak during terminal stance, and the impulse over the entire stance phase. The relative magnitude (ranges) between these features, and the timing of these features have also been studied relative to knee OA. There are, however, conflicting results regarding differences in these moment features with knee OA (Mills et al., 2013). Some studies have reported higher peak KAM with knee OA (Baliunas et al., 2002, Hurwitz et al., 2002) while others have reported no difference (Mundermann et al., 2004, Landry et al., 2007a, Astephen et al., 2008a, Zeni and Higginson, 2009). A difference in the late stance KAM between moderate severity (KL 3) and controls was reported (Thorp et al., 2006), however others have found no differences in late stance relative to early stance with OA (Landry et al., 2007a, McKean et al., 2007). The mid-stance KAM differentiated groups with different levels of OA clinical severity (Astephen et al., 2008a) and radiographic severity (Thorp et al., 2006). The mid-stance value, captured with PCA, was higher with clinical symptoms of OA compared to a group with the same structural evidence of OA but no symptoms (Astephen Wilson et al., 2016). Lewek et al. (2004)

reported greater peak KAM for OA compared to control, however it is evident from the waveform included in the publication that the midstance difference was more profound, yet not analyzed or reported. Beyond the failure to report similar waveform features, the inconsistency in findings may be rooted in the inconsistencies in determining the severity and location of knee OA. Studies that found increases in knee adduction moments typically studied OA patients with primarily medial compartment pathology (Baliunas et al., 2002, Lewek et al., 2004, Rudolph et al., 2007, Schipplein and Andriacchi, 1991, Schmitt and Rudolph, 2007), while studies that included OA located in various compartments of the knee may have been less likely to find a difference (Kaufman et al., 2001, Messier et al., 2005).

During walking, the sagittal plane moment alters between an external flexion moment (KFM) in early stance to an external knee extension moment (KEM) in late stance. The KFM is an estimation of the net moment that must be overcome by the knee extensor muscles (internal knee extension moment). In a functionally healthy person, this moment is not heavily contested by the antagonist muscle group, as demonstrated by the generally low hamstrings activation in the stance phase of walking (Hubley-Kozey et al., 2009). Amplitude features of the flexion moment were included in a discriminant model between a cohort with severe knee osteoarthritis and controls (Deluzio and Astephen, 2007), where the OA patients had a lower overall magnitude of the flexion moment during stance accompanied by a different pattern of the flexion-extension moment throughout stance phase. There are three general theories as to why this change is observed: (1) strength deficits leading to altered stride characteristics (shorter steps, reduced walking speed, etc.), (2) co-contraction of the antagonist to stabilize the diseased joint, reducing the net moment for the same quadriceps torque, or (3) change kinematic strategy to shift load to hip and/or ankle. Childs et al. (2004) hypothesized that reduced knee motion stiffens the knee, making it less capable of dissipating potentially harmful localized impact loads. In addition to knee motion (range of knee flexion angle), the knee angle at impact has been shown to be correlated with regulating shock transmission through the body, where a straighter leg results in a greater effective axial stiffness of the body, and a reduced ability to attenuate shock (Lafortune et al., 1996). The relationship between impact attenuation capacity and OA has been studied indirectly in humans, and

is speculated to be a product of decreased muscle strength, and the resulting fatigue failure of the natural shock absorbers, a risk factor for the development of OA (Folman et al., 1986)

The portion of the net joint moment that creates torque around the long axis of the tibia, the knee rotation moment (KRM), is not well understood in the context of knee OA. In theory, if the friction in the joint is higher due to cartilage degeneration with OA, torque in this plane could be transferred to the joint tissues, creating an abnormal shear stress. McKean et al. (2007) found less early stance external KRM with OA (PCA feature), where women with OA had less early stance external KRM compared to asymptomatic women but no difference between male groups. Astephen et al. (2008a) also found that only those with severe clinical OA just prior to total knee arthroplasty had reduced late stance internal KRM. The torque imposed on the ground during the stance phase of the gait cycle, referred to as the "free moment" contributes to the transverse plane joint torque. Reduced magnitude or range of internal-external knee moments could reflect a change in gait strategy where rotational torque is minimized.

Prolonged activation of a muscle group beyond the necessary activation for typical gait is a sign of abnormal function. The co-contraction of an antagonist muscle group in a population with knee OA is typically interpreted as a means to increase the overall stiffness of the joint to increase stability (Rudolph et al., 2007, Rutherford et al., 2013). The cost of this adaptation is an increase in energy consumption (Waters et al., 1987) and an increase in the compressive force in the joint (Brandon et al., 2014), which also may be related to structural disease progression (Hodges et al., 2016). High self-report of symptoms and worse structural severity have been linked to abnormal muscle activation patterns (Hubley-Kozey et al., 2009, Rutherford et al., 2013, Rutherford et al., 2011, Zeni and Higginson, 2009), although there are inconsistencies in the methods and the respective findings, making it difficult to generalize the relationship. Methodological variations include the specific muscles measured and the muscle pairs grouped for calculating co-contraction indices.

Lewek et al. (2004) defined co-contraction as the simultaneous activation of agonist and antagonist muscles, and measured the co-contraction of muscle pairs that were on the same side (for example medial hamstrings with medial quadriceps). Out of

the four pairs of muscles examined, significantly higher vastus medialis-medial gastrocnemius co-contraction indices (17% vs. 11%) with knee OA were found compared to asymptomatic controls (Lewek et al., 2004). Using the same equation but different muscle pairs, Childs (2004) found higher co-contraction indices for the vastus lateralis-medial hamstring pair and for the tibialis anterior-medial gastrocnemius pair (Childs et al., 2004). This finding was generalized to longer durations of muscle activity during the gait cycle compared to controls. The amount of co-contraction may be relative to the severity of the disease as those with moderate OA did not have as pronounced co-contraction as reported with more severe knee OA (Hubley-Kozey et al., 2006). Vastus lateralis and the lateral hamstring activity have also been reported to be higher for severe OA compared to an asymptomatic control group (Hubley-Kozey et al., 2009) and speculated as a mechanism to un-load the medial compartment.

2.9 Joint Mechanics, Muscle Activation and Knee OA Progression

OA is a progressive disease and this progression can be measured by the worsening of symptoms (self-reported pain for example), and by the change in joint structure (radiographically measured joint space narrowing, for example), both of which can affect the overall function of the joint independently and concomitantly. The natural progression of knee OA is slow, and not linear with time, as indicated by evidence of long stable periods (Arden and Nevitt, 2006), however studies of varying duration have reported significant relationships between baseline joint biomechanics during walking and future structural and clinical progression of knee OA. Five studies of medial compartment knee OA structural progression found that peak external KAM at baseline was greater for those who progressed within 1-6 years with progression defined either radiographically or using MRI (Miyazaki et al., 2002, Chang et al., 2007, Woollard et al., 2011, Chang et al., 2015, Chehab et al., 2014). This result is not unanimous, as Bennell et al. (Bennell et al., 2011) related the KAM impulse and not the peak KAM with medial tibial cartilage volume loss, while another study only found the association between a higher baseline peak KAM and KAM impulse and medial tibial cartilage volume loss for participants with a high body mass index (BMI) (Brisson et al., 2017). While considering a clinical progression criterion of requiring total knee arthroplasty (TKA), again the peak

KAM (when normalized to height and mass) and KAM impulse were higher at baseline for those later recommended for the procedure (Hatfield et al., 2015a).

The ability to actively generate torque in the frontal plane is limited, and resisting an external adduction torque is achieved through activation of flexors and extensors, thereby increasing the compressive forces across the joint (Lloyd and Buchanan, 2001, Hsieh and Walker, 1976, Markolf et al., 1976). A statically determinant model predicted that a greater knee adduction moment would correspond to increased load on the medial compartment relative to that of the lateral compartment (Schipplein and Andriacchi, 1991), where a high adduction moment in a person with lateral laxity was speculated to lead to a situation where the entire joint reaction would be transferred through the medial compartment. This increased focal stress on the medial compartment is thought to lead to further cartilage damage/thinning, creating varus deformity and subsequently a higher external KAM. This has been referred to as the "viscous cycle" of knee OA mechanics (Felson 2013). One recent study longitudinally measured the change in peak KAM and KAM impulse over two years and found a significant increase with time (Mahmoudian et al., 2018). This study did not measure changes in joint structure, so it is unknown if this is related to the worsening structure or symptoms.

Differences in the knee flexion moment have also been related to knee OA clinical progression (Hatfield et al., 2015b), with contradictory findings for structural progression (Chang et al., 2015, Chehab et al., 2014). In a population at risk for future development of knee OA (post ACL reconstruction), the knee flexion moment explained a portion of the variance in the estimated medial tibiofemoral compartment load above that when only the KAM was considered in a model of contact force (Manal et al., 2015). The KRM has not been studied in connection to knee OA structural progression.

Only a few studies have documented the change in muscle activation patterns associated with knee OA progression. Participants with a longer duration of medial muscle co-contraction at baseline had a corresponding decrease in medial tibial cartilage volume at one year (Hodges et al., 2016). Using a clinical progression metric of recommendation for TKA within seven years of the baseline measurement, Hubley-Kozey et al (Hubley-Kozey et al., 2013a) found that those who progressed to TKA had significantly higher overall activity of all muscles at baseline. General increases in

muscle activation amplitude could be a compensation for OA related muscle strength deficits, however the co-contraction and stance phase prolonged activation are likely strategies to stabilize the joint, increasing the total load on the knee joint and contributing to the cycle of overload progression.

2.10 Summary

While there has been substantial growth in the understanding knee OA from a biomechanics perspective, there remains many gaps in our knowledge of the interaction between joint mechanics and knee OA initiation and progression. The three-year progression study was designed to address some of these gaps by using a shorter timeline of progression while maintaining radiographs as the method to monitor progression. It includes features of knee joint loading in three dimensions and muscle activation patterns, while using PCA to extract the most important features of the biomechanical data. This study also measured biomechanics at two timepoints to address the lack of current literature on how gait changes overtime with and without knee OA diagnosis and progression; a critical piece to understanding mechanical cause and effects of knee OA progression.

Due to the association between abnormal frontal plane knee biomechanics and the sex disparity of joint injuries and OA development, identifying the sex-specific maturation patterns of running and walking gait serves as a foundational piece to understanding relative mechanical predisposition of individuals. This information will create a bridge between healthy and OA biomechanics by the identification of mechanical risk factors during gait that may be linked to future susceptibility of knee OA. While sport has often been used in the discussion of the over-load theory of knee OA initiation, the role of load type on the differential risk between sports is based primarily on retrospective data. Studying female university student-athletes, representing a high-load-dose model, will enable the quantification of the changes to the knee joint, using MRI, based on the type of sport participation and magnitude and pattern features of joint moments, helping to better define abnormal forces in the context of knee joint damage.

CHAPTER 3
Methods

This chapter provides details of the methodologies of the three separate studies included in this thesis: (1) The Three-Year Knee OA Progression Study, (2) The Longitudinal Study on Adolescent Biomechanics, and (3) Collegiate Athlete Knee Joint Health Study. The Three-Year Progression Study was a longitudinal study at Dalhousie University's Dynamics of Human Motion Laboratory (DOHM) and was used to address the first two aims of this thesis. The Adolescent Biomechanics Study is a longitudinal study being conducted at Acadia University's motion Laboratory of Applied Biomechanics (mLAB), and the baseline data from this study was used for Aim 3. Data from this study was also used to build principal component models of adolescent and young athletes running and walking knee moments, which were used in the analysis for Aim 4. The Collegiate Athlete Knee Joint Health Study was a pilot study designed, funded and completed for this thesis to address Aim 4.

3.1 Participant Datasets

3.1.1 Three-Year Progression Study

A dataset of 188 asymptomatic and 240 moderate OA participants whose gait patterns were captured in the DOHM laboratory was used to build principal component models of asymptomatic and moderate knee OA gait biomechanics (Asym-Mod-OA PC Model). This dataset included data from a longer-term (7-9 years) OA progression study, as well as the data from participants in the Three-Year Progression Study. All asymptomatic participants were recruited from the general public with no known symptoms or history of knee OA. For moderate knee OA participants for both studies, diagnosis was completed by an orthopaedic surgeon based on clinical signs and symptoms, consistent with the American College of Rheumatology (ACR) criteria (Altman et al., 1986). All Mod-OA participants had predominantly medial compartment involvement as determined by the ratio of medial to lateral grade of joint space narrowing (Scott et al., 1993). Participants were excluded if they had any major surgery or trauma to

the lower extremities and screened for any neurological or pathological conditions that could affect walking gait. Participants were also excluded if they had any other form of arthritis, or if they were scheduled to receive a joint replacement surgery. Informed consent, in accordance with the Nova Scotia Health Authority Research Ethics Board and Dalhousie University Ethics Review Board, was obtained from all participants. Demographics for the PC model participants and the Three-year study are provided in Tables 3.1 and 3.2.

Table 3. 1 Demographics of Asymptomatic (Asym) and Moderate OA (Mod-OA) Subjects in the Asym-Mod-OA PC Model

	N	Sex	Age (years)		Mass (kg)		Height (m)		BMI (kg/m^2)		Speed (m/s)	
		F:M	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Asym	188	126:63	50.9	(8.9)	75.6	(15.3)	1.69	(0.09)	26.5	(4.6)	1.37	(0.17)
Mod-OA	240	81:159	58.7	(8.4)	91.1	(17.5)	1.72	(0.10)	30.6	(5.1)	1.23	(0.20)

Table 3. 2 Demographics of the Three-Year Progression Study (Chapters 4 and 5) Asym and Mod-OA

	N	Sex	Age (years)		Mass (kg)		Height (m)		BMI (kg/m^2)		Speed (m/s)	
		F:M	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Asym	21	17:4	53.7	(8.1)	75.8	(14.4)	1.66	(0.09)	27.4	(4.2)	1.32	(0.17)
Mod-OA	31	10:21	57.6	(6.9)	91.4	(17.5)	1.73	(0.09)	30.4	(4.7)	1.27	(0.17)

3.1.2 Longitudinal Study on Adolescent Biomechanics

Participants were recruited by an email sent out to Acadia University's varsity teams and local youth soccer and basketball associations. Local athletes who were part of Acadia Performance Training were also recruited through a lab demonstration. Informed consent was obtained by all athletes and/or parent(s) or guardian(s) prior to testing. All participants completed a questionnaire to determine their puberty development score ((Carskadon and Acebo, 1993), Table 3.3). Carskadon and Acebo (1993) developed the

self-rating scale to measure children's pubertal development without physician examination, pictorial representations or interview. The physical development items in the survey included questions about changes in height, growth of body hair, skin changes (pimples, for example), deepening of voice (males), facial hair (males), breast development (females), and menstruation (females). Responses were recorded on a four-point scale: (1) not yet started, (2) barely started, (3) definitely started, (4) seems complete.

Table 3. 3 Demographics of the Longitudinal Study on Adolescent Biomechanics Subjects

Puberty	Sex	N	Age (years)		Mass (kg)		Height (cm)		Walking speed (m/s)		Running speed (m/s)	
			Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Pre	M	18	9.5	(1.5)	34.5	(8.6)	139.2	(7.8)	1.4	(0.1)	3.5	(0.5)
	F	9	9.4	(1.2)	32.1	(19.0)	141.7	(6.4)	1.4	(0.1)	3.5	(0.3)
Early	M	10	11.1	(1.7)	38.8	(10.0)	147.6	(7.5)	1.2	(0.2)	3.7	(0.5)
	F	6	10.7	(0.8)	38.7	(5.5)	147.1	(7.5)	1.5	(0.3)	3.6	(0.5)
Mid	M	13	13.8	(1.6)	55.4	(7.8)	170.4	(6.9)	1.4	(0.1)	4.4	(0.5)
	F	18	12.1	(1.6)	44.7	(8.8)	155.1	(6.5)	1.4	(0.2)	3.9	(0.5)
Late	M	17	17.1	(3.2)	73.1	(10.3)	178.6	(7.1)	1.4	(0.1)	4.5	(0.3)
	F	29	14.9	(2.4)	59.5	(8.6)	165.8	(7.6)	1.4	(0.2)	4	(0.5)
Post	M	28	21.3	(2.5)	84.1	(11.0)	182.1	(6.9)	1.4	(0.2)	4.7	(0.5)
	F	47	20	(2.0)	69.9	(10.9)	169.1	(10.9)	1.4	(0.2 0	4.2	(0.3)

3.1.3 Collegiate Athlete Knee Joint Health Study

Participants were recruited from the Acadia Women's Varsity Basketball (BB) and Cross-country (XC) running teams (Table 3.4). After receiving written consent, each participant completed questionnaires related to demographics, sport participation history, injury history and MRI screening. Exclusion criteria included a history of trauma or injury to the lower extremities or lower back. Participants who had experienced an ankle

sprain were eligible only if the injury had occurred at least three months prior to the test date and were cleared for return to sport by a trained practitioner or therapist.

Table 3. 4 Demographics of Collegiate Athlete Knee Joint Health Study Subjects

	N	Age (years)		Mass (kg)		Height (cm)		Walking Speed (m/s)	
		Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
XC	12	20.3	(1.8)	59.4	(6.1)	167.1	(4.0)	1.4	(0.2)
BB	10	20.2	(2.0)	75.8	(18.8)	171.4	(8.9)	1.5	(0.2)

3.2 Biomechanics Data Collection Protocols

3.2.1 Three-Year Progression Study

At each visit to the gait lab, markers were placed on the most affected limb for OA participants and a randomly selected limb for the asymptomatic participants (Figure 3.1). Sixteen infrared light emitting diode (IRED) markers were placed on each participant, with single markers being fixed to the shoulder (not pictured in Figure 3.1), greater trochanter, lateral epicondyle of the femur, and lateral malleolus of the tibia and four rigid tracking clusters each with three non-collinear IRED markers being fixed to the pelvis, thigh, shank, and foot (Cappozzo et al., 1997). Virtual markers were created using a marker digitizing probe for the right and left anterior superior iliac spine, medial epicondyle, fibular head, tibial tuberosity, medial malleoli, second metatarsal and heel of the gait-tested leg and foot. The virtual markers in conjunction with the single IREDs were used to define anatomical coordinate systems. Marker position was based on standardized protocols to measure segment motion and define the joint coordinate system (Grood and Suntay, 1983, Landry et al., 2007a). Surface electrodes (10 mm diameter, 20 mm inter-electrode distance) were attached in a bipolar configuration over seven muscle sites using standardized procedures (Hubley-Kozey et al., 2006): the rectus femoris (RF), vastus lateralis and medialis (VL, VM), lateral and medial hamstrings (LH, MH), lateral and medial gastrocnemius (LG, MG), and a reference electrode on the shaft of tibia.

A standing calibration trial was collected with the subject standing in a neutral position with feet shoulder width apart. The infrared markers were captured at 100Hz

using a 2 sensor Optotrak optoelectronic motion analysis system (Northern Digital, Incorporation, Waterloo, ON, CA). All participants walked shod at their self-selected speed while three-dimensional (3D) marker position data and external ground reaction forces were measured. Ground reaction forces were measured using an AMTI force platform (Advanced Mechanical Technology, Incorporation, Watertown, MA, USA) at 2000 Hz. Walking speed was measured with two infrared light timing gates controlled by LabVIEW (National Instruments Corporation, Austin, TX, USA). A minimum of five trials for each participant were collected and averaged.

Raw EMG signals were amplified (8-channel AMT system, Bortec Inc., Calgary, AB, Canada) and sampled at 2000Hz. Following the walking trials, a series of exercises previously described (Hubley-Kozey et al., 2006) were performed after the walking trials to elicit maximum voluntary isometric contractions (MVIC), seven performed on a Cybex dynamometer (Lumex, Brooklyn, NY, USA), and one resisted standing heel rise exercise. Each exercise was performed twice, with verbal encouragement and a minimum of one-minute rest between exercises. The average torque over a one-second steady state window during the exercises was used as a measure of knee extensor and knee flexor strength. A participant bias trial was sampled with participants lying relaxed and supine.

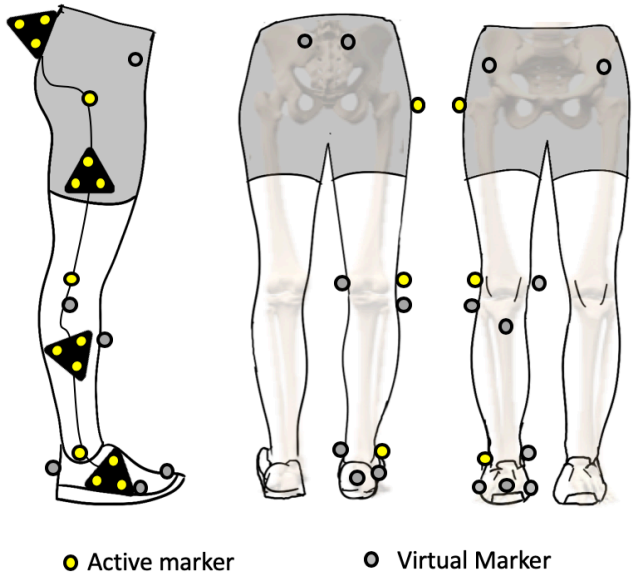


Figure 3. 1 Marker Position for Three-Year Progression Study (illustration adapted from Phinyomark et al., 2017)

3.2.2 Longitudinal Study on Adolescent Biomechanics

For the mLAB data, individual passive markers were fixed bilaterally to anatomical landmarks, including superior iliac crest, anterior superior iliac spine (ASIS), posterior superior iliac spine (PSIS), femoral epicondyles, fibular heads, tibial tuberosities, malleoli, and first, second and fifth metatarsals (Figure 3.2). Rigid clusters with four non-collinear markers were attached to each thigh and shank and three-marker clusters to each rearfoot to track each respective segment. A standing calibration trial was collected with the subject standing in a neutral position with feet shoulder width apart. Markers on the first metatarsals, second metatarsal, medial heel, medial malleoli, and medial epicondyles were removed after a standing calibration trial. All other markers were tracked during the walking and running trials. The sacrum marker was added during the data collection for the Collegiate Athlete Knee Joint Health Study. This marker was not part of the marker-set of the larger database and was added to facilitate tracking of the pelvis segment when the ASIS and superior crest markers were out of view during data collections on the treadmill.

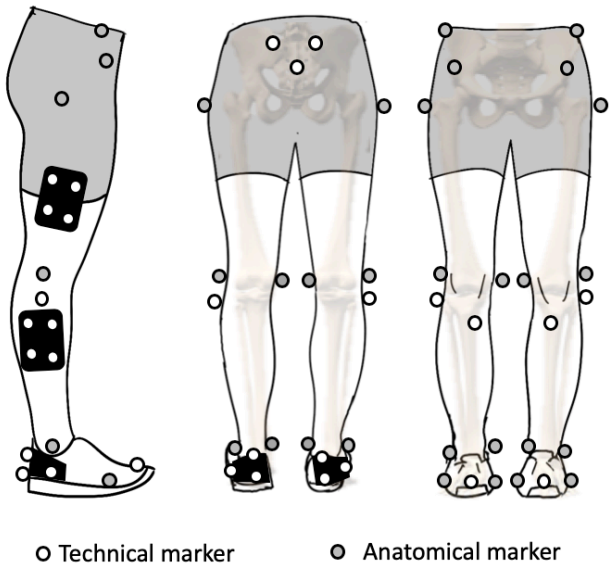


Figure 3. 2 Marker Positions for the Longitudinal Study on Adolescent Biomechanics and the Collegiate Athlete Joint Health Study

All participants walked shod at their self-selected speed while three-dimensional marker position data and external ground reaction forces were measured. Participants also

performed running trials at two thirds (66.7%) of their maximum 60m sprint speed which was measured prior to the start of the data collection on a running track. Four trials of each movement were collected. Gait speed was measured using Fusion Smart Speed timing gates (Fusion Sport, Brisbane, Australia) and marker position data were collected with a passive motion capture system (Qualisys, AB, Sweden), at 250 Hz and three AMTI floor embedded force platforms at 2000 Hz.

3.2.3 Collegiate Athlete Joint Health Study

Study data were collected at the mLAB using the same marker placement protocol and equipment as the mLAB Adolescent Biomechanics Study. Participants completed five successful trials (clean foot strike on a force plate) for each foot, for over-ground walking at a self-selected speed and overground running at 4m/s +/-5%.

3.3 Data Processing

3.3.1 Three-Year Progression Study

Custom Matlab (The Mathworks Inc., Natick, MA, USA) code was used to calculate three-dimensional net resultant moments at the knee joint during gait using a previously described inverse dynamics procedure (Landry et al., 2007a) with segment mass/inertia properties from Clauser et al. (Clauser et al., 1969). Data were filtered using a second order bi-directional Butterworth filter with a cut off frequency of 8 Hz for kinematic data and 60 Hz for force data. Anatomical/bone embedded coordinate systems were used to describe the three-dimensional motion of the body (Figure 3.3). Three dimensional rotations were calculated using the Cardan/Euler Model (Woltring, 1994) using the sequence: flexion/extension, ad/abduction, and internal/external rotation (YXZ) at the knee and plantar/dorsiflexion, inversion/eversion and ad/abduction (YXZ) at the ankle. Segment angular velocities and accelerations were determined and then Newton's second law was used to solve for the resultant ankle joint force and moment. This, in turn, was used to calculate the resultant knee force and moment. The net external knee moment was expressed in the joint coordinate system, which defines flexion/extension (KFM) about the medial/lateral axis of the thigh, internal/external rotation (KRM) about the long axis of the shank, and adduction/abduction (KAM) about an axis mutually

perpendicular to both the flexion/extension and internal/external rotation axis (Grood and Suntay, 1983).

Gait events (touch down and take off) were determined using a ground reaction force threshold of 5N. All gait waveforms were time normalized to stance phase of the gait cycle from 0% (touch down) to 100% (take off). The magnitudes for all moment waveforms were normalized to body mass. EMG data were time normalized to the full gait cycle, from 0% at first heel-strike to 100% at second heel strike (determined kinematically). EMG data were magnitude normalized to the maximum activation of each muscle during MVIC exercises. Data was collected for at least five gait cycles per visit and ensemble averaged.

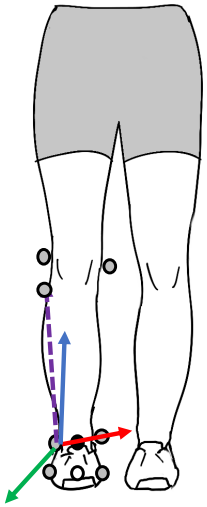
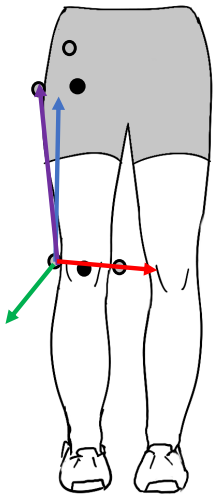
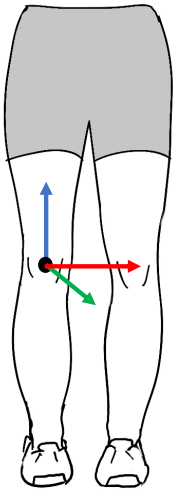
DOHM Shank ACS	**DOHM Thigh ACS**	**DOHM:** JCS
		
v1 = MedMal - LatMal; **v2** = FH - LatMal; **v3** = cross(v1,v2); **v4** = cross(v3,v1); **ML** = v1/norm(v1); **PA** = v3/norm(v3); **DP** = v4/norm(v4);	**v1** = ME - LE; **v2** = GT - LE; **v3** = cross(v1,v2); **v4** = cross(v3,v1); **ML** = v1/norm(v1); **PA** = v3/norm(v3); **DP** = v4/norm(v4);	ML_{thigh} X DP_{shank} = $AP_{Floating\ Axis}$

Figure 3. 3 Segment Anatomical Coordinate Systems and the Joint Coordinate System Used for the Three-Year Progression Study

3.3.1 Adolescent Biomechanics and Collegiate Athlete Joint Health Studies

mLAB data were processed in Visual3D (C-Motion, Inc., Germantown, MD) using a similar inverse dynamics procedure to the Three-Year Progression Study with the following exceptions: Dempster (1955) was used for segment mass and segment inertial properties (geometry) from Hanavan Jr (1964), anatomical/bone embedded coordinate systems (Figure 3.4), and data were filtered using a bi-directional (second order) Butterworth filter with a cut off frequency of 12 Hz for both kinematic and kinetic data.

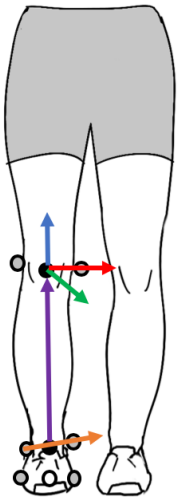
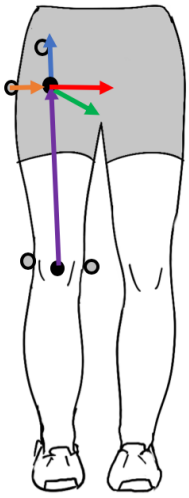
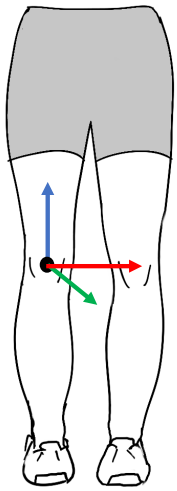
mLAB: Shank ACS	**mLAB:** Thigh ACS:	**mLAB:** JSC
		
v1 = KJC – AJV; **v2** = MedMal – LatMal; **v3** = cross(v2, v1); **v4** = cross(v1, v3); **DP** = v1/norm(v1); **AP** = v3/norm(v3); **ML** = v4/norm(v4);	**v1** = HJC – KJV; **v2** = HJC - GT **v3** = cross(v2, v1); **v4** = cross(v1, v3); **DP** = v1/norm(v1); **AP** = v3/norm(v3); **ML** = v4/norm(v4);	ML_{thigh} X DP_{shank} =$AP_{Floating\ Axis}$

Figure 3. 4 Segment Anatomical Coordinate Systems and the Joint Coordinate System Used for the Adolescent Biomechanics and Collegiate Athlete Studies

Gait events (touch down and take off) were determined using a ground reaction force threshold of 10N. All gait waveforms were time normalized to stance phase of the

gait cycle from 0% (touch down) to 100% (take off). The magnitudes for all moment waveforms were normalized to body mass. Data were collected for at least four gait cycles per visit and ensemble averaged.

3.4 Principal Component Analyses

For each study, the average, time normalized waveforms for each participant were combined into an n x p data matrix X, where n is the number of observations, and p is the number of variables representing each observation (p=101). A separate data matrix was created for each knee joint moment (KAM, KFM, KRM) and for each movement (running only for mLab PC model, walking), resulting in 9 PC models: 3 DOHM-walking, 3 mLAB-walking, 3-mLAB-running. For electromyography data, muscles from the same group were combined into the same data matrix. For example, the medial and lateral gastrocnemius (LG, MG) muscle activation waveforms were combined into the same matrix to create one PCA model for gastrocnemii EMG. The same was done for the three quadriceps (RF, VL, VM) and two hamstrings (LH, MH), resulting in three EMG PC models.

Knee moment data were centered around zero by subtracting the mean ($\tilde{X} = (X - \bar{X}$). The covariance matrix of each knee moment data and the cross-product matrix for EMG data were used to extract eigenvectors (U). Orthogonal transformations ($Z = U^T X$) were completed for each data matrix, converting the original 101 correlated waveform variables into 101 new uncorrelated principal components (PCs). The U matrix is a transformation matrix that rotates the original data into the new coordinate system. The column vectors of U are the principal component loading vectors. PCs are arranged in decreasing order of sample variance, each representing an independent feature of the original data. To achieve data reduction, principal components explaining a small portion of the data variance were dropped from the model using a 90% trace criteria (Jackson, 1993). Interpretations of the PCs were accomplished through examining the shape of the loading vector, and the individual gait waveforms that corresponded to high and low PC scores (Jones and Rice, 1992) (Appendix A).

3.4.2 PC Scores

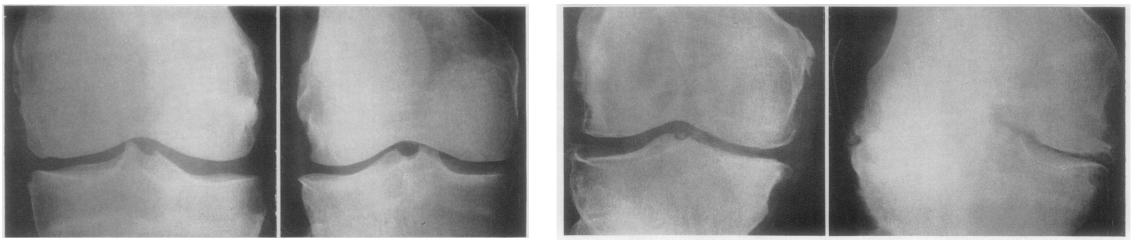
A PC score is the projection of a given observation (waveform) onto the principal component loading vector, and a measure of the distance a given waveform is from the mean ($PCscores = \tilde{X} \cdot U$). The knee moment and EMG (walking) waveforms from the Three-Year Progression Study (n=52) were projected onto the kinetic and EMG PC models from the DOHM database. The knee moment (running and walking) waveforms from the Collegiate Joint Health Study (n=22) were projected onto the mLAB PC models.

3.5 Imaging

Medical imaging was used throughout this thesis to quantify the integrity of the knee joint. In Chapters four and five, the severity of knee OA was determined using standard radiographs, scored according to the Kellgren and Lawrence (KL) scale (Kellgren and Lawrence, 1952). The space between the femur and tibia, a surrogate for cartilage volume, was scored using the Baltimore Longitudinal Study on Aging Atlas of Knee Osteoarthritis scale (Scott et al., 1993). Predominant medial compartment involvement was determined by comparing the joint space narrowing (JSN) score from the medial and lateral compartments, including individuals into the study when the medial compartment score was equal or greater than the lateral. Chapter seven explored the use of MRI to score the knees of healthy asymptomatic female athletes before and after one season of sport participation using a whole joint approach (MOAKS) (Hunter et al., 2011b).

3.2.1 Three-Year Progression Study

Asymptomatic and moderate OA participants had standard anterior-posterior radiographs completed on their gait tested leg at baseline and again at follow up. An experienced orthopaedic surgeon (WDS, kappa = 0.99, (Hatfield et al., 2015b) scored the radiographs for both KL grade (Kellgren and Lawrence, 1952) and joint space narrowing (JSN) (Scott et al., 1993).

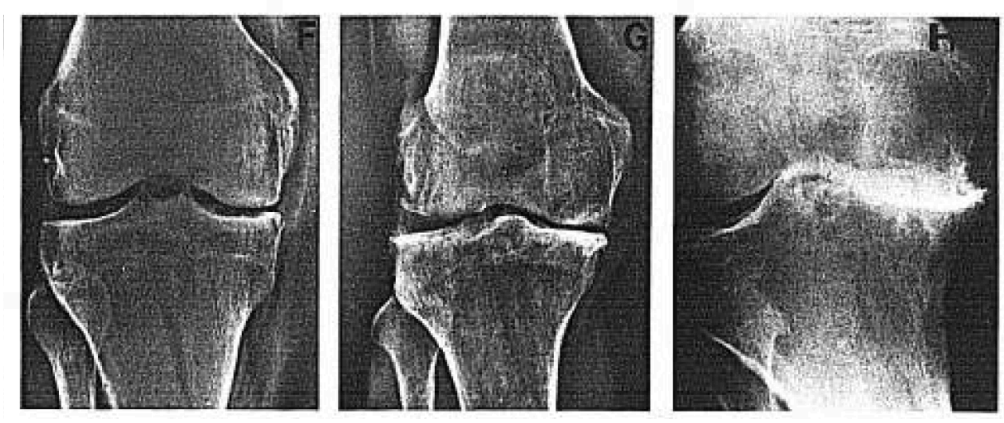


Grade 1 **Grade 2** **Grade 3** **Grade 4**

Figure 3. 5 Standard Examples of KL Grades 1(left) to 4 (right) Severity for Osteoarthritis of the Knee (Kellgren and Lawrence, 1957)

The KL score divides osteoarthritis into five grades: (0) none, (1) doubtful, (2) minimal, (3) moderate, and (4) severe.

The Baltimore Longitudinal Study of Aging Atlas of Knee Osteoarthritis was presented as an atlas of individual features of osteoarthritis of the knee (Scott et al., 1993). Joint space narrowing was divided into four categories: (0) normal, no narrowing, (1) minimal but definite narrowing, (2) moderate narrowing, and (3) severe narrowing, "bone one bone" (Figure 3.6). Baseline and follow-up radiographs were scored in pairs by an experienced orthopaedic surgeon, who was blind to clinical diagnosis but not to timepoint.



Grade 1 **Grade 2** **Grade 3**

Figure 3. 6 Atlas Images Showing Medial Compartment Narrowing = 1 (Left), Medial Compartment Narrowing = 2 (Center), and Medial Compartment Narrowing = 3 (Right) (Scott et al., 1993)

Progression was defined by at least a one grade worsening of medial joint space score narrowing from baseline to follow-up, thereby dichotomising all participants as "progressors" and "non-progressors".

3.2.2 Collegiate Athlete Joint Health Study

MRIs were acquired using a GE Medical Systems 3T Discovery MR750 magnet and a GEM flex medium array placed around the subject's test knee. 3D CUBE proton density weighted and 2D Sagittal and Coronal proton density weighted and fat saturated sequences were used for this study. Each participants' baseline and follow up MRIs were scored by an experienced musculoskeletal radiologist. The radiologist was blind to sport but not to timepoint of the MRIs.

Table 3. 5 Magnetic Resonance Imaging Parameters

Parameter	**2D Coronal**	**2D Sagittal**	**3D CUBE**
TR (msec)	1800	1800	2000
TE (msec)	27.7	29.7	39.0
Image dimensions (mm)	512 x 512 x 30	512 x 512 x 28	320 x 320 x 240
Voxel Dimensions (mm)	0.31 x 0.31 x 3.39	0.31 x 0.31 x 2.74	0.5 x 0.5 x 0.38
Slice Thickness (mm)	3	3	1
Interslice Gap (mm)	3.6	3.6	0.5
Proton Density Weighted	Yes	Yes	Yes
Fat Saturation	Yes	Yes	No

TR = repetition time; TE = echo time.

All MRIs were evaluated using the MRI Osteoarthritis Knee Score (MOAKS) by a single musculoskeletal radiologist (Dr. Ryan MacDougall). The radiologist evaluated the baseline and follow-up paired scans, and was not blinded to the time points of MRI but blind to sport. The MOAKS divides the knee into 14 articular subregions to score

cartilage defects and bone marrow lesions (BMLs) and six tibiofemoral and six patellofemoral subregions to score osteophytes (Hunter et al., 2011b). Medial and lateral meniscus lesions were scored separately and divided into anterior, posterior, and central subregions. Cartilage defects were graded based on size from 0 to 3 (percentage of the surface area: 0 = none; 1 = <33%; 2 = 33%-66%; and 3 = >66%) and depth (percentage of the lesion depth to full thickness: 0 = no full-thickness loss; 1 = <10%; 2 = 10%-75%; and 3 = >75%). BMLs were based on size only (percentage of the surface area affected: 0 = none; 1 = <33%; 2 = 33%-66%; and 3 = >66%). Osteophytes were graded according to size based on how far they extended from the joint: 0 = none; 1 = small; 2 = medium; and 3 = large. Meniscal tears were described as absent or present and by type (vertical, horizontal, or complex). Meniscal maceration was described as absent or present and by type (partial, complete, or progressive). Meniscal extrusion was described by size: 0 =<2 mm; 1 = 2-2.9 mm; 2 = 3-4.9 mm; and 3 = >5 mm. Hoffa fat pad synovitis was graded as 0 (none), 1 (mild), 2 (moderate), or 3 (severe).

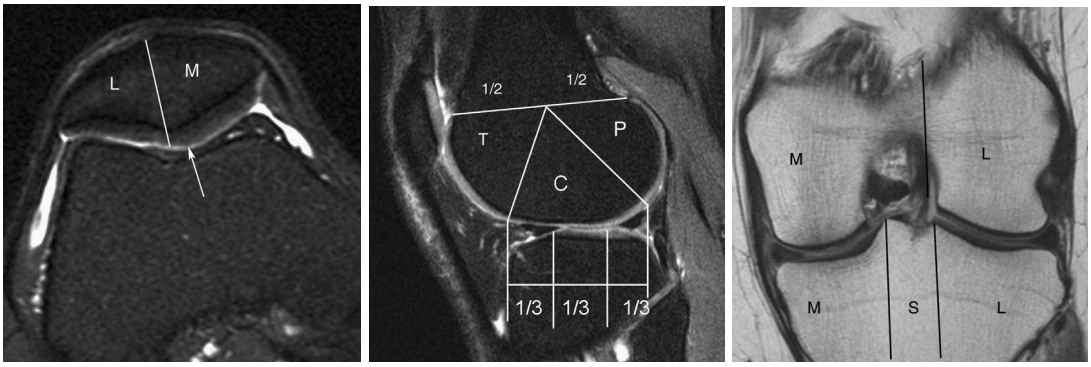


Figure 3. 7 Regional Subdivisions for MOAKS (Hunter et al., 2011b)

Worsening of OA features in each compartment was defined as any increase in the score (in any corresponding subregions for that compartment). Therefore, either progression of an OA feature (increase in defect severity) or a new OA feature (from no defect to present defect) from baseline to follow-up was classified as worsening. This definition is reliable and sensitive to changes in ACL-injured patients and other populations at high risk for OA (Runhaar et al., 2014, van Meer et al., 2016).

CHAPTER 4

Longitudinal Evidence Links Joint Level Mechanics and Muscle Activation Patterns to Three-Year Medial Joint Space Narrowing

4.1 Background

Knee osteoarthritis (OA) is well-recognized as a progressive disorder, characterized by the interplay between structural joint degeneration and the expression of clinical symptoms. The rate of knee OA structural progression is difficult to monitor and quantify at a population level and it remains unclear why certain individuals progress more quickly through the disease than others (Felson, 1993). Although there are currently no effective treatments for knee OA, it has been suggested that adopting patterns of locomotion that reduce the load on the knee joint may reduce the rate of OA progression (Andriacchi et al., 2004); a hypothesis driving a branch of research into non-surgical interventions for individuals with knee osteoarthritis (such as high tibial osteotomy, gait re-training, braces, etc.). It is therefore critical to understand which types of joint loads are related to structural progression of knee OA and, specifically, if different patterns of joint loading are related to accelerated rates of structural progression.

Gait has been used extensively as a model of joint loading and an objective assessment of joint function in an osteoarthritic population. The past decade of gait-knee-OA research has uncovered several correlations between biomechanical features of gait and worsening of the knee joint related to OA structural progression (Miyazaki et al., 2002, Bennell et al., 2011, Chehab et al., 2014, Chang et al., 2015). Specific attention has been placed on the external knee adduction moment (KAM) in these studies, due to its relationship to the dynamic load on the medial compartment (Schipplein and Andriacchi, 1991), the utility in differentiating OA by severity (e.g. (Mundermann et al., 2004)), and the early evidence in predicting longitudinal radiographic progression (Miyazaki et al., 2002). The early stance moment (Miyazaki et al., 2002), peak moment (Chehab et al., 2014), stance phase impulse (Chang et al., 2015), and the pattern of the moment during

stance (Hatfield et al., 2015a) have all been associated with some aspect of OA progression. The seminal prospective study of biomechanical predictors of medial compartment knee osteoarthritis progression (Miyazaki et al., 2002) used a 6-year follow-up period, while studies using MRI features of joint changes to assess structural worsening (Bennell et al., 2011, Chehab et al., 2014, Chang et al., 2015) have measured changes from 12 months to 5 years. Differences between the longitudinal endpoints and the imaging modality used to quantify joint change have made confirmation of the relevant features to OA progression based on radiographic imaging, the current standard of assessment, difficult. While sagittal plane moment patterns were predictive of clinical progression to TKA (Hatfield et al., 2015b), there have been inconsistent results with respect to structural OA progression (Chehab et al., 2014, Chang et al., 2015). Furthermore, data regarding the role of the transverse plane moments along with the contributions to joint loading from muscle activity, a primary contributor to the joint loading environment (Herzog et al., 2003), are not well represented in the current literature and warrant further investigation.

The sensitivity of biomechanical features of gait to structural changes in the joint is an essential feature of its utility, however the sensitivity of gait is not isolated to structural changes that occur with knee OA. As a result, biomechanical studies of more severe OA populations are often confounded by gait differences due to reduced walking speed (Landry et al., 2007a), obesity (Runhaar et al., 2011) and pain (Astephen Wilson et al., 2011), potentially masking the relationship between structural changes and joint loading. Furthermore, OA clinical diagnosis occurs late in the disease process, while it is known that many adults will have signs of structural degradation of the joint prior to symptoms manifesting (Felson, 1993) which may be indicative of a pre-knee OA state. Taken together, this motivates the need to look at biomechanical mechanisms for structural degradation of the knee joint earlier in the disease process, including prior to clinical diagnosis, while symptoms and comorbidities are less severe.

The objective of this study was to determine if a three-year longitudinal end point, reflecting the earliest detectible change in radiograph, corroborates what has been shown for longer term radiographic progression, or provides more insight into factors that may be implicated in accelerated and early radiographic progression in knee joint

degeneration. We hypothesize that individuals who progress within this timeline will have distinct features of joint mechanics and muscle activation that are associated with early structural changes, unique from those associated with progression later in the disease process.

4.2 Methods

Thirty-one individuals with moderate knee OA and twenty-one asymptomatic adults completed the longitudinal portion of this study. Individuals with knee OA were recruited from the Orthopaedic and Sports Medicine Clinic of Nova Scotia and the Orthopaedic Assessment Clinic at the QEII Health Sciences Centre and asymptomatic participants were recruited via local and online advertisements. OA participants were diagnosed by an experienced orthopaedic surgeon (WDS) following the American College of Rheumatology criteria (Altman et al., 1986) using a combination of radiographs and physical and clinical examinations. All OA participants had baseline medial compartment OA, defined as having radiographic evidence of greater or equal medial joint space narrowing (MJSN) relative to lateral JSN (Scott et al., 1993). Participants with OA were deemed to have mild to moderate severity at baseline, defined as per our previous studies according to: having Kellgren and Lawrence (KL) scores between 1 and 3 (Kellgren and Lawrence, 1957); self-reported ability to walk a city block; self-reported ability to jog five metres and walk upstairs in a reciprocal manner; and not being candidates for total knee replacement surgery (Hubley-Kozey et al., 2006, Harding et al., 2012, Amiri et al., 2015). For all participants, exclusion criteria included history of any neuromuscular disease, other forms of arthritis, or major surgery to the lower limb that could affect gait (Hubley-Kozey et al., 2006). All individuals signed a written consent form in accordance with the institutional ethics review.

All participants visited the Dynamics of Human Motion laboratory at baseline for three-dimensional, self-selected speed over ground walking gait analysis to measure kinematics, kinetics, and electromyography (EMG) (seven muscle sites). Participants completed a WOMAC OA-specific questionnaire prior to testing at each time point (Bellamy et al., 1988). The test leg was the affected side for the participants with OA and a randomly selected leg for controls. Walking speed was monitored using an infrared

timing system and participants were required to complete five trials within 5% of their self-selected speed, capturing the typical mechanical environment of each individual, after a brief warm-up, which has been shown to be a reliable protocol (Robbins et al., 2013). Motion data were captured using an Optotrak™ system (Northern Digital Inc., Waterloo, ON, Canada) at 100Hz and external ground reaction forces were measured using an AMTI™ force plate (AMTI Inc., Watertown, MA, USA) captured at 2000Hz, synchronized and down-sampled to match motion data. Four three-marker triads of infrared light-emitting diodes were placed on the sacrum, lateral thigh, lateral shank and foot segments. Individual diodes were placed on the greater trochanter, lateral epicondyle, lateral malleolus and shoulder. Eight virtual markers were identified on anatomical points during quiet standing, including the right and left anterior superior iliac spines, medial epicondyle, fibular head, tibial tuberosity, medial malleolus, second metatarsal and calcaneus.

Surface electrodes (10 mm diameter, 20 mm inter-electrode distance) were attached in a bipolar configuration over seven muscle sites using standardized procedures (Hubley-Kozey et al., 2006): the rectus femoris (RF), vastus lateralis and medialis (VL,VM), lateral and medial hamstrings (LH, MH), lateral and medial gastrocnemius (LG,MG), and a reference electrode on the shaft of the tibia. Raw EMG signals were amplified (8-channel AMT system, Bortec Inc., Calgary, AB, Canada) and sampled at 2000Hz. Following the walking trials, a participant bias trial was sampled with participants lying relaxed and supine. A series of exercises previously described (Hubley-Kozey et al., 2006) were performed after the walking trials to elicit maximum voluntary isometric contractions (MVIC), seven performed on a Cybex dynamometer (Lumex, Brooklyn, NY, USA), and one resisted standing heel rise exercise. Each exercise was performed twice, with verbal encouragement and a minimum of one-minute rest between exercises. The average torque over a one-second steady state window during the exercises was used as a measure of knee extensor and knee flexor strength.

Custom Matlab (The Mathworks Inc., Natick, MA, USA) code was used to create a model and calculate the three-dimensional knee joint angles and net resultant moments during gait according to the joint coordinate system (Grood and Suntay, 1983) and a previously described inverse dynamics procedure (Landry et al., 2007a). Joint moments

were normalized to body mass (Nm/kg) and joint angles were referenced to a standing calibration trial. All EMG processing was completed in Matlab using previously published methods (Hubley-Kozey et al., 2006). Briefly, the EMG data were corrected for bias, full-wave rectified, and low pass filtered at 6Hz using a Butterworth filter. For the normalization exercises, a moving window algorithm was used to determine the 0.1 second window in which the maximum EMG amplitude occurred for each muscle. The EMG waveforms were amplitude normalized to MVIC. Five trials were averaged for each participant and time-normalized to one complete gait cycle from initial (0%) to second (100%) foot contact with the ground for joint angles and EMG waveforms, and to stance phase of one gait cycle from initial contact (0%) to terminal stance (100%) for moments.

All participants underwent baseline and approximately three-year follow-up standardized X-rays of their most affected OA knee joint (in the case of bi-lateral knee OA) or gait-tested knee joint (for the asymptomatic group). The OARSI-OMERACT definition of knee OA radiographic progression, along with the recommended dichotomous rating of the study participants as either 'progressors' or 'non-progressors' (Ornetti et al., 2009b) was adopted for this study. The 'Progression Group (PG)' included individuals who had at least a one grade increase in the medial joint space narrowing (JSN) score from baseline to follow-up (Scott et al., 1993). All grading was performed by an experienced orthopaedic surgeon, blinded to the baseline radiograph classification, with shown intra-rater reliability (WDS, kappa = 0.99 for medial JSN, (Hatfield et al., 2015b)). The 'Non-progression group (NPG)' included individuals that did not have an increase in their MJSN score at three years.

A gait waveform analysis technique using principal component analysis (PCA) (Deluzio and Astephen, 2007) was applied to a larger gait dataset of 240 individuals with moderate knee OA (58.7 (8.4) years, BMI 30.6 (5.1) kg/m^2) and 188 asymptomatic individuals (50.9 (8.9) years, BMI 26.5 (4.6) kg/m^2) to extract stable and robust mutually uncorrelated patterns that optimally describe the variability among observations of the knee adduction (KAM), rotation (KRM) and flexion (KFM) moments, and to each muscle group EMG data (quadriceps, hamstrings, gastrocnemius). The first three PCs for each variable were retained and used for the analysis, capturing over 90% of the total

variability explained (Jackson, 1993) and interpreted according to techniques described by Deluzio and Astephen (2007). Data for the 52 individuals in the current study were projected onto these PCs to calculate PC scores based on the defined features. In addition, conventional discrete features, including the peaks and mid-stance values for the KAM and the KAM impulse, were calculated and used for direct comparison to existing literature. The first KAM peak was the maximum moment between 0-40% of stance, the second KAM peak was the maximum moment between 70-90% of stance, and the impulse was calculated using numerical integration of stance phase.

Student's t-tests were performed for each retained PC and discrete variable to examine differences between the PG and NPG ($\alpha = 0.05$). Due to the mixture of clinical knee OA and asymptomatic participants in the PG and NPG, a secondary analysis was completed to compare the OA participants in the NPG (OA-NPG), the asymptomatic participants in the NPG (ASYM-NPG), and the PG. A series of one-way analysis of variance (ANOVA) models with a Bonferroni correction for multiple comparisons was completed for variables that had a significant difference in the two-group analysis. Due to the low number of asymptomatic participants in the PG (n=3), this group was not further subdivided for statistical testing, but was included as a separate group for visual interpretation in graphical representations of the data.

4.3 Results

Four knee OA participants had a baseline medial JSN of three and were not included in the analysis as this baseline score prevents structural progression based on the definition used. Of the remaining 48 participants, ten individuals displayed medial JSN progression at three years (3/21 asymptomatic, 7/27 OA), a smaller percentage than anticipated based on previous publications of a similar duration follow-up (Mikesky et al., 2006). One of the asymptomatic participants in the PG was diagnosed with medial compartment tibiofemoral OA within the three-year follow-up period, while the other two had structural worsening without a change in clinical status. One OA participant in the progression group was recommended for a total knee arthroplasty (TKA) during the course of the study, representing a change in clinical OA severity (Hatfield et al., 2015b) in addition to structural worsening. One participant in the PG and two in the NPG were

not included in the EMG analyses due to either data quality or the inability to complete the MVICs required for amplitude normalization.

Table 4. 1 Participant Baseline Demographics

	PG (n=10, *n=9)		NPG (n=38)		P-value	OA-NPG (n=20)		ASYM-NPG (n=18)	
	Mean	(SD)	Mean	(SD)		Mean	SD	Mean	SD
Gender (F:M)	3:7		22:16		0.10	7:13		15:3	
Age (years)	61.3	(6.3)	54.1	(7.4)	**0.01**	55.9	(6.1)	52.3	(8.2)
Mass (kg)	89.0	(20)	83.1	(18)	0.38	89.1	(17.7)	76.5	(15.3)
BMI (kg/m^2)	29.7	(5.4)	28.9	(4.7)	0.65	29.7	(4.9)	28.1	(4.3)
Time to follow-up (yrs)	2.97	(0.4)	2.93	(0.3)	0.69	2.92	(0.3)	2.91	(0.2)
Speed (m/s)	1.32	(0.2)	1.29	(0.2)	0.62	1.27	(0.2)	1.32	(0.1)
Group (OA:ASYM)	7:3		20:18		0.30				
MJSN (0:1:2:3)	1:6:3:0		1:22:15:0		0.30	1:6:13:0		0:16:2:0	
KL Global (1:2:3:4)	1:5:4:0		2:24:12:0		0.99	2:10:8:0		0:14:4:0	
Pain Sum (/20)	5.5	(4.7)	2.5	(3.3)	**0.02**	4.5	(3.2)	0.1	(0.2)
Stiffness Sum (/8)	2.6	(2.3)	1.5	(1.8)	0.11	2.5	(1.8)	0.4	(0.9)
Function Sum (/68)	17.7	(16.0)	8.5	(11)	**0.04**	15.0	(11.1)	1.1	(2.5)
WOMAC Total (/96)	25.8	(23.0)	12.5	(15)	**0.04**	22.0	(15.3)	1.6	(3.5)
*Knee Ext. Strength (Nm)	123.9	(31.3)	130.3	(41.9)	0.67	143.1	(45.8)	116.0	(31.7)
*Knee Flex. Strength (Nm)	64.9	(23.4)	58.1	(31.4)	0.54	66.1	(33.6)	49.2	(25.0)
*Plantarflex. Strength (Nm)	106.3	(28.8)	97.9	(34.95)	0.50	102.1	(39.3)	93.2	(29.4)

*Indicates reduced sample for mean **Mann-Whitney U-test for MJSN, KL and WOMAC scores

The PG was on average seven years older (P=0.01), but did not walk significantly slower, did not have lower strength, and had similar BMIs to the NPG. There were no significant differences in the baseline KL grades and medial JSN scores between groups, however the PG scored higher on the WOMAC sub-scales for pain (P=0.02), and function (P=0.04) and had higher total WOMAC scores (P=0.04) than the NPG at baseline (Table 4.1). The secondary analysis revealed that these differences were due to

the lower WOMAC scores of the ASYM-NPG as the OA-NPG and PG were not significantly different from each other.

The PG had higher first peak of the KAM during stance (P=0.02) and greater early to mid-stance differences in the KAM (KAM PC2; P=0.02) (Table 4.2, Figure 4.1 - top row). There were no differences in the mid-stance minimum KAM or the second peak of the KAM. The PG displayed greater range of net external to internal rotation moments from early to late stance (KRM PC1; P = 0.05) (Table 4.2, Figure 4.1 (middle row)). There were no significant differences in the knee flexion moment between groups (Figure 4.1, bottom row).

Table 4. 2 Baseline Gait Variables that are Significantly Different Between the Progression (PG) and Non-Progression (NPG) Groups (α= 0.05)

	VE %	Units/ Interpretation	PG Mean (SD)		NPG Mean (SD)		% Diff	P-value
KAM Peak 1	N/A	Nm/kg	0.57	(0.14)	0.47	(0.12)	18.6	**0.02**
KAM PC2	14.8	Early to mid-stance diff.	0.15	(0.40)	-0.11	(0.38)	N/A	**0.02**
KRM PC1	49.3	Range, early to late stance	0.28	(0.42)	-0.01	(0.39)	N/A	**0.05**
LG PC3	2.6	Mid to late stance activity	-24.09	(36.62)	1.87	(31.13)	N/A	**0.05**
LH PC1	81.0	Overall magnitude	135.84	(63.93)	90.92	(40.42)	N/A	**0.02**
LH PC2	8.8	Diff., early to mid-stance	14.57	(55.86)	-20.67	(25.64)	N/A	**0.01**

VE = Variance Explained

The lateral hamstring muscle activity magnitude was overall higher in the PG (PC1; P=0.02), and there was less difference from early to mid-stance activity, interpreted as more prolonged activity through stance (PC2; P=0.01) (Figure 4.3). Additionally, the PG had a higher early- to mid-stance and very late stance activity (at approximately 20% and 60% of the gait cycle) of the lateral gastrocnemius muscle than the NPG (PC3; P = 0.05) (Figure 4.3). There were no significant group differences in the

activation of the medial gastrocnemius, medial hamstrings or any of the quadriceps muscles (Figure 4.2, Figure 4.3).

Results of the three-group analysis indicated that there were no significant differences in the gait biomechanics of the ASYM-NPG and OA-NPG, however there were also no significant differences between the PG and the OA-NPG. The PG had a significantly greater first peak of the KAM compared to the ASYM-NPG (P=0.02), but no difference compared to the OA-NPG (P=0.14). Similarly, the KRM PC1 difference and LG PC3 difference were significant between the PG and ASYM-NPG, but no significant differences were found between the OA-NPG and the other groups. The remaining significant differences found in the two-group analysis were not statistically significant when the groups were further subdivided (KAM PC2, LH PC1, LH PC2).

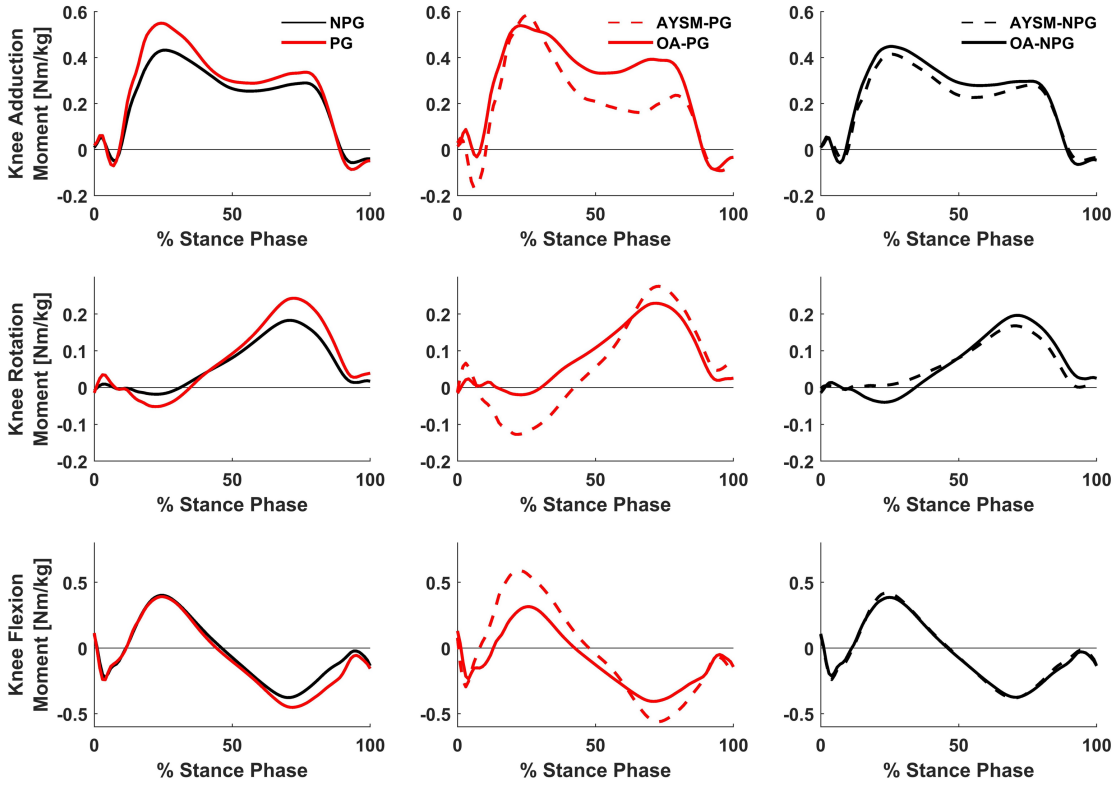


Figure 4. 1 Ensemble Averaged External Knee Joint Moment Waveforms for PG (Red) and NPG (Black) (Left Column). The Middle and Right Columns Display the Average Waveforms for OA (Solid) and ASYM (Dashed) Participants in Each Progression Group.

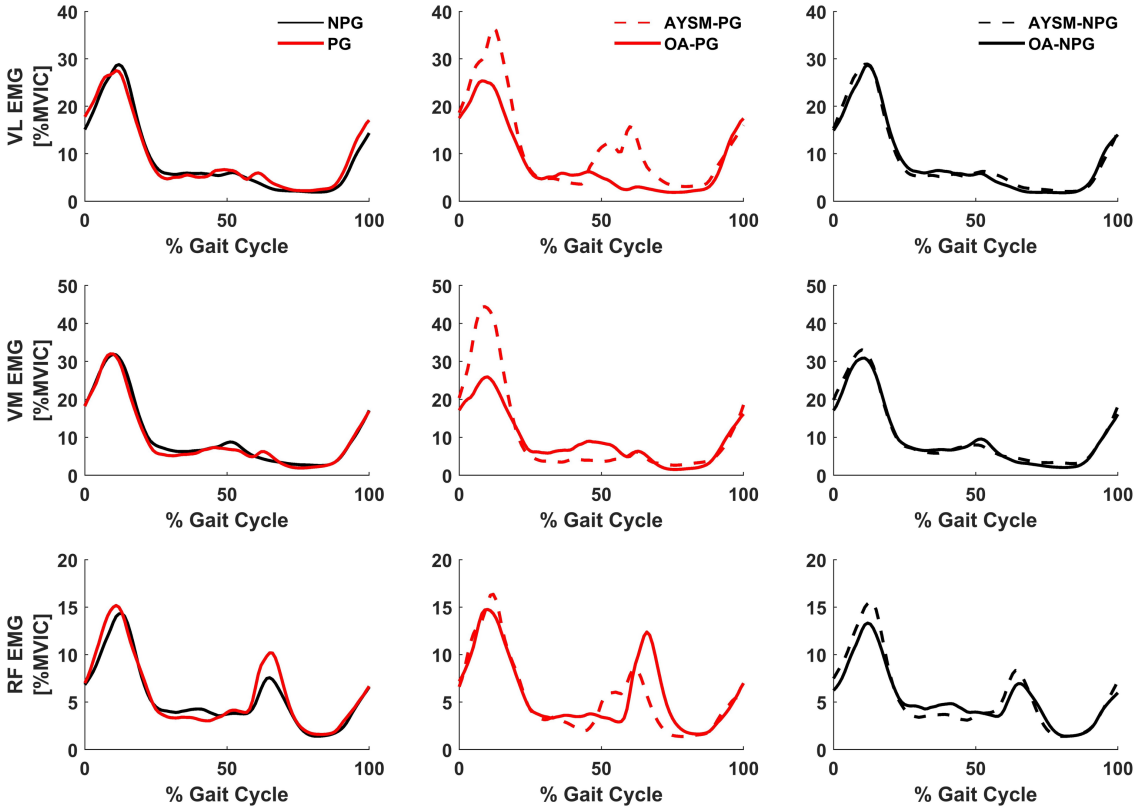


Figure 4. 2 Ensemble Averaged Quadriceps EMG Waveforms for PG (Red) and NPG (Black) (Left Column). The Middle and Right Columns Display the Average Waveforms for OA (Solid) and ASYM (Dashed) Participants in Each Progression Group.

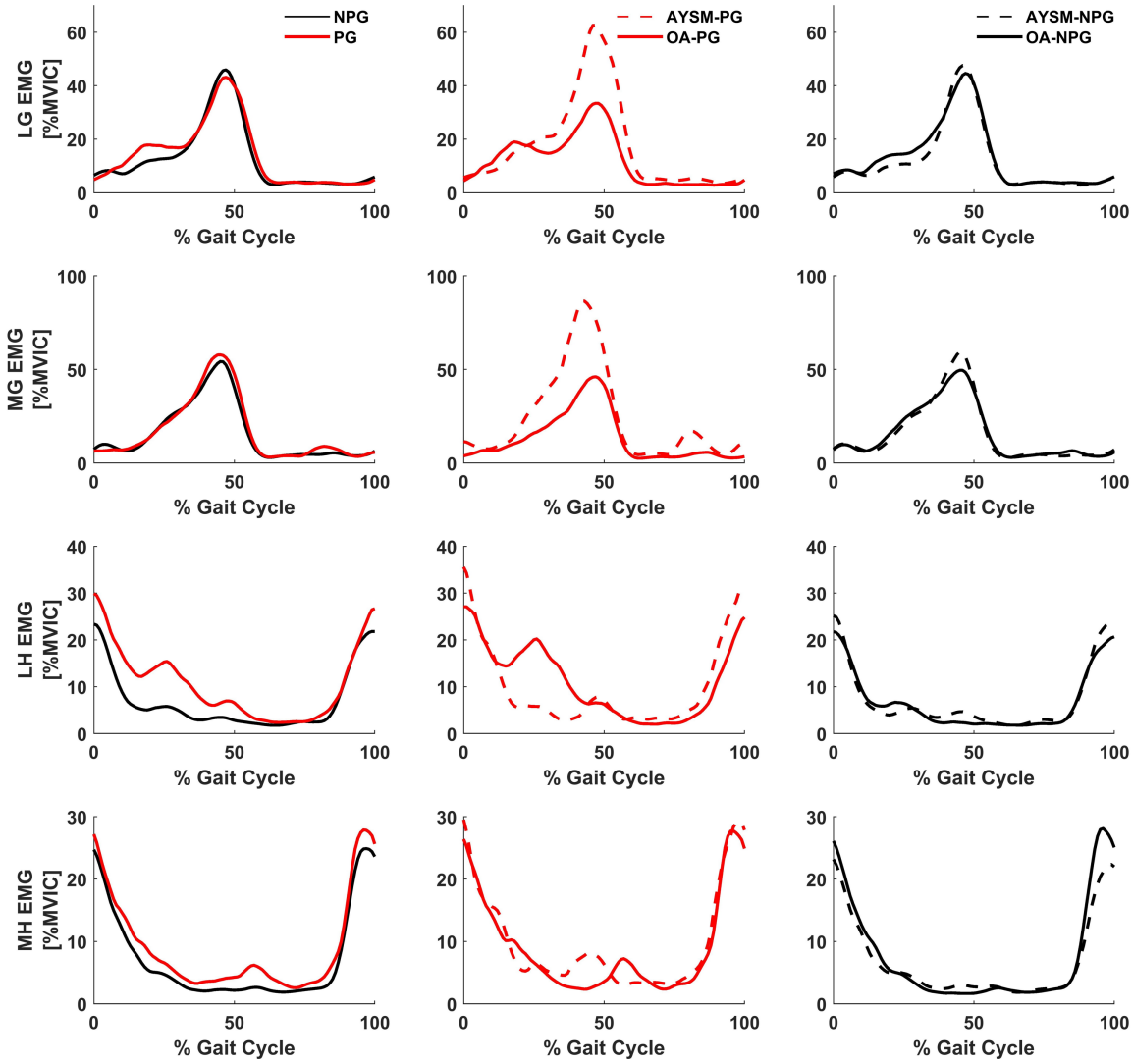


Figure 4. 3 Ensemble Averaged Gastrocnemius and Hamstring EMG Waveforms for PG (Red) and NPG (Black) (Left Column). The Middle and Right Columns Display the Average Waveforms for OA (Solid) and ASYM (Dashed) Participants in Each Progression Group.

4.4 Discussion

This study captured a shorter term (three year) radiographic progression of medial tibiofemoral joint space narrowing in a combination of asymptomatic and clinically diagnosed medial compartment knee OA participants. In three years, there was a

relatively low percentage of participants that progressed than what has been previously reported (Miyazaki et al., 2002, Mikesky et al., 2006), however significant differences in key biomechanics and muscle activation waveforms were found for those who progressed radiographically compared to those who did not.

The PG in this study were on average seven years older than the NPG. Despite a large age difference, baseline gait speed, BMI, and lower extremity muscle strength -- potential contributors to changes in gait biomechanics or muscle activation observed in this study -- were not different between groups. The PG's WOMAC scores, although low, were almost double that of the NPG for each dimension, implying higher baseline levels for self-report pain, function, and stiffness. The baseline differences in age and symptoms of the PG weaken the interpretation of the biomechanical and neuromuscular results stemming from purely structural changes at the joint level.

There were no statistically significant differences identified in the baseline KAM impulse or overall magnitude of KAM during stance (PC1) between the PG and NPG, but a significant difference in the first peak of KAM was observed. The higher peak moment supports the longer-term radiographic progression results of Miyazaki et al. (2002) and also reflects the differences found between people who progressed to TKA from those that did not (Hatfield et al., 2015b). The PG had significantly greater difference between the magnitude of first peak and midstance KAM magnitude, captured by the second principal component of the waveform (PC2). This differential feature was primarily a result of the greater first peak (Figure 4.2) as there was no difference between the KAM midstance magnitude (Table 4.2). Lower KAM 'unloading' at mid-stance has been previously associated with longitudinal clinical progression to TKA (Hatfield et al., 2015b) and with cross-sectional clinical OA severity (Astephen et al., 2008b), (Rutherford et al., 2008b). In a recent study (Astephen Wilson et al., 2016) of symptomatic and asymptomatic groups of individuals with the same radiographic OA grade (Kellgren and Lawrence, 1957), the symptomatic group walked with less mid-stance KAM unloading than the asymptomatic group, despite similar structural damage. These current results suggest that higher peak KAM, but not necessarily more constant or overall magnitude of KAM, is associated with structural OA progression at three years.

Interestingly, a significant difference in the pattern of the transverse plane moment of the knee during stance in those with three-year structural progression was identified, with the PG having a significantly larger range of external to internal rotation moment throughout stance (KRM PC1). This pattern difference, qualitatively, was more evident in the ASYM-PG (Figure 4.1), and merits further research to understand if this gait feature is consistently present at early stages of knee articular cartilage structural degradation. Only a few studies to date have examined the potential contribution of the knee internal rotation moment with respect to OA and those that have done so present conflicting results. It has been previously reported that individuals with OA had a higher knee internal rotation moment magnitude during stance phase (Gok et al., 2002), however the authors provided insufficient information to facilitate a discussion of this finding, particularly if the convention used was internal or external moments, or if the observed change was in early or late stance. Landry et al. (Landry et al., 2007a) used PCA to extract features and also found a significant group (OA versus Asymptomatic) effect for KRM PC1, however the effect was opposite: that OA participants had significantly lower (external) knee external rotation moment magnitudes during early stance. Although this moment is often left uninterpreted due to variability, the first principal component of the transverse plane moment at the knee joint, representing the range from external rotation moment to internal rotation moment, has been shown to have good test-re-test reliability (ICC 0.84 (CI: 0.60 -0.94) (Robbins et al., 2013). We chose to use the joint coordinate system (JCS) (Grood and Suntay, 1983) to model the loading of the knee joint, and therefore the transverse plane moment in this study is about an approximate long axis of the tibia. The sensitivity of this moment to common coordinate system definitions should be established to facilitate the use and discussion of this moment in future gait studies, similar to what has previously been done for the KAM (Brandon and Deluzio, 2011). The interaction of this moment with other gait features should also be explored further. It also may not be the transverse loading alone that is of concern, but the coupling of the frontal and transverse moments that result in joint damage. The coupling of the KAM and KRM has been previously studied with respect to ACL strain whereby the combined knee valgus and internal rotation moments increased ACL strain more than either moment did alone (Shin et al., 2011). The potential coupling of these two moments with respect to

knee OA is novel and requires further research, specifically, as to whether the resultant knee rotation moment is associated with greater shear stress on the joint and articular cartilage within the joint.

Statistically significant differences in the activation of the lateral hamstrings and lateral gastrocnemius during gait between the PG and NPG were found. Although the differences are small in magnitude, the PG displayed greater overall activation of the lateral hamstrings during gait (PC1), and less difference in activity from early to mid-stance (PC2), in addition to higher early- to mid-stance activity of the lateral gastrocnemius muscles. Higher and more prolonged stance phase activity of the lateral hamstrings has been previously associated with moderate knee OA (Hubley-Kozey et al., 2006) (Benedetti et al., 2003), and a higher Kellgren Lawrence structural severity grade (Rutherford et al., 2013). Recently, higher lateral hamstring activity (PC1) with symptomatic OA compared to asymptomatic with the same structural grade was also found (Astephen Wilson et al., 2016), consistent with the PG in this study having higher self-report WOMAC pain at baseline. There were no statistically significant group differences in lower extremity muscle strength measured during the MVICs, thus it is unlikely that the muscle activity differences found here are reflective of differences in muscle strength between the groups. The torque values (representing muscle strength) in the current study were slightly higher than those previously reported for similar groups of asymptomatic and participants with moderate OA (Hubley-Kozey et al., 2006), but still within an expected, typical range.

The theories regarding the mechanical rationale for higher lateral site muscle activity include a neuromuscular strategy to unload the medial compartment of the knee in early stance, and a mechanism to increase knee joint stability throughout stance (Schipplein and Andriacchi, 1991). Interestingly, Brandon et al. (2014) showed that prolonged lateral activation increases lateral tibiofemoral contact forces while preventing medial forces from increasing; however, total contact force is increased in the trade off to improve joint stability. Despite being a compensation to potentially unload the medial compartment, it is possible that the higher and more prolonged lateral muscle activity during stance contributes to higher overall joint loading, and therefore, contributes to accelerated structural degradation of the medial compartment. These results and

interpretation are cautioned by the small sample size and lack of consistent substantiation in the current literature. The only other study that longitudinally examined the effect of muscle activity during gait on changes in the medial cartilage volume at 12 months (using MRI) found that longer duration of medial site muscle co-contraction (medial hamstrings, quadriceps) was associated with more cartilage loss (Hodges et al., 2016). It is possible that both prolonged medial side or prolonged lateral side activity can have negative consequences on medial joint cartilage, but clearly more research is needed.

Although limited to qualitative comparisons, the three asymptomatic participants that had medial joint space narrowing had distinct knee moment waveforms from their OA-progression counterparts. The larger range of internal to external rotation moment and the larger peak-to-midstance differential of the knee adduction moment, patterns not typical of medial compartment OA gait, were more pronounced in this sub-set of the progression group, potentially driving the main group effect. These patterns are interesting but require further investigation to understand the implications on the loading of knee joint in a "pre-OA model."

The rationale for looking earlier in the disease process and even before a clinical diagnosis has been made to reduce the potential for confounding factors of more severe stages of OA, thereby enabling a more focused study on the relationship between joint mechanics and structural changes. This methodological decision resulted in a low percentage of individuals who progressed, and an inability to statistically separate the asymptomatic participants from the OA participants in the progression group. It remains difficult to discern whether the significant age difference, and self-report of symptoms at baseline were the larger signal of future progression and how much information was gained by the differences in knee mechanics and muscle activation. There is a clear need to understand the indications of rapid future degeneration of the knee joint to intervene appropriately and in a timely manner. The definition of subgroups based on the rate in which the joint deteriorates may lead to improved and targeted interventions.

4.5 Conclusion

In general, the walking gait biomechanics of the progression group in this three-year radiographic study aligned well with previously reported characteristics of

diagnosed or symptomatic osteoarthritis, such as higher first peak adduction moment and higher and more prolonged lateral site muscle activity during gait. This indicates that these may be important features of OA structural progression regardless of the disease phase or follow-up time. The higher rotation moment range during stance found with the progression group is a novel finding that points to a need to better understand torsional joint loading and its implications for shear loading of the knee joint tissues. It should be noted that despite the statistically significant findings presented, the progression cohort represented a relatively small sample with variability in characteristics (gender, baseline disease state, age, etc.), and so the strength of the current results should be further validated with independent test sets. The sample size in the present study also prevented the exploration of meaningful multivariate relationships among the features identified, which could provide insight into how these features may interact in progressing joint structural damage.

CHAPTER 5

Three-Year Changes in Knee Moments and Muscle Activation Patterns With and Without Knee Osteoarthritis Clinical Diagnosis and Structural Progression

5.1 Introduction

Functional declines associated with knee osteoarthritis (OA) are most evident in later stages of the disease, characterized by muscle strength deficits (Slemenda et al., 1997), joint instability (Fitzgerald et al., 2004) and an inability to accomplish activities of daily living (Fitzgerald et al., 2004). As there may be a greater opportunity to successfully intervene at an earlier stage to mitigate functional losses (Roos and Arden, 2016), there has been a shift towards understanding and describing knee OA earlier in the disease process (Luyten et al., 2012), including early changes in joint level mechanics (Mahmoudian et al., 2017). Joint level mechanics provide an objective assessment of joint function and the opportunity to measure disease progression at a functional level. Longitudinal changes in gait may reflect a shift away from optimal joint mechanics and mark the start of a decline in general knee joint function, either triggering the OA process or accelerating an existing process. There is a high incidence of structural deterioration of the knee joints of undiagnosed asymptomatic individuals (Astephen Wilson et al., 2016), indicating that an OA diagnosis alone is not enough to understand functional implications of early structural changes in the knee joint. Worsening of radiographic features associated with knee OA (Scott et al., 1993) in a normal, elderly population are not always correlated to changes in functional walking ability (Lynn et al., 2007), underscoring the importance of investigating early changes in neuromuscular patterns and joint kinetic features which may precede gross motor changes in early knee OA.

Prospective research has revealed that higher than typical knee adduction moment (KAM) features during gait are associated with worsening of radiographic markers (Miyazaki et al., 2002, Davis et al., 2019) (Chang et al., 2007) and MRI features (Chang et al., 2015, Woollard et al., 2011) related to knee OA progression. The theory that higher

medial joint loads precipitate cartilage loss, creating a structural deformity which further propagates higher medial joint load (Felson et al., 2003) has not been well supported with evidence due to the lack of prospective data on the change in gait mechanics in concert with change in joint structure. Therefore, it is not yet known if the features of knee joint loading which are present prior to structural progression, continue to change with the structural changes at the joint.

The majority of knee-OA-biomechanics studies have focused primarily on the frontal plane moment, and as a result, less is known about the relationship between the other planes of loading. Findings linking the peak knee flexion moment (KFM), an indication of greater compressive loads on the joint, to knee OA structural progression (Chang et al., 2015, Chehab et al., 2014, Davis et al., 2019) have been inconsistent, and investigations into the potential role of the transverse plane loading with structural OA are not well represented in the current literature. Changes in muscle activation patterns with structural progression has also been inconsistent. Longer activation times of medial knee joint muscles has been suggested to accelerate cartilage loss (Hodges et al., 2016), while prolonged activation of lateral muscles has also been recently associated with three-year structural progression of knee OA (Davis et al., 2019). Assessing the relative stability, quantified by the effect of time of each feature, of these metrics with and without OA diagnosis and structural progression will aid in the association of knee joint loading parameters to knee OA structural progression.

The purpose of this study was to quantify changes in knee joint moments and muscle activation patterns during walking at a self-selected speed between baseline and a three-year follow-up for asymptomatic individuals (ASYM) and individuals diagnosed with moderate levels of medial compartment knee OA who do not progress clinically or structurally in three years (OA), and those who experienced medial joint space narrowing during the three-year study (Progression Group; PG). We hypothesized that at three years follow-up, the joint moment patterns of the PG would move towards more severe radiographic knee OA patterns, specifically higher peak KAM and KAM impulse and prolonged activation of muscles to stabilize the worsened structure of the affected joint (Hodges et al., 2016, Rutherford et al., 2013). We hypothesized that without changes in joint structure or clinical status, the OA and ASYM groups would not have significant

deviations in gait mechanics or muscle activation patterns in three years and therefore would display “stable” gait.

5.2 Methods

The procedures followed were in accordance with the ethical standards of the Nova Scotia Health Authority Research Ethics Board. Twenty-one asymptomatic adults and thirty-one individuals diagnosed with moderate, medial compartment knee OA were recruited for this study. Participants with knee OA were diagnosed by an experienced orthopedic surgeon following American College of Rheumatology (ACR) criteria, including both radiographic and clinical symptoms (Altman et al., 1986). The distinction of moderate knee OA was made based on relatively high joint function (participants self-report they could walk a city block, jog five meters and ascend/descend stairs) and were not yet scheduled for arthroplasty surgery (Hubley-Kozey et al., 2006). The predominance of medial compartment OA was determined by a greater medial than lateral joint space narrowing (JSN) score (Scott et al., 1993). For all participants, exclusion criteria included a history of any neuromuscular disease, any other form of arthritis, or major surgery to the lower limb that could affect gait. All individuals signed a written consent form in accordance with the institutional ethics review.

Baseline and three-year follow-up gait analyses were performed at the Dynamics of Human Motion laboratory following a standardized protocol (Davis et al., 2019) which has been shown to be reliable for joint moments (Robbins et al., 2013) and electromyography (Hubley-Kozey et al., 2013b). Motion data were captured using an Optotrak™ system (Northern Digital Inc., Waterloo, ON, Canada) at 100Hz and external ground reaction forces were measured using an AMTI™ force plate (AMTI Inc., Watertown, MA, USA) captured at 2000Hz.

Bipolar surface electromyography (EMG) electrodes (10 mm diameter, 20 mm inter-electrode distance) were attached to the skin over seven muscle sites using standardized procedures (Hubley-Kozey et al., 2006): the rectus femoris (RF), vastus lateralis and medialis (VL, VM), lateral and medial hamstrings (LH, MH), lateral and medial gastrocnemius (LG, MG), and a reference electrode on the shaft of the tibia. Raw EMG signals were amplified (8-channel AMT system, Bortec Inc., Calgary, AB, Canada)

and sampled at 2000 Hz, and synchronized with the motion capture system. A bias trial and series of exercises previously described (Hubley-Kozey et al., 2006) were performed after the walking trials to elicit maximum voluntary isometric contractions (MVIC) and obtain knee extensor and flexor strength along with plantarflexion strength.

Custom Matlab (The Mathworks Inc., Natick, MA, USA) code was used to calculate the three-dimensional net resultant external moments during gait using a previously described inverse dynamics procedure (Landry et al., 2007a). Joint moments were normalized to body mass (Nm/kg) and projected onto the joint coordinate system (Grood and Suntay, 1983). Moment waveforms were time normalized to the stance phase of one gait cycle from initial contact (0%) to terminal stance (100%). All EMG processing was completed in Matlab using previously published methods (Hubley-Kozey et al., 2006) shown to yield good to high between day reliability (Hubley-Kozey et al., 2013b). EMG data were full wave rectified, low pass filtered at 6 Hz, amplitude normalized to MVIC, and time-normalized to one complete gait cycle from initial (0%) to second (100%) foot contact with the ground.

Principal component analysis (PCA) was applied to a larger dataset of 240 individuals with moderate knee OA and 188 asymptomatic individuals to extract stable and robust mutually uncorrelated amplitude and pattern features (Principal Components, PCs) within gait waveform data that optimally describe the variability among observations of knee moments and muscle activation patterns (Chapter 3). PC scores were calculated for the 48 participants in this study at baseline and follow-up by calculating the dot product between the individual subject waveform and each respective PC. Reconstruction errors were calculated for each participant to ensure the PCs from the larger dataset were representative of the current cohort. Conventional metrics for the KAM were also calculated to facilitate comparison to existing literature, including the impulse (Nm*s/kg), first (0-40% stance) and second (70-100% stance) peak, and the midstance minimum (40-70% stance) (Nm/kg).

All participants underwent baseline and three-year follow-up standardized X-rays of their gait-tested knee joint. Joints were graded based on Kellgren and Lawrence criteria (Kellgren and Lawrence, 1957) and medial and lateral joint space narrowing (JSN) (Scott et al., 1993). All grading was performed by an experienced orthopaedic

surgeon, with a high intra-rater reliability (WDS, kappa = 0.99 for medial JSN, (Hatfield et al., 2015b)). Structural progression was defined by a one grade increase in medial JSN at follow-up compared to baseline.

Baseline demographic data were compared using one-way ANOVAs or Kruskal Wallace tests where appropriate. Generalized Estimating Equations were used to test for significant group-by-time interactions using a linear regression model. Tukey HSD post-hoc tests were completed for variables with a significant group main effect. All statistical tests were performed in SPSS (SPSS, IBM SPSS Statistics v. 24).

5.3 Results

Three ASYM participants and seven OA participants had increased medial joint space narrowing scores at three years and were combined into one progression (PG) group. Four OA participants had a baseline medial JSN score of three, preventing further structural progression based on the study definition and were excluded from the analysis, leaving 18 participants in the ASYM and 20 in OA groups. Two of the ten participants in the PG group had a change in clinical status at follow-up in addition to the change in medial joint space: one ASYM participant was diagnosed with knee OA and one OA participant was recommended for a total knee replacement during the course of the study. The ASYM participant who was diagnosed with knee OA, however, had no change in WOMAC scores at follow-up, indicating that the diagnosis may not correspond to worsening symptoms.

There were several demographic variables that differed among the three groups at baseline (Table 5.1). The ASYM group had a higher proportion of women and lower radiographic scores for medial JSN than the OA group. The WOMAC sub-scores were significantly lower for the ASYM group compared to both the OA and PG groups, but not significantly different between OA and PG groups. There were no significant demographic differences between the PG and OA groups (Table 5.2).

Table 5. 1 Baseline Group Demographics

	P-value	ASYM Mean	ASYM SD	OA Mean	OA SD	PG Mean	PG SD
Sample size		18		20		10	
*Sex (F:M)	**0.004**	15:3		7:13		3:7	
*JSN Medial (0:1:2:3)	**0.009**	0:16:2:0		1:6:13:0		1:6:3:0	
*JSN Lateral (0:1:2:3)	0.754	12:6:0:0		15:4:1:0		8:2:0:0	
*KL Global (1:2:3:4)	0.800	0:14:4:0		0:2:10:8		1:5:4:0	
Age (years)	**0.008**	52.95	8.47	55.85	6.08	61.30	6.27
Mass (kg)	0.062	76.98	15.06	89.10	17.70	88.96	19.95
BMI (kg/m^2)	0.521	28.05	4.30	29.70	4.90	29.67	5.36
Speed (m/s)	0.565	1.32	0.13	1.27	0.18	1.32	0.19
*WOMAC Pain Sum (/20)	**0.000**	0.06	0.24	4.50	3.24	5.50	4.70
*WOMAC Stiffness Sum (/8)	**0.001**	0.44	0.92	2.45	1.85	2.60	2.32
* WOMAC Function Sum (/68)	**0.000**	1.06	2.46	15.00	11.09	17.70	16.42
* WOMAC Total (/96)	**0.000**	1.56	3.48	21.95	15.27	25.80	23.12
Knee extension torque (Nm/kg)	0.426	1.50	0.30	1.63	0.43	1.44	0.33
Knee flexion torque (Nm/kg)	0.285	0.64	0.26	0.73	0.31	0.82	0.25
Plantarflexion torque (Nm/kg)	0.611	1.22	0.32	1.15	0.34	1.28	0.24

*Kruskal-Wallis Test

Interaction effects

The WOMAC sub-scores for pain ($P < 0.001$), stiffness ($P=0.002$), function ($P=0.001$) and the total WOMAC score ($P<0.001$) had significant group-by-time interactions. Post hoc analysis revealed no change in the WOMAC scores for ASYM or PG, while all three sub-scores and the total score for the OA group were significantly lower at follow-up, indicating a fluctuation in the self-report of symptoms (Figure 5.1). There were no significant group by time interaction effects for any knee joint moment or EMG variable.

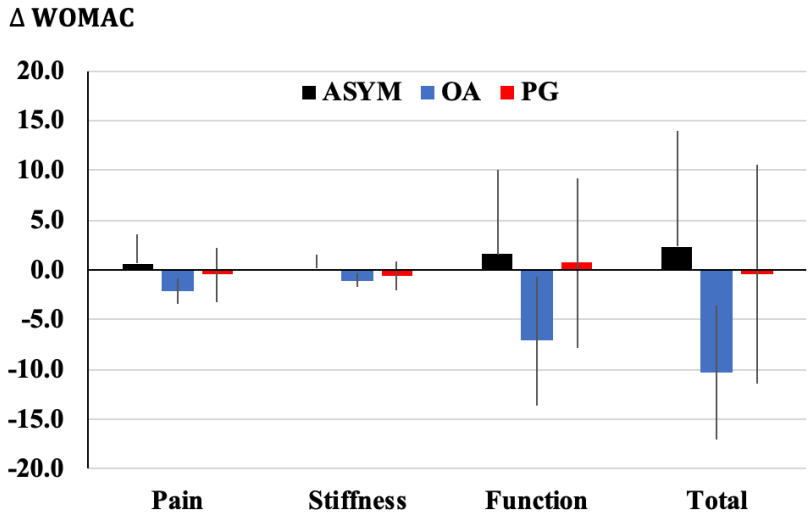


Figure 5. 1 Change in WOMAC Scores from Baseline to Follow-Up

Table 5. 2 Pair-wise comparisons for demographic variables with significant group differences baseline

Description	ASYM – OA P-value	ASYM – PG P-value	OA – PG P-value
*Sex (M/F)	**0.010**	**0.021**	0.846
*JSN Medial (0:1:2:3)	**0.009**	0.689	0.131
Age (years)	0.267	**0.006**	0.120
*WOMAC Pain (/20)	**0.000**	**0.000**	0.681
*WOMAC Stiffness (/8)	**0.000**	**0.027**	0.846
*WOMAC Function (/68)	**0.000**	**0.002**	0.846
*WOMAC Total (/96)	**0.000**	**0.002**	0.846

*Mann-Whitney U Test

Group main effects

The three groups were distinguished by significant differences in the KAM impulse (p=0.050), KAM first peak (p=0.033), KRM PC1 (p=0.002) and LG PC3 (p=0.021). For KAM impulse and first peak, post hoc analysis revealed significant differences between ASYM and PG only (p=0.013, p=0.004 respectively), while for

KRM PC1 and LG PC3 there were significant differences between ASYM and OA (p=0.014) and ASYM and PG (p=0.001) but no difference between OA and PG.

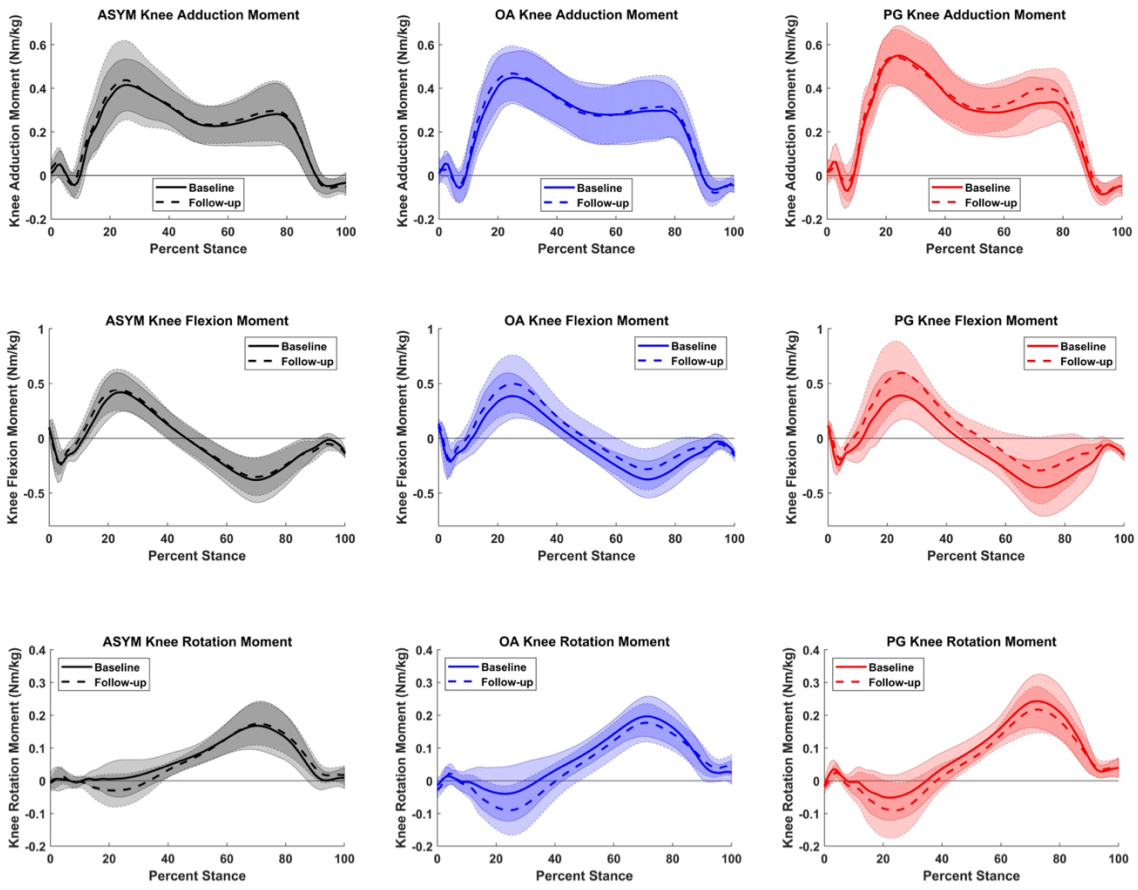


Figure 5. 2 Knee Joint Moment Waveforms for Baseline (Solid) and Follow-Up (Dashed) for the Three Groups

Time main effects

There were no significant changes over time for mass, BMI or gait speed for any group. There was a significant main effect of time effect for all three strength measures (knee extension (KE) torque (P<0.001), knee flexion (KF) torque (P<0.001) and plantarflexion (PF) torque (P=0.006)) at follow-up, where torques at follow-up were lower than at baseline (Table 5.3). The knee flexion torque trended towards a significant group by time interaction (p=0.058) with the PG having a substantially greater reduction than the other two groups.

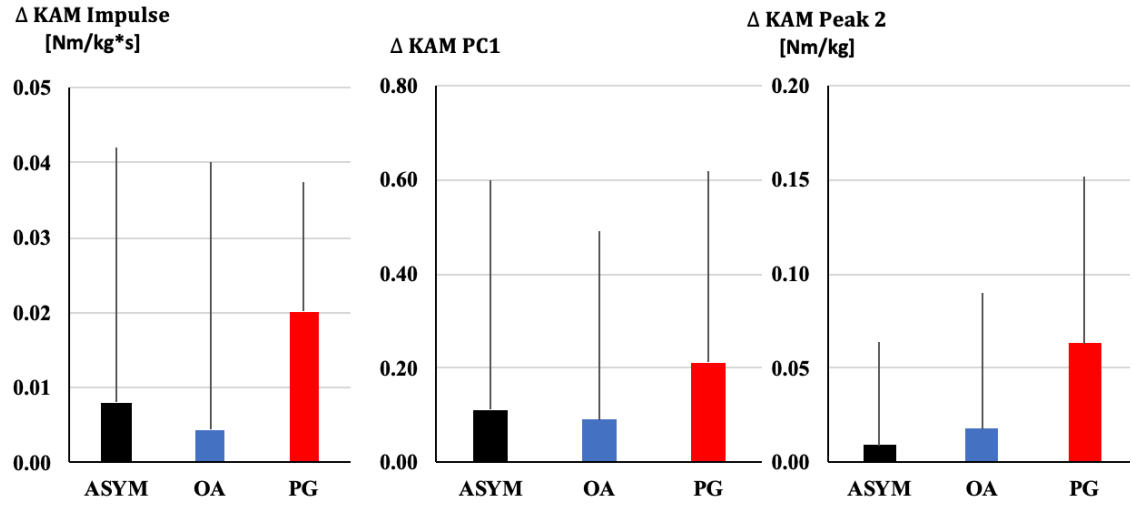


Figure 5. 3 Three-Year Change for KAM Impulse (Left), KAM PC1 (Middle) and KAM Peak Two (Right) for ASYM (Black), OA (Blue) and PG (Red). Error Bars are Standard Deviations

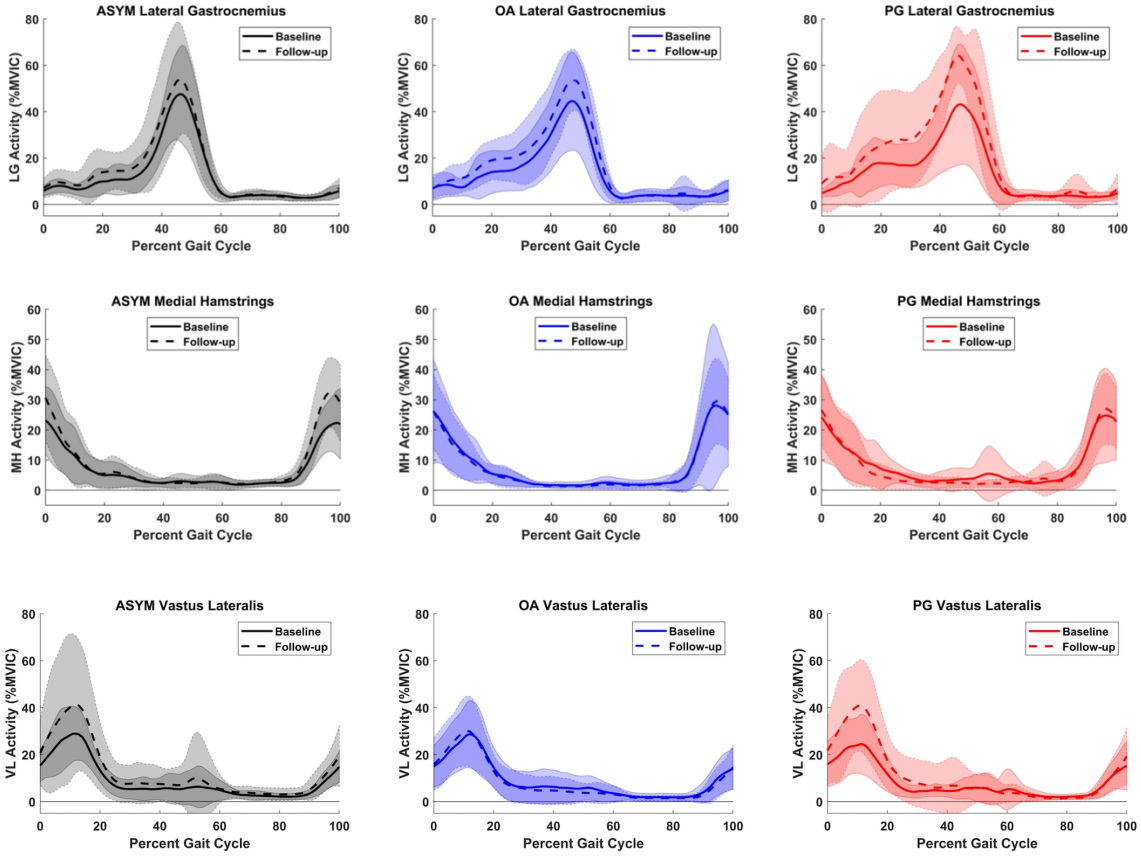


Figure 5. 4 Ensemble Average EMG waveforms for LG, MH and VL at Baseline (solid) and Follow-up (dashed) for ASYM (Black), OA (Blue) and PG (Red).

Table 5. 3 Variables with a Significant Interaction Effect or Main Effect of Group or Time

	Generalized Estimating Equations (GEE)			Difference (FU-BL)					
	p-value			ASYM (n=18)		OA (n=20)		PG (n=10)	
	Group	Time	G*T	Mean	SD	Mean	SD	Mean	SD
Pain	<0.01	0.08	**<0.01**	0.67	1.33	-2.10	2.85	-0.50	2.80
Stiffness	<0.00	0.01	**<0.01**	0.11	0.68	-1.05	1.43	-0.60	1.43
Function	<0.01	0.16	**<0.01**	1.56	6.49	-7.10	8.55	0.70	8.46
Total	<0.01	0.06	**<0.01**	2.33	6.73	-10.25	11.55	-0.40	10.96
KE Torque (Nm/kg)	0.40	**<0.01**	0.62	-0.24	0.24	-0.21	0.44	-0.14	0.24
KF Torque (Nm/kg)	0.31	**<0.01**	0.06	-0.07	0.13	-0.06	0.22	-0.17	0.11
PF Torque (Nm/kg)	0.33	**0.01**	0.17	-0.29	0.35	-0.12	0.28	-0.06	0.40
KAM Impulse (Nm/kg*s)	**0.05**	**0.01**	0.17	0.01	0.03	0.00	0.04	0.02	0.02
KAM Peak 1 (Nm/kg)	**0.03**	0.52	0.94	0.01	0.11	0.01	0.09	0.00	0.09
KAM Peak 2 (Nm/kg)	0.07	**0.01**	0.18	0.01	0.05	0.02	0.07	0.06	0.09
KAM PC1	0.06	**0.03**	0.72	0.11	0.49	0.09	0.40	0.21	0.41
KAM PC3	0.69	**0.01**	0.52	0.05	0.24	0.99	0.21	0.17	0.33
KFM PC1	0.65	**<0.01**	0.06	0.22	0.91	0.64	0.99	1.09	1.05
KFM PC2	0.58	**0.01**	0.16	-0.05	1.28	-0.49	1.22	-0.87	1.06
KRM PC1	**<0.01**	0.06	0.80	0.16	0.41	0.13	0.37	0.05	0.42
KRM PC2	0.24	**<0.01**	0.15	-0.07	0.27	-0.24	0.39	-0.24	0.31
LG PC1	0.38	**<0.01**	0.33	28.07	96.93	37.04	83.07	84.22	93.44
LG PC3	**0.02**	0.34	0.82	-3.27	26.85	-8.46	23.88	-9.81	63.54
VL PC1	0.40	**0.02**	0.33	43.21	95.94	6.65	59.43	31.18	60.45
MH PC2	0.73	**0.01**	0.46	-18.69	21.94	-10.55	-29.74	-6.78	-29.04

Moment and EMG variables with a significant main effect of time are summarized in Table 5.3. Multiple features of the KAM, the early stance flexion moment magnitude (KFM PC1), the range of early stance flexion moment to late stance extension

moment magnitude (KFM PC2) and mid- to late-stance internal rotation magnitude (KRM PC2) had significant time effects. Three EMG variables had a main effect of time: LG PC1, VL PC1 and MH PC2 (Figure 5.6).

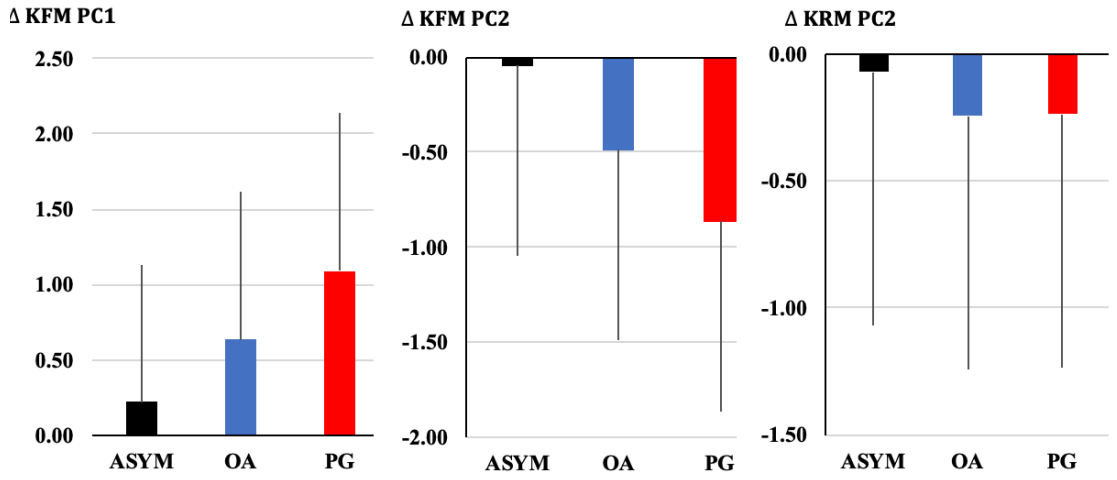


Figure 5. 5 Three-Year Change for KFM PC1 (Left), KFM PC2 (Middle) and KRM PC2 (Right) for ASYM (Black), OA (Blue) and PG (Red). Error Bars are Standard Deviations

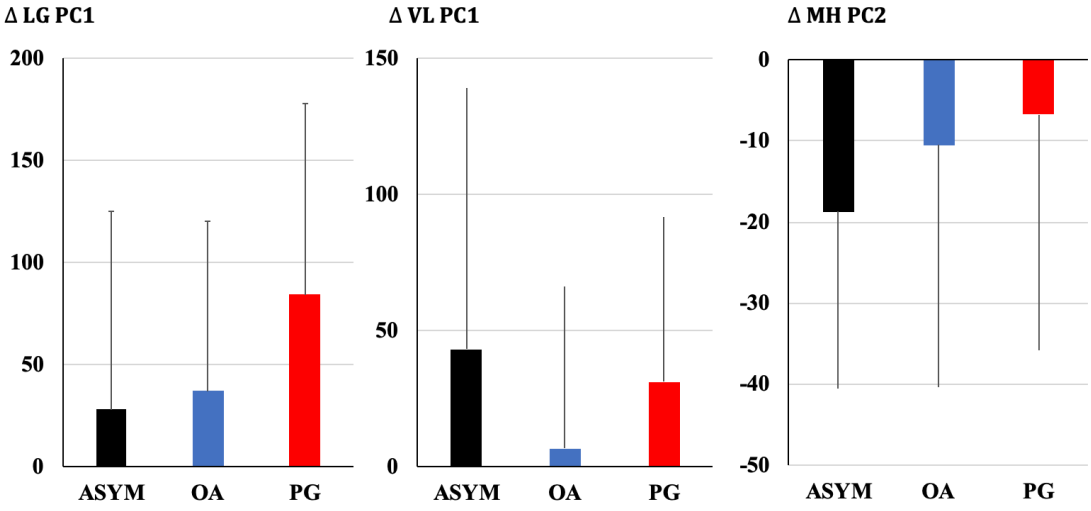


Figure 5. 6 Three-Year Change for LG PC1 (Left), VL PC1 (Middle) and MH PC2 (Right) for ASYM (Black), OA (Blue) and PG (Red). Error Bars are Standard Deviations

5.4 Discussion

This was the first study to assess how knee joint moments and muscle activation patterns change over time with and without clinically diagnosed medial compartment knee OA and structural progression. Because structural joint changes can and do occur regardless of clinical symptoms, understanding structural progression independent of any clinical changes is a step towards understanding the progressive deterioration of joint structures and joint function that occur with and at times prior to knee OA diagnosis. The need to better understand early knee OA motivated the comprehensive radiographic and biomechanical evaluation of both asymptomatic and moderate knee OA cohorts. Due to the low incidence of radiographic changes in the ASYM group, it was not possible to analyze the asymptomatic participants who progressed separately, and this remains a target for future research.

The study did not result in any group by time interaction effects for knee joint moment or EMG features, however the magnitude of the three-year change in knee moment variables with a significant main effect of time were greatest in the PG group and lowest in the ASYM group. The relatively small sample and large variance in three-year changes in knee moment PCs may have limited the analysis, however the interesting trends observed deserve further research. The self-reported clinical symptoms did not increase over time for the PG group, and therefore the changes in gait observed are unlikely a response to worsening clinical symptoms, but rather to the reduction in joint space for the PG, or other neuromuscular changes and compensations that have a low correlation to clinical symptoms. The measured improvement in reported symptoms of the OA group is interesting and may provide insight into gait modifications to reduce pain and prevent structural worsening, however the magnitude of the differences are below the minimum clinically important difference (MCID) for WOMAC that has been determined for TKA patients (Escobar et al., 2007). Although it is not known what the MCID for this moderate OA cohort is, these changes may not be clinically relevant.

The ASYM group in the present study was predominantly female (15/18) and relatively young (mean age 52 years at baseline) and did not exhibit age-related changes in gait that have been previously attributed to two-year longitudinal changes in an older control group of women (mean age 63 years) (Mahmoudian et al., 2017). The ‘stability’

of the average gait pattern of the ASYM group is an important finding, adding confidence to the use of ASYM gait patterns as a metric of non-diseased mechanics, however it does not address the relative stability of each individual participant's gait over a three-year period. Some ASYM cases showed substantial variation between baseline and follow-up, highlighting the need to better understand the natural variability of individual gait patterns and the effect of knee OA on this variability.

The KAM impulse had a significant main effect of time where the magnitude of the change was greatest for the PG group, which was more than two times greater than the other groups (although not statistically compared). Mahmoudian (2017) recently reported increases in the KAM impulse in a cohort of women with "established knee OA" (KL > 2) over two years, however structural changes were not measured, and it was unclear if this change was related to structural progression. While the increased KAM impulse in this study seems to be driven by a higher second peak in the PG group, Mahmoudian et al., (2017), suggested the finding in their study was due to an increase in the midstance KAM. A high midstance KAM has recently been attributed to knee OA symptoms rather than radiographic severity (Astephen Wilson et al., 2016), however both pattern changes could signal greater loading of the medial compartment, which could have implications for progression.

The greater knee flexion moment magnitude in early stance (KFM PC1) and lower late stance extension moment magnitude (KFM PC2) at follow-up were most evident in the OA and PG groups and there was a trend towards a significant interaction effect for KFM PC1 (P=0.06). Previous cross-sectional research showed that severe OA cohorts tended towards a lower flexion moment in early stance compared to asymptomatic controls (Deluzio and Astephen, 2007). However, the lower knee flexion moment associated with knee OA has also been attributed to the symptoms of knee OA as opposed to the structural severity (Astephen Wilson et al., 2016). Hatfield et al. (Hatfield et al., 2015b), found reduced knee flexion to extension moment range was associated with longitudinal (7-9 years) clinical OA progression, but not necessarily with degenerative changes. Chehab et al., (2014) found that cartilage thinning and reduction of the medial-to-lateral thickness ratio during a five-year follow-up period were associated with higher KFM at baseline. The results of this study suggest that increases in the stance

phase KFM in the early stages of radiographic knee OA may correspond to further worsening of the joint structure by increasing the total load on the knee joint. Mahmoudian et al., (2017) reported a decreased second peak of the external knee flexion moment after two-years in women with established OA. The waveforms presented were not typical as there was no extension moment in mid-to-late stance and an exaggerated flexion moment in late-stance. The overall effect on the waveform is a shift in the overall magnitude (y-direction), and therefore might correspond to the KFM PC1 differences found in this study.

As resultant moments underestimate the joint load when antagonist muscle activation is present, it is likely that the total knee loading environment was higher for PG than estimated by the KFM alone, due to higher and more prolonged activation of the LG (group main effect). Increased LG activation with OA has been previously reported (Rudolph et al., 2007) and proposed as a mechanism to limit knee motion or a strategy to improve stability at the joint. Recent modeling of the change in contact forces with increased lateral muscle activation suggests that this strategy does not seem to reduce medial compartment contact forces (Brandon et al., 2014); an idea supported by the structural worsening of the PG group, concurrent with increased lateral site muscle activation in this study. It is unclear what the effect of alteration in vastus lateralis and medial hamstring activation may have on the loading environment of the knee.

Both PG and OA groups had changes in the KRM that tended towards external rotation during mid-stance at follow-up. Knee OA has been previously associated with less early stance external KRM (McKean et al., 2007) and less late stance internal KRM in a severe clinical OA cohort (Astephen et al., 2008a). It remains unclear what the relationship between alterations in the KRM and knee OA is, however, the reoccurrence of the association to knee OA highlights the potential importance of this gait variable (Chapter 4, Davis et al., 2019). A change in rotational loading may have implications for shear loading of the joint and therefore a general change in the type of load borne by the structures of the joint at different points in the gait cycle. In a prospective study on gait following ACL reconstruction (ACL-R), increased peak knee flexion moment and similar shift in the rotation moment at mid-stance were found over time (Erhart-Hledik et al., 2017). An increase in the KFM following reconstruction surgery is often attributed to

improvements in quadriceps strength and function (Lewek et al., 2005), however the ACL-reconstruction population is at high risk of future development of knee OA, and this current study suggests there is a potential risk of a higher KFM and altered KRM related to the future structural progression of knee OA.

The similarity in the longitudinal changes in the sagittal and transverse plane observed (qualitatively) in the OA and PG groups suggest that the OA group may have had some level of structural change that was below a grade change detectible on the radiograph, but precipitated changes in joint mechanics in a similar manner to PG. It could also be that the baseline symptoms and structural disease resulted in a progressive decline in function over time, regardless of further structural worsening. In this view, the change in patterns of knee joint loading and muscle activation are more sensitive than a change in radiographically scored medial joint space narrowing grade. A second follow-up measurement of radiographic severity and gait assessment would allow for a more refined view of this relationship. Due to the stability of the self-reported symptoms in the PG and the decreased symptoms of the OA group, the changes in gait over time were likely reflecting the structural disease before symptoms created a need for compensation.

5.6 Conclusion

The biomechanical and muscular activation patterns that changed over time with OA and medial joint space narrowing (PG) provide evidence of higher general load on the knee joint that may precipitate the structural changes observed. There was a difference in the overall stability of gait patterns based on clinical status, providing initial evidence for the potential use of gait mechanics as an indicator of structural changes in the knee joint. The stability of the ASYM group over the three-year follow-up period supports the use of longitudinal gait analysis to identify local mechanical factors related to knee OA progression.

CHAPTER 6

Sex and Puberty Dependent and Independent Features of Knee Joint Moments During Over-Ground Walking and Running

6.1 Background

Adolescent and young adult women have a greater probability of incurring an overuse or traumatic knee injury compared with their male counterparts (Knowles, 2010, Murphy et al., 2003, Dugan, 2005, Myer et al., 2010). This has been partly attributed to musculoskeletal changes that occur during puberty, such as delayed hamstring strength relative to quadriceps (Quatman-Yates et al., 2013) and altered lower limb biomechanics (Hewett et al., 2006, Ford et al., 2010). Not only is joint trauma associated with significant pain and reduced physical function, it is also associated with an increased risk for musculoskeletal diseases such as post-traumatic knee osteoarthritis (OA) (Ajuied et al., 2014, Lohmander et al., 2004). The identification of individuals who are at a high-risk for future joint injury and subsequent knee OA is of clinical interest as prevention of knee OA through prevention of injuries to the joint is the single greatest opportunity to alleviate the physical and fiscal burden of the disease (Roos and Arden, 2016).

Abnormal frontal plane knee biomechanics have been associated with the sex disparity of joint injuries (Myer et al., 2015) and identified as risk factors for the later development of patellofemoral pain syndrome in runners (Stefanyshyn et al., 2006), knee pain in adulthood (Amin et al., 2004), and a potential risk factor for knee OA development (Lynn et al., 2007). Females tend to exhibit greater frontal plane moments in the stance phase of walking (Ro et al., 2017), running (Ferber et al., 2003), or in the plant limb during a variety of movements (McLean et al., 2005) compared with males. This may place abnormal stress on joint structures leading to premature failure (Kanamori et al., 2000, Lloyd and Buchanan, 2001, Hewett et al., 2005). There are, however, exceptions to these sex-specific differences with males having higher external knee adduction moments (KAM) than females with severe knee OA (Astephen Wilson et al., 2015), indicating that the relationship to joint mechanics is not necessarily constant or

pre-determined by sex. An increase in the peak external knee flexion moment (KFM) during running from pre-puberty to mid-puberty to late-puberty has been previously shown (Sayer et al., 2018), which could be partially attributed to lower limb growth and running speed. Although less is known about abnormal transverse plane moments, the consequence of an increased torque at the knee could be greater cartilage stress which was observed in females with patellofemoral pain, who ran with greater femur rotation (Liao et al., 2015). Altered patterns of the external knee rotation moment (KRM) have also recently been related to knee OA structural progression (Davis et al., 2019).

Sex differences in both the rate of knee injuries and frontal plane knee biomechanics emerge during puberty (Hewett, 2015, Ford et al., 2010, Quatman et al., 2006, Wild et al., 2016). Females undergo a substantial change in static frontal plane lower extremity alignment (Froehle et al., 2013), and research has demonstrated a reduction in neuromuscular control of the knee in postpubescent versus prepubescent females (Hewett et al., 2004, Ford et al., 2010, Kim and Lim, 2014). Rapid increases in height and center of mass during puberty (Hewett et al., 2004) in combination with females' musculoskeletal changes might contribute to changing biomechanical strategies throughout pubertal development (Wild et al., 2016).

Walking gait is the primary model used to study knee OA in older adults (Andriacchi et al., 2004), however, applying this model to young athletes may facilitate a submaximal assessment of joint function (Barrios et al., 2016). Researchers have used sport specific movements at game-level intensity to evaluate the mechanics of athletes and their subsequent risk of injury (Landry et al., 2007b). It is not known if walking knee mechanics capture similar biomechanical differences because of puberty stage that are seen in sport specific movements under which knee injuries tend to occur. By studying the most prominent pattern differences in knee joint loading during walking and running that occur due to physical maturation and the potential interactions between sex and pubertal stage, early mechanical signs of risk for chronic abnormal joint loading prior to irreversible joint damage may be identified. The objective of this study was to examine the effect of sex and maturation (puberty stage) on pattern and magnitude features of knee joint moments during walking and running gait in healthy athletic adolescents. We hypothesized that sex specific differences in knee joint loads will depend on puberty

stage and that females at later puberty stages will exhibit higher peak moments in the frontal plane during walking and running. We also hypothesized that knee moment patterns of walking would be able to discriminate sex and puberty to the same degree as running moment patterns.

6.2 Methods

6.2.1 Participants

Participants were recruited from the Annapolis Valley Minor Basketball and Soccer Associations, as well as from other sporting associations including minor and varsity soccer, basketball, volleyball, lacrosse, rugby, and football (Table 6.1). Participants were included if they were between the ages of 8-25 years, thereby including the full range of puberty stages for both males and females. Exclusion criteria included a history of trauma or injury to the lower extremities or lower back. Participants who had experienced an ankle sprain were eligible only if the injury had occurred at least three months prior to the test date and were cleared for return to sport by a trained practitioner or therapist.

Table 6. 1 Distribution of Primary Sport Participation

Sport	N	Sport	N
Baseball	2	Hockey	15
Basketball	52	Rugby	12
Football	17	Lacrosse	2
Handball	1	Soccer	71
Volleyball	5	Multi-sport	8

6.2.2 Data Collection

The collection of data was approved by Acadia University Research Ethics Board. Data were collected at the John MacIntyre motion Laboratory of Applied Biomechanics (mLAB) at Acadia University between June 2015 and December 2017. After receiving written consent by the participant and/or their parent/guardian, the participant completed questionnaires related to demographics, sport involvement and to pubertal status to

determine their puberty development score (Carskadon and Acebo, 1993). Participants completed the testing in their personal indoor footwear typically used for training or competition, compression shorts, and a tight-fitting shirt provided by the examiner. Participants' height, mass, maximum calf and thigh circumference for both legs, and foot width were measured.

Retro-reflective markers (14 mm) were attached to the participant's body to collect three-dimensional position data. The lower extremity maker-set included rigid clusters (rigid square plastic plates each with four non-collinear markers attached) fixed to the bilateral thighs, shanks and three-marker clusters attached to the rearfoot of both feet. Single markers were attached with double sided tape to anatomical bony landmarks, including right and left: posterior superior iliac spine, anterior superior iliac spine, greater trochanter, medial and lateral femoral condyles, tibial tuberosity, fibular head, medial and lateral malleoli, and first, second and fifth metatarsals (Chapter 3, Figure 3.2). Clusters were attached by Velcro to Fabrifoam compression wraps at the shank and thigh and further secured to the legs using tape.

A 12-camera motion capture system (Qualisys Oqus 4, Qualisys Track Manager (QTM) software (Qualisys, AB, Sweden)) was used to record the three-dimensional position of the retro-reflective markers during each trial at a sampling rate of 250 Hz. Ground reaction forces were simultaneously measured by three floor-imbedded force plates (Advanced Mechanical Technology, Inc., Watertown, MA), at a sampling rate of 2000 Hz. Participants completed multiple trials of self-selected speed over-ground walking and over-ground running at two thirds (66.7%) of maximum sprint speed. Maximum sprint speed was determined prior to the data collection on a 400m running track. Speed was monitored using Fusion Sport SmartSpeed timing gates (Fusion Sport, Brisbane, Australia) and four trials of each movement were recorded.

6.2.3 Data Analysis

Net external knee joint moments during the stance phase of running and walking were calculated in Visual3D (C-motion, Inc., Rockville, MD), using an inverse dynamics approach (Chapter 3). The foot, shank, thigh and pelvis were each modeled as a rigid body with a local coordinate system located at the segment's center of mass for each

respective segment. Three dimensional rotations were calculated using the Cardan/Euler Model (Woltring, 1994) and flexion/extension, ad/abduction, and internal/external rotation (XYZ) sequence. External moments were projected onto the Joint Coordinate System (Grood and Suntay, 1983) with flexion-extension moment (KFM) about the femoral embedded flexion axis, internal-external rotation (KRM) about the long axis of the tibia segment, and ad-abduction (KAM) about the mutually perpendicular axis to flexion and rotation. Kinematic and kinetic data were low pass filtered using a second-order bidirectional Butterworth filter with a 12 Hz cut off frequency. Each waveform (right and left legs from each participant) was amplitude normalized to body mass and time normalized to stance using 101 datapoints. The four trials of each movement for each subject and each leg were averaged and used in the subsequent analysis. Principal component (PC) scores were calculated for each participant's average waveform using the mLAB PC model (Chapter 3). The first three PCs for each moment were retained for analysis, which explained approximately 90% of the variance in the original dataset (Jackson, 1993).

6.2.4 Statistical Analysis

Interactions between sex and puberty were calculated for each PC score using a 2-factor analysis of variance (ANOVA: sex, puberty status). Puberty was separated into five categories (Carskadon and Acebo, 1993): pre, early, mid, late and post. Significant interactions were further analyzed using one-way ANOVAs for significant within sex puberty differences. Where there were significant main effects of puberty, Tukey post-hoc analyses were completed.

To test the hypothesis that the PC features of knee moment patterns of running and walking gait would be similar in ability to discriminate between sex and puberty cohorts, stepwise linear discriminant analyses were completed. To simplify the analysis and improve the sample size for each category, pre, early and mid-puberty were combined into one group: PRE-EARLY-MID (n= 74) while late and post puberty were combined into a second group: LATE-POST (n=121). Cross-validated classification rates were used to compare running and walking knee moments on the usefulness to differentiate between puberty and sex.

6.3 Results

Participant demographic and speed data are presented in Table 6.2.

Table 6. 2 Participant Data

Puberty	Sex	N	Age (years)		Mass (kg)		Height (m)		Walking speed (m/s)		Running speed (m/s)	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Pre	M	18	9.5	1.5	34.5	8.6	1.39	7.8	1.36	0.13	3.48	0.55
	F	9	9.4	1.2	32.1	19.0	1.42	6.4	1.44	0.10	3.46	0.33
Early	M	10	11.1	1.7	38.8	10.0	1.48	7.5	1.23	0.19	3.69	0.50
	F	6	10.7	0.8	38.7	5.5	1.47	7.5	1.45	0.25	3.59	0.47
Mid	M	13	13.8	1.6	55.4	7.8	1.70	6.9	1.44	0.15	4.42	0.46
	F	18	12.1	1.6	44.7	8.8	1.55	6.5	1.41	0.21	3.92	0.52
Late	M	17	17.1	3.2	73.1	10.3	1.79	7.1	1.36	0.14	4.53	0.35
	F	29	14.9	2.4	59.5	8.6	1.66	7.6	1.44	0.15	3.98	0.51
Post	M	28	21.3	2.5	84.1	11.0	1.82	6.9	1.37	0.18	4.70	0.46
	F	47	20.0	2.0	69.9	10.9	1.69	10.9	1.39	0.18	4.20	0.30

6.3.1 Walking Results

There were no sex by puberty interaction effects for walking speed. There was a main effect of sex on walking speed, where females walked slightly faster (1.41 m/s) compared to males (1.36 m/s).

KAM PC1, a feature representing the overall magnitude of the moment throughout stance phase of the gait cycle did not have a significant sex by puberty interaction effect, but both main effects were significant (Table 6.3, Figure 6.1). Male subjects had a significantly greater KAM PC1 score, indicating a greater overall magnitude of the frontal plane moment. While the general trend was towards a higher KAM PC1 score with more advanced puberty stages, post hoc testing revealed that there was no difference between pre-, early- and mid-puberty, but all three were lower than late- and post-puberty. There was no difference between late- and post-puberty (Figure 6.1). KAM PC2 and PC3 also had significant main effects of sex. Females had a greater

difference between the first and second peak (KAM PC2) and less difference between mid-stance to late-stance (KAM PC3) compared to males.

Table 6. 3 Analysis of Variance results for knee joint moment PC features during overground walking

		Variance Explained (%)	Puberty*Sex	Sex	Puberty
KAM	PC1	66.9	0.727	**<0.001**	**<0.001**
	PC2	15.6	0.145	**<0.001**	0.175
	PC3	7.5	0.219	**<0.001**	0.748
KFM	PC1	66.1	**0.014**	0.901	0.247
	PC2	20.3	0.464	0.524	**<0.001**
	PC3	6.1	0.406	0.130	**<0.001**
KRM	PC1	68.3	0.608	**<0.001**	**<0.001**
	PC2	13.4	**0.035**	0.337	0.020
	PC3	9.0	0.054	0.218	**0.003**

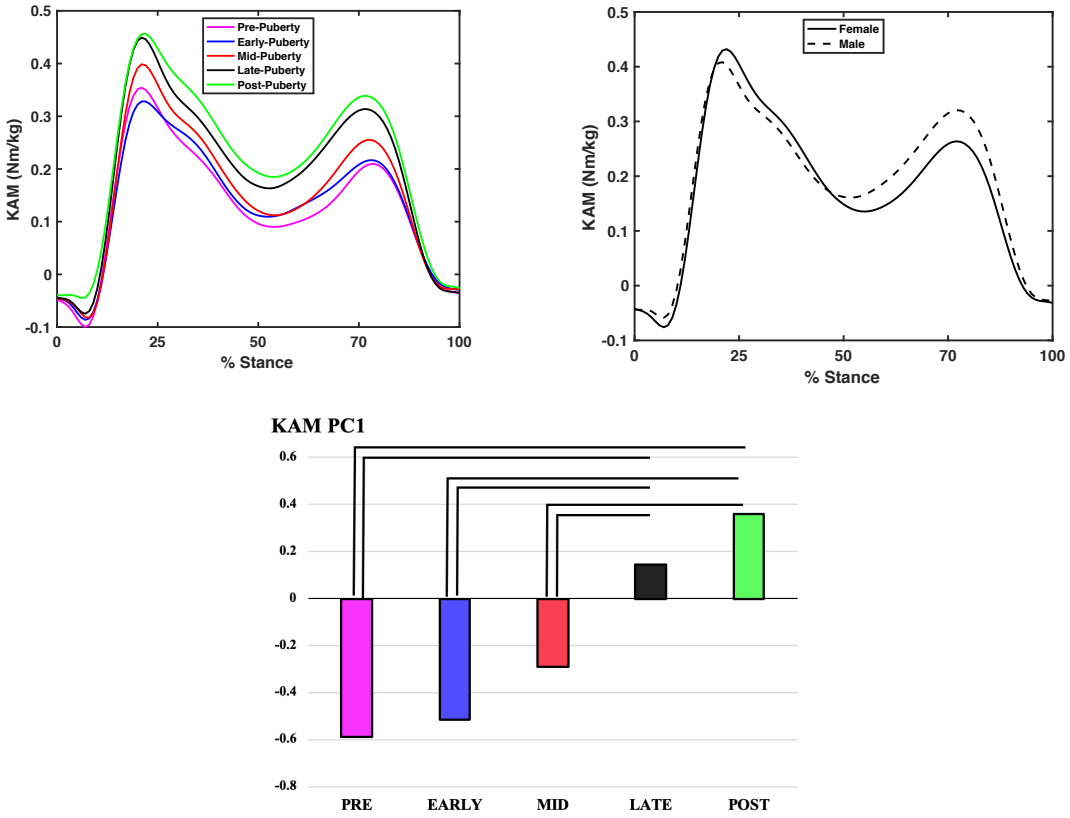


Figure 6. 1 KAM Mean Waveforms for Each Puberty Category (Top Left), Ensemble Average Waveforms for Each Sex (Top Right), and KAM PC1 Scores (Bottom). Line Indicates Significant Post-Hoc Comparison

KFM PC1 describes a shift towards flexion moment with high scores associated with higher flexion moment magnitude in early stance and lower extension moment magnitude in late-stance (Table 6.3, Figure 6.2). KFM PC1 had a significant interaction effect (P=0.01). Females had significantly greater KFM PC1 in late-puberty compared to mid-puberty (P=0.03), while there was no significant puberty effect for the male cohort (Table 6.4).

Table 6. 4 Post Hoc Analysis for PC Features with Significant Interactions

Movement	Moment	PC	Female Post-hoc	Male Post-hoc
Walking	KFM	PC1	3-4 (0.03)	None
	KRM	PC2	None	4-5 (0.03)
Running	KAM	PC1	1-4 (0.05), 1-5 (0.01)	3-5 (0.01), 4-5 (0.05)
	KAM	PC2	1-4 (0.05), 1-5 (0.01), 3-4 (t, 0.07), 3-5(0.01)	1-5 (<0.01), 2-5 (<0.01), 3-5 (<0.01), 4-5 (t, 0.06)
	KRM	PC1	None	1-3 (0.01), 2-3 (0.01), 3-5 (0.02)

1 = Pre, 2=Early, 3=Mid. 4=Late, 5=Post; t=trend

Table 6. 5 Post Hoc Analysis for PC Features with Significant Main Effect of Puberty

Movement	Moment	PC	Puberty Post-hoc
Walking	KAM	PC1	1-4 (<0.01), 1-5 (<0.01), 2-4 (<0.01), 2-5 (<0.01), 3-4 (0.01), 3-5 (<0.01)
	KFM	PC2	1-5 (0.05), 3-5 (<0.01)
	KFM	PC3	1-4 (t, 0.06), 1-5 (0.04), 3-4 (0.03), 3-5 (0.02)
	KRM	PC1	1-4 (<0.01), 1-5 (<0.01), 2-4(0.03), 2-5 (<0.01), 3-5 (<0.01)
	KRM	PC3	1-4 (0.01), 1-3 (t, 0.09), 2-3 (t, 0.07), 2-4(0.01)
Running	KAM	PC3	1-5 (0.02)
	KFM	PC1	1-2 (<0.01), 1-3(<0.01), 1-4 (<0.01), 1-5(<0.01), 2-4(<0.01), 2-5 (<0.01), 3-4(0.02), 3-5(<0.01)
	KRM	PC3	1-5 (0.01), 3-5 (t, 0.06)

1 = Pre, 2=Early, 3=Mid. 4=Late, 5=Post

KFM PC2, representing the range of the flexion-extension moment, had a significant main effect of puberty (P<0.001). Later puberty stages corresponded to lower knee KFM PC2 scores and therefore less range from peak flexion to peak extension moment. Post Hoc analysis revealed a significant difference between pre-puberty and post-puberty (P=0.05), and mid-puberty and post-puberty (P<0.01). KFM PC3, a feature capturing a phase shift, with higher scores having earlier peak flexion moments, had a

significant main effect of puberty with the later stages of puberty having significantly greater PC3 scores than the earlier stages (Table 6.5, Figure 6.2).

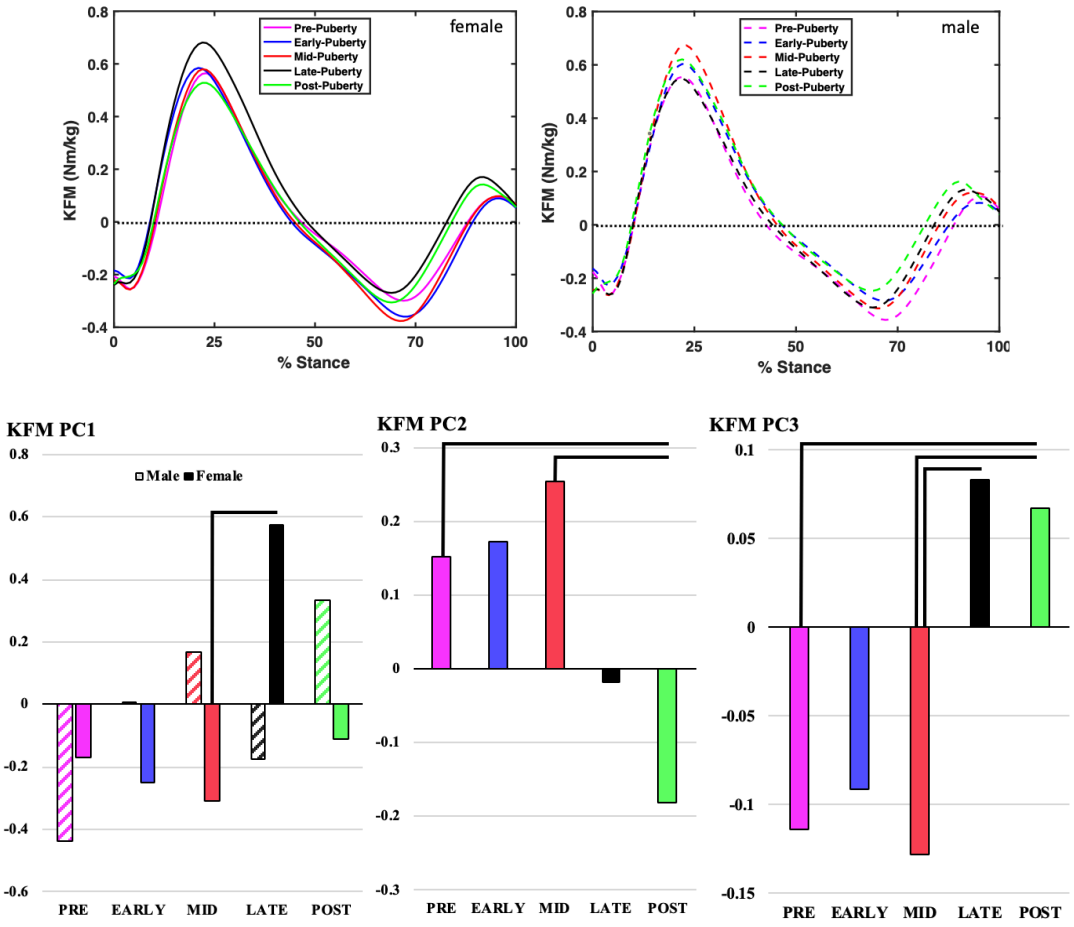


Figure 6. 2 KAM Mean Waveforms for Each Puberty Category for Females (Top Left) and Males (Top Right), and KAM PC1-3 Scores (Bottom). Line Indicates Significant Post-Hoc Comparison

KRM PC1 represented the overall magnitude of internal rotation moment during stance and had a main effect of puberty ($P<0.001$) and a main effect of sex ($P<0.001$) (Table 6.3, Figure 6.3). Later stages of puberty had higher internal rotation moments. Pre- and early-puberty had significantly lower KRM PC1 than late-puberty and post-puberty. Post-puberty KRM PC1 was significantly greater than that for mid-puberty as well. Males had higher KRM PC1 scores than females.

A significant sex by puberty interaction was found for KRM PC2 (0.035), a feature capturing the magnitude of the early stance external rotation moment. Males had a significantly higher PC2 score in post-puberty compared to late-puberty, meaning a greater difference between early stance external rotation moment and late stance internal rotation moment. There were no significant differences in this moment feature for females (Table 6.4).

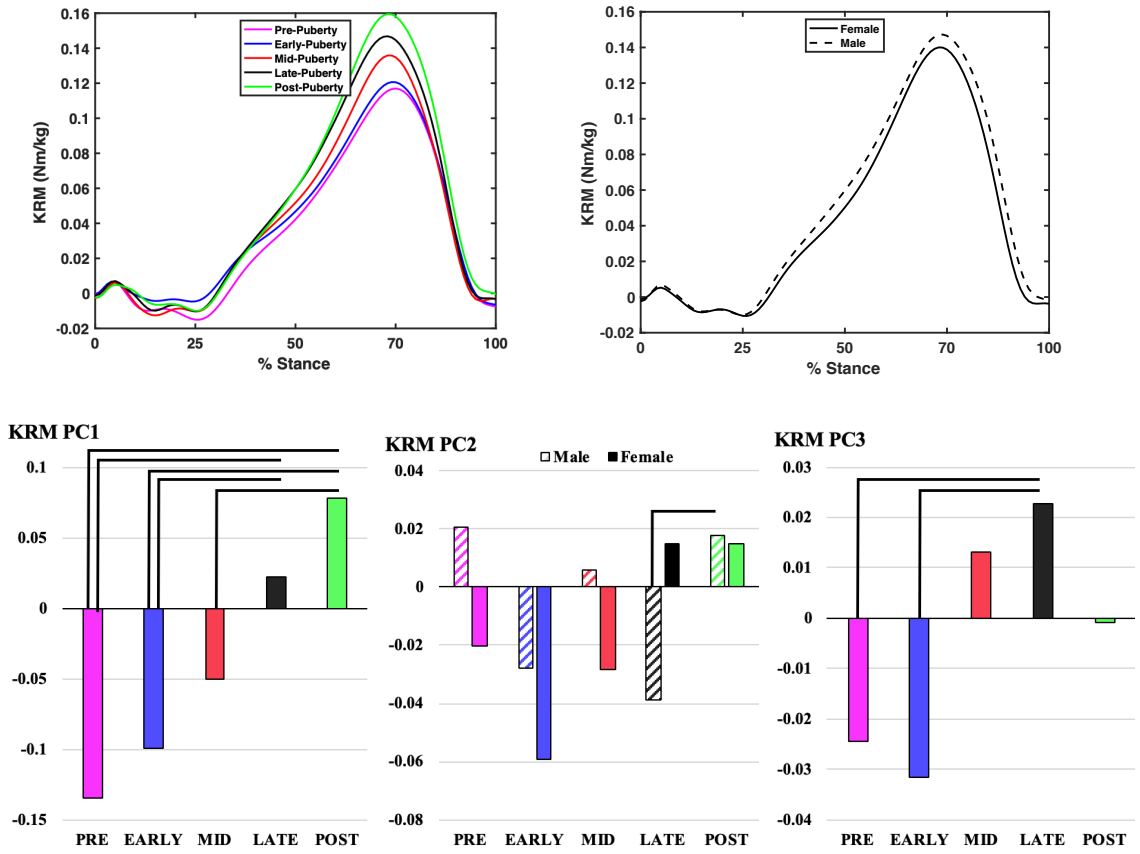


Figure 6. 3 Puberty Mean KRM Waveforms (Top Left) and Sex Mean Waveforms (Top Right) and KRM PC1 Scores (Bottom Left) and KRM PC2 Scores (Bottom Right)

6.3.2 Running Results

The interaction effect between sex and puberty was trending towards significance for running speed (P =0.09). There were significant main effects of puberty and sex where males ran faster (4.2 m/s) than females (4.0 m/s) and pre-puberty and early puberty

ran slower than the later puberty stages. Analysis of variance results are presented in Table 6.6.

Table 6. 6 Analysis of Variance Results for Knee Joint Moment PC Features During Overground Running

		Variance Explained (%)	Puberty*Sex	Sex	Puberty
KAM	PC1	76.3	**0.018**	0.413	<0.001
	PC2	11.5	**0.014**	<0.001	<0.001
	PC3	7.5	0.219	0.920	**0.015**
KFM	PC1	80.6	0.070	0.110	**<0.001**
	PC2	11.1	0.109	0.621	0.736
	PC3	3.6	0.060	0.104	0.672
KRM	PC1	81.1	**0.003**	0.629	0.088
	PC2	12.4	0.160	**<0.001**	0.071
	PC3	3.8	0.089	0.437	**0.001**

Two features of the KAM during running, PC1 and PC2 had a significant interaction effect (P=0.018, P=0.014, respectively). Running KAM PC1, similar to walking, was a magnitude feature, explaining variance from 10-90% of stance phase. The female cohort had an increase in KAM PC1 with increasing puberty stage, similar to the result found in walking, with pre-puberty being significantly lower than late- and post-puberty. The male cohort, however, had the lowest PC1 scores at mid-puberty, with mid-puberty and late-puberty significantly lower than post-puberty (Table 6.4).

KAM PC2 characterizes a pattern change from a single peak KAM at midstance (low PC2 scores), to a pattern that has two peaks: a local maximum in early stance and a second in late stance (high PC2 scores) (Appendix A). While the female pattern of the KAM did not change throughout each puberty stage, the male KAM pattern switched towards higher PC2 scores (bi-modal KAM) during the later puberty stages with pre-, early- and mid-puberty having lower scores that post-puberty (Table 6.4). KAM PC3 captured the relative moment in early stance (1-30%) to late stance (40-80%). High PC3

scores have a greater proportion of moment in early stance. There was a main effect of puberty where the peak KAM was shifted earlier in stance phase with later stages of puberty, with a significant difference between pre- and post-puberty (0.02) and trending between mid- and post-puberty (P=0.06).

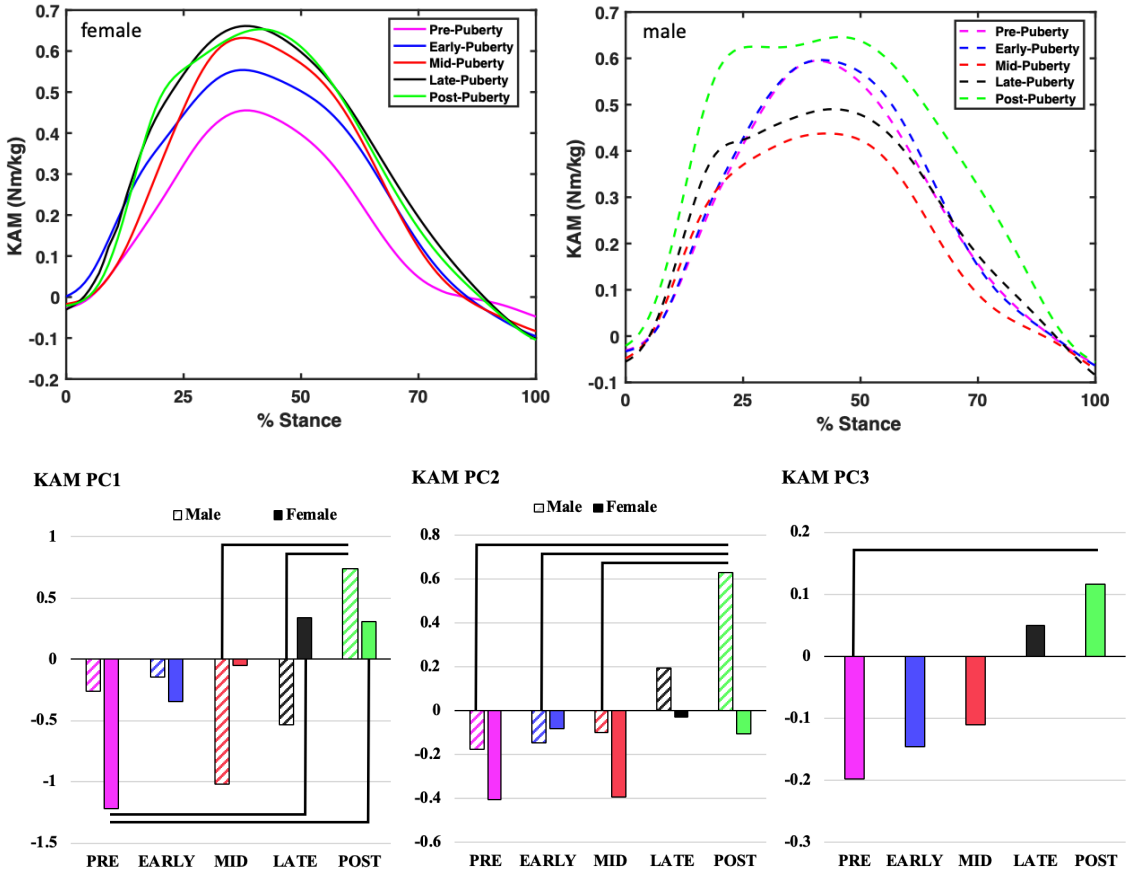


Figure 6. 4 Running KAM Mean Waveforms for Each Puberty Category for Females (Top Left) and Males (Top Right), and KAM PC1-3 Scores (Bottom). Line Indicates Significant Post-Hoc Comparison

KFM PC1 had a main effect of puberty (P<0.001). There was a significant progressive increase in the overall magnitude of the flexion moment from pre-puberty to late-puberty. There was no difference between late-puberty and post-puberty (Table 6.5).

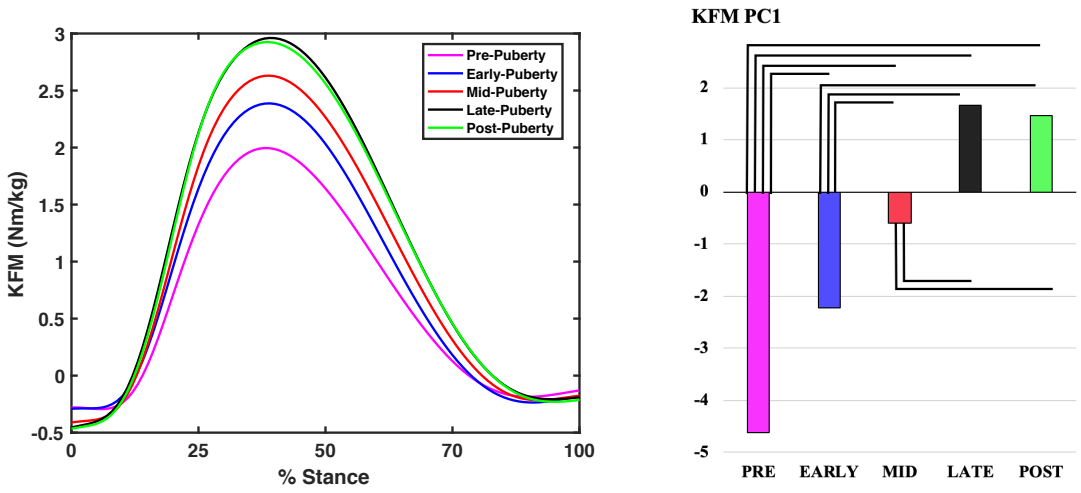


Figure 6. 5 Puberty Ensemble Average Running KFM Waveforms (Left) and PC1 Scores For Each Puberty Stage (Right)

KRM PC1, a magnitude feature of the transverse plane moment had a significant interaction effect. There was no effect of puberty for females, but males had significantly lower scores (i.e. lower internal rotation moments) at mid-puberty compared to pre-, early- and post-puberty. KRM PC2 captured a pattern change where high scores had a greater difference between early and late stance. This feature had a main effect of sex, where females had lower scores (less difference between early and late stance internal rotation moment). KRM PC3 also captures a pattern change, with low scores having two-peaks and high scores having a greater single peak moment in mid-stance. This feature had a main effect of puberty, where later puberty stages corresponded to lower KRM PC3 scores. Pre- and Mid- had significantly higher KRM PC3 scores than Post-puberty.

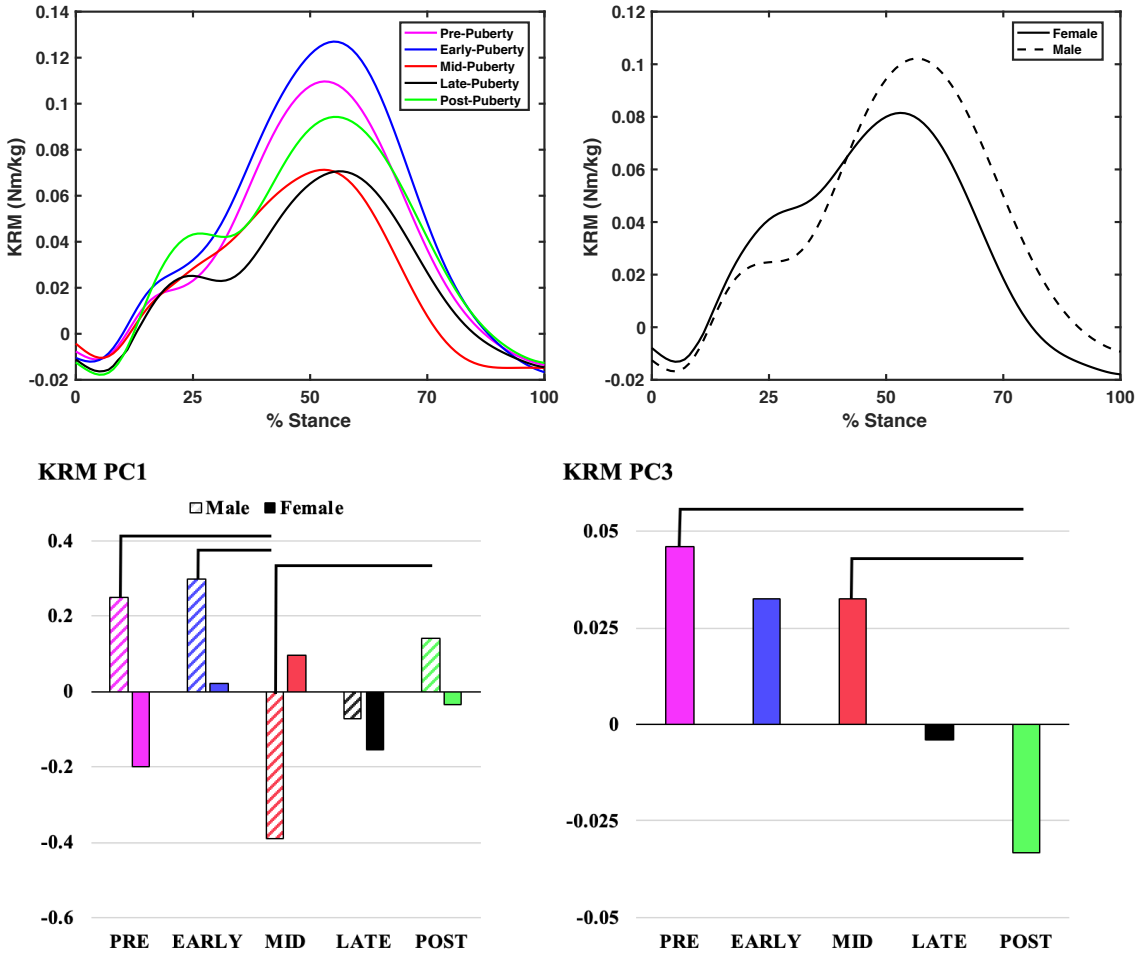


Figure 6. 6 Puberty Mean Running KRM Waveforms (Top Left) and Sex Mean Waveforms (Top Right) and KRM PC1 Scores (Bottom Left) and KRM PC2 Scores (Bottom Right)

6.3.3 Linear Discriminant Analysis (LDA)

The results of the stepwise linear discriminant analyses are presented in Table 6.7.

Table 6. 7 Discriminant Function Standardized Canonical Coefficients and Classification Rates for each LDA

Walk-Puberty		Walk-Sex		Run-Puberty		Run-Sex	
Variable	Coeff.	Variable	Coeff.	Variable	Coeff.	Variable	Coeff.
KAM_PC1	0.816	KAM_PC3	0.758	KFM_PC1	0.775	KRM_PC2	0.820
KFM_PC2	-0.422	KAM_PC2	-0.646	KAM_PC2	0.420	KFM_PC1	-0.443
KRM_PC3	0.393	KRM_PC1	0.291	KAM_PC1	0.345	KAM_PC2	0.387
KFM_PC1	0.337			KRM_PC1	-0.285		
KFM_PC3	0.264			KRM_PC3	-0.211		
Classification	72.2%	Classification	70.2%	Classification	75.4%	Classification	61.6%

Three walking-PCs separated females from males with a correct classification rate of 70.2 percent. Three running-PCs also were retained in the running sex discriminant model, having a correct classification rate of 61.6 percent (Table 6.7). Five walking-PCs separated PRE-EARLY-MID from LATE-POST puberty with a cross-validated correct classification rate of 72.2 percent. Five running-PCs separated PRE-EARLY-MID from LATE-POST puberty with a correct classification rate of 75.4 percent (Table 6.7). Three of the five variables (KAM PC1, KFM PC1, KRM PC3) were the same between both discriminant models. Walking and running Canonical Discriminant Functions were created using the unstandardized coefficients and each participant's discriminant score calculated (Figure 6.7):

$$LDF_{Walking} = (1.059*KAM\_PC1) + (0.247*KFM\_PC1) - (0.569*KFM\_PC2) + (0.646*KFM\_PC3) + (4.92*KRM\_PC3) \quad (6.1)$$

$$LDF_{Running} = (0.169*KAM\_PC1) + (0.532*KAM\_PC2) + (0.221*KFM\_PC1) - (0.415*KRM\_PC1) - (1.441*KRM\_PC3) \quad (6.2)$$

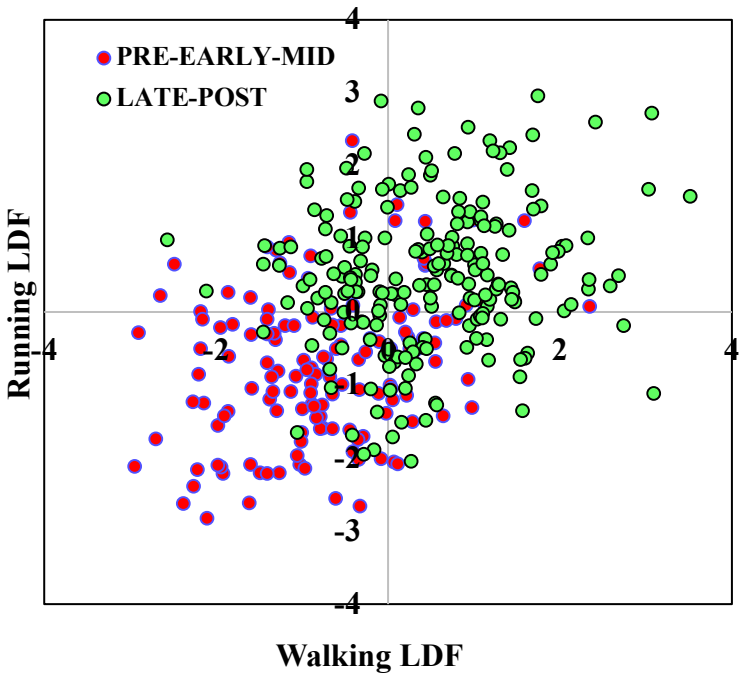


Figure 6. 7 Scatter plot of Pre-Early-Mid (Red) and Late-Post (Green) Walking and Running Discriminant Scores

6.4 Discussion

There were significant sex and puberty differences in almost every feature of knee moments when running and walking, a signal of the continued change in biomechanics with maturation and the significant sex differences that exist, both independent and dependent of puberty. A child reaches the capacity for an adult-like gait early in life (Sutherland, 1997, Ounpuu et al., 1991, Oeffinger et al., 1997), and while a given person may perform their walking pattern in a characteristic way such that it is recognizable at a distance (Winter, 1991), certain aspects of gait seem to be continuously evolving throughout life in a response to growth, maturation, and pathology. Walking is an essential aspect of human mobility, and as a result, gait has been used as a predominant model for applied and fundamental biomechanics research, however, this is the first comparison of the sex and puberty discriminate efficacy of running and walking gait in a sample of athletic adolescents.

Similar to previous findings on running gait (Sayer et al., 2018) the moment in the frontal plane during walking was higher at later puberty stages, and in contrast to previous research (Ro et al., 2017) females had lower moment magnitude than males. The running KAM had a significant puberty-sex interaction for PC1 and PC2. The magnitude feature of the KAM (PC1) for females was higher at later puberty stages, with no difference between late-puberty and post-puberty females. These results are in agreement with recent research reporting that late/post-pubertal females displayed a higher KAM compared with the prepubertal group when running barefoot (Sayer et al., 2018). For males, the post-puberty group had a greater magnitude compared to mid- and late-puberty males. Taken together, females ran with higher frontal plane moments earlier in their maturation stage compared to males. This corresponds to the timing of sex differences in the rate of knee injuries (Hewett, 2015, Ford et al., 2010, Quatman et al., 2006, Wild et al., 2016) and reduction in neuromuscular control of the knee in post-pubescent versus pre-pubescent females (Hewett et al., 2004, Ford et al., 2010, Kim and Lim, 2014).

What was more striking than the magnitude difference in the running analysis was the pattern change of the KAM (PC2) following puberty for the males, that did not occur with females. This pattern change resulted in a more rapid increase in the moment during early stance, followed by a plateaued region between 15-50% of stance. The post-puberty males had a shift in the pattern towards a more evident two-peak waveform. This is a shift from the single peak at midstance found for both females and earlier-puberty males. Prolonged load in the frontal plane while walking, described as a lack of mid-stance unloading, has been linked to longitudinal clinical progression to total knee arthroplasty (Hatfield et al., 2015b) and with cross-sectional clinical OA severity (Astephen et al., 2008a, Rutherford et al., 2008a). This pattern difference at mid-puberty for running corresponded to a lower overall magnitude of the moment until post-puberty for males. At post-puberty, the new pattern was maintained but with greater magnitude. The lack of published waveforms or waveform analysis techniques to study changes in pubertal development limits the ability to determine how common this finding is. Chester and Wrigley (2008) used PCA to study joint moment changes with age but did not report frontal or transverse plane findings. Without explicitly testing for changes in pattern, the waveforms of faster walking speeds in a healthy cohort of adults had a dynamic two-peak

moment where very slow speeds were associated with no mid-stance unloading (Schwartz et al., 2008). Landry (2007a) also found a speed effect in the frontal plane, where both OA and control groups had higher adduction moments during mid-late stance (KAM PC2) at their self-selected walking speed than the fast speed. In this study similar pattern change was observed in the KRM during running with a main effect of puberty (KRM PC3). For males and females, later puberty stages had two distinct peaks of the KRM; one at around 25% of stance and a second one at 50% of stance. Speed not only affects the magnitude of joint loading during walking and running, but also how the joint is loaded dynamically throughout the gait cycle, which may be an important signal in the developing knee joint.

KFM PC1 for walking displayed an interaction effect between puberty and sex where late-puberty females had a significantly greater peak flexion moment and lower peak extension moment compared to pre-puberty, while there were no puberty specific differences in this feature of male gait. Later puberty stages also had lower late stance extension moment magnitudes during walking (KFM PC2). A previous study using PCA to test for difference in joint moments with age found the opposite effect of age on KFM PC2. The oldest group of children (9-13) demonstrated larger peak internal extensor moments during the first half of stance and larger peak knee flexion moments in late stance compared to the youngest age groups (3-4 and 5-6) (Chester and Wrigley, 2008). The differences in KFM findings of Chester and Wrigley (2008) could be related to younger ages studied and the significant increase in walking speed with age. A lower late stance extension moment in older cohorts may be related to a shift towards hip and ankle power for propulsion (Hortobágyi et al., 2016). During running, KFM PC1 (magnitude of the knee flexion moment) had significant increases with each puberty stage until late-puberty. This magnitude increase has been previously reported for overground barefoot running where late/post-pubertal and early/mid-pubertal females displayed a higher peak KFM compared to the prepubertal group (Sayer et al., 2018). The increase in KFM could partially be explained by the increased running speed which was significantly faster for late- and post-puberty (Petersen et al., 2014).

The walking KRM PC2, a feature capturing early stance external rotation moment relative to late stance internal rotation moment had a significant interaction effect, but

there were no significant within sex differences. The mean PC scores seemed to alternate between positive and negative for males and females in each puberty category without an intuitive pattern. This moment feature has previously been characterized by low reliability (Robbins et al., 2013) and it may therefore not provide a strong and consistent cross-sectional signal.

The loss of knee function with severe OA is coupled with a generally less dynamic pattern of joint loading, as identified through the reduced change in pattern over the course of the gait cycle (Astephen et al., 2008a). The more dynamic pattern of the KAM and KRM during running started to appear in mid-puberty. There is a general gap in the literature of early adulthood and middle-age changes in mechanics. Ideally longitudinal cohort research should be carried out to fill in the typical patterns of three-dimensional joint loading incrementally throughout life. All three planes of knee moments were retained in the discriminant models for this study and previous research has shown joint injuries in females to be a multi-factorial and multi-dimensional problem (Stracciolini et al., 2013, Sigward and Pollard, 2012, Wild et al., 2016, Stefanyshyn et al., 2006). More research is needed that comprehensively evaluates the pattern of joint loading in three dimensions. The lack of previous literature on the KRM added to the difficulty in interpreting the mechanisms behind these differences and the meaningfulness of the transverse plane loading.

The addition of muscle activation patterns through electromyography to this analysis would help uncover mechanisms behind some of the kinetic differences measured in this study. For example, Lazaridis et al. (Lazaridis et al., 2010) reported that prepubescent males displayed greater co-contraction of their tibialis anterior, soleus, and medial gastrocnemius muscles when landing from a box-drop jump compared with their adult male counterparts, a potential strategy to increase ankle stability. Sex specific differences in the muscle activation patterns during the pre-contact phase of a cross cutting task have also been identified that may have implications in joint protection and joint stability of female athletes (Landry et al., 2007b). It was recently suggested that the primary benefit of co-contraction is the ability to engage both the stretched and shortened muscles in the corrective response of a movement and thereby improve performance, indicating that co-contraction is not purely a strategy for stability (Salib 2019).

Expanding this model of adolescent running and walking to a non-athlete cohort may reveal the biomechanical strategies that are specific to this kinaesthetically aware cohort of athletes.

In support of hypothesis two, both running and walking resulted in similar classification rates between puberty groups, with the running model having slightly better classification than the walking model. The walking model outperformed running for discriminating between females and males. The PC feature with the largest contribution to the puberty discriminant model was KAM PC1 for walking, and KFM PC1 for running. These variables both had strong main effects of puberty in the analysis of variance. While this data does not reflect whether walking gait is an adequate model to study adolescent injury risk, it does suggest that walking may be as sensitive as higher stress activities, in this case running, to puberty and sex effects. Walking gait assessment is methodologically easier to administer than most intense sport specific movements in a laboratory environment and could dramatically reduce barriers to more frequent biomechanical monitoring of high-risk athletic cohorts.

The sample size for the pre-puberty and early-puberty cohorts, especially for females, was very small and may have limited the ability to discern differences within the early stages of puberty. As this study is a cross-sectional view of puberty stages, we can only speculate to the relative timing of these biomechanical changes, and the same patterns of change may not be evident in longitudinal data of the same individuals. This is also an athletic cohort, which may reduce the ability to generalize these results to the larger population. To understand the implications of these differences in knee joint loading patterns in terms of injury development, prospective research linking timing of maturation and biomechanics to future injuries is needed, which is a goal of the larger Longitudinal Study on Adolescent Biomechanics. How and when biomechanics mature may be just as important to what they mature to be. Future studies should include how mechanics change during both low stress (walking) and high stress (sport movements) with training, anatomy and puberty. It remains unclear what the cumulative effect of high intensity or high-volume sport is on the developing joint, and this knowledge is needed to improve strategies for injury prevention.

6.5 Conclusion

Walking and running gait were both characterized by significant sex and puberty differences in all three planes. Later puberty stages had higher frontal and transverse plane moments when walking and altered patterns of frontal and transverse plane moments when running. Discriminant models using the patterns of knee moments during walking gait were as good at classifying participants based on puberty status and sex as running models and may be a useful tool in young athlete monitoring in the future. Further research is needed to link features of joint loading during walking and running gait in adolescence to future injury and OA risk.

CHAPTER 7

The Effect of Sport Type and Knee Mechanics on the MRI Detected Changes in the Knees of Female Collegiate Athletes

7.1 Background

Acquired biomechanical disorders account for the largest proportion of knee osteoarthritis (OA) cases, a subset of the disease which is initiated by chondral or osteochondral trauma, and traumatic joint injuries such as anterior cruciate ligament (ACL) and meniscal tears (Ryd et al., 2015). Participating in sport inherently increases an individual's risk of developing knee OA by increasing the risk of these acquired biomechanical disorders (Felson et al., 2000). While traumatic injuries requiring medical attention such as ACL ruptures and meniscal tears are well documented, there is a lack of information on micro-injuries/traumas to the knee joint resulting from sport participation, as these are often asymptomatic (Connor et al., 2003, Major, 2006) or may be the result of failure over a prolonged period of time (Gardiner et al., 2016). Micro-injuries to the knee joint are an important piece in understanding the pathomechanics of knee OA as undetected injuries may put an individual into a "pre-OA" state and possibly account for a large portion of idiopathic knee OA cases (Buckwalter, 2003).

The time course of symptomatic knee OA, from an initiating event such as ACL or meniscal injury, ranges from 10-20 years (Roos et al., 1995). To study a pre-OA joint state, it is essential to study young individuals who are at a higher risk of developing knee OA later in life. Two factors that have been associated with an increased risk of developing knee OA include being female (Felson et al., 2000) and overloading the joint (Vannini et al., 2016). Female collegiate level student-athletes, therefore, provide an interesting model to study the effect of a prolonged high stress joint environment on the presence of micro trauma inside the joint that may be related to the future development of knee OA.

Not all sports are equal in terms of the increased risk for knee OA. Sports that involve twisting, turning, rapid acceleration/deceleration, and jumping impart high biomechanical forces to the knee joint, and have been associated with joint degeneration

that would likely lead to OA (Radin et al., 1991a, Felson et al., 2000, Muthuri et al., 2011). This increased risk for the development of OA is independent of major joint injury (Vingård et al., 1993, Kujala et al., 1994, Kujala et al., 1995, Spector et al., 1996, Buckwalter and Lane, 1997a). The volume of participation is also a factor with elite and professional athletes reporting higher rates of knee OA than their recreational counterparts (Roos, 1998). Collegiate cross-country running and basketball athletes are both exposed to very high volumes of intense physical activity, however basketball is characterized by high torsional loading, and fast accelerations and decelerations, features that are associated with higher rates of knee OA (Brukner et al., 2004), while current evidence suggests that running is not associated with an increased prevalence of knee OA (Miller, 2017). It is therefore hypothesized that basketball athletes would incur more micro-damage to the knee joint as a result of participation compared to runners. The lack of prospective research on these cohorts limits the ability to relate the extreme joint loading associated with elite sport participation to a failure threshold and tissue damage.

While the type of movements that comprise a given sport can help identify "riskier" sports, joint level mechanics may help to explain variance in risk for micro-injury within a sport. For example, the frontal plane load on the knee, often estimated by the external knee adduction moment (KAM), has been linked to injuries to various structures within the joint. A higher external knee abduction moment during the landing phase of a jump has been related to the occurrence of anterior cruciate ligament (ACL) injuries (Hewett et al., 2005) and the internal abduction moment impulse to the development of patellofemoral pain syndrome in runners (Stefanyshyn et al., 2006). Female athletes have different biomechanical strategies during sport specific movements compared to male athletes, including a more extended knee at initial foot contact during jump landings and side-cuts (Yu et al., 2006, Yi et al., 2004). Females also tend to be quadriceps-dominant while running, landing from a jump, stopping and cutting (Baur et al., 2010, Chappell et al., 2007, Beaulieu et al., 2008), and tend to have increased valgus angles when landing from a jump (Jacobs et al., 2007) and performing side-cut maneuvers (Beaulieu et al., 2008). Links to the role of these biomechanical strategies and joint level structural changes over one season of sport participation have not been studied directly. It is not known if the same mechanisms responsible for major joint injuries such

as ACL ruptures (Hewett et al., 2005), are also responsible for micro-injuries that could lead to knee OA. This gap in our knowledge is due to a lack of prospective research quantifying both joint level mechanics and changes in joint tissue in a young, healthy female athlete population.

In a healthy joint, repetitive loading can cause acute subchondral damage which is balanced by consistent repair. When damage persistently exceeds repair, bone marrow lesions (BMLs) can develop (Sharkey et al., 2012). BMLs are commonly seen in traumatic joint injuries, in areas of cartilage loss, and following meniscal tears (Lim et al., 2013). Damage to the meniscus and the presence of BMLs may be markers of early knee OA (Felson et al., 2007, Roemer et al., 2009, Roemer et al., 2010). Recent studies suggest that BMLs correlate with cartilage degeneration (Hunter and Felson, 2006, Hunter et al., 2006) and that BMLs may be an imaging marker for subsequent OA development (Hunter and Felson, 2006).

Magnetic resonance imaging (MRI) facilitates morphological assessment of cartilage, meniscus, and other intra-articular and peri-articular soft tissues, including bone marrow changes (Hunter et al., 2011b), and therefore is an important tool in identifying trauma to the knee joint that may be related to future knee OA. Several semi-quantitative grading scales for MR images have been developed to measure and score the relative severity of defects in the entire joint organ that may be associated with future development of knee OA (Peterfy et al., 2004, Hunter et al., 2011b). While these scores are typically used for individuals with or at risk of developing knee OA, semi-quantitative scoring or MRIs of asymptomatic athletes may be a method to measure micro-damage to the entire joint and facilitate an analysis of the relationship between the damage and joint level mechanics.

The purpose of this study was to measure the effect of one season of collegiate sport participation on joint integrity, measured with MRI and scored using the MRI Osteoarthritis Knee Score (MOAKS), and to determine if the type of sport (cross country running (XC), basketball (BB)) and joint level mechanics were linked to MRI signal worsening. We hypothesized that BB would result in a greater amount of MRI signal abnormalities at baseline and a greater proportion would have MRI worsening at follow up compared to XC. We also hypothesized that those who had MRI worsening during the

season would have different biomechanical patterns during running and walking, specifically higher frontal and transverse plane moments.

7.2 Methods

7.2.1 Participants

The collection of data was approved by Nova Scotia Health Authority and Acadia University Research Ethics Boards. Subjects were recruited from the Acadia Women's Varsity Basketball and Cross-Country running teams (Table 7.1). After receiving written consent, each participant completed questionnaires related to demographics, sport participation history, injury history and MRI screening. Exclusion criteria included a history of trauma or injury to the lower extremities or lower back. Participants who had experienced an ankle sprain were eligible only if the injury had occurred at least three months prior to the test date and were cleared for return to sport by a trained practitioner or therapist.

XC athletes trained seven days per week, with a morning and afternoon session on both Tuesdays and Thursdays, totaling nine training sessions per week. Training consisted of a combination of drills, speed work and longer group runs on trails. Group runs were typically between 50-75 minutes in duration, while other training sessions were 1-1.5 hours in duration. For a typical week in-season, BB would practice 3-5 times. Practices at the beginning of the week were often more difficult, involving full court running drills and contact drills. The day before game day included half court drills focused on strategical aspects of the sport. Each player would also participate in two individual sessions a week. These practices included 2-5 players and were skill based with a focus on shooting and ball handling. Players often went to the gym on their own time to work on shooting and 1-2 weight-room sessions a week. There were typically two games per week, which would either be spaced apart by one day or back to back. During the season, Sunday was usually a day off.

Table 7. 1 Subject characteristics

	N	Age (years)		Mass (kg)		Height (cm)		Walking Speed (m/s)		Time to follow up (days)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
XC	12	20.3	1.8	59.4	6.1	167.1	4.0	1.35	0.20	163.6	8.6
BB	10	20.2	2	75.8	18.8	171.4	8.9	1.52	0.25	187.0	11.1

7.2.2 MRI Acquisition

Unilateral knee MRIs were taken at baseline (pre-season) and follow-up (post season) using the same 3T MRI and Flex coil (GE Medical Systems 3T Discovery MR750). The sequences consisted of 3-dimensional proton density–weighted isotropic turbo spin echo acquisition (CUBE), and 2D sagittal and coronal proton density, fat saturated images (Chapter 3). Subjects were asked to limit physical activity the day prior to the MRI and were inactive for at least one hour before, although physical activity prior to the MRI was not recorded.

7.2.3 MRI Scoring

All MRIs were evaluated using the MRI Osteoarthritis Knee Score (MOAKS) by a single musculoskeletal radiologist (Dr. Ryan MacDougall). The radiologist evaluated the baseline and follow-up scans paired (not blinded to the time points of MRI) and blind to sport category. The MOAKS divides the knee into 14 articular subregions to score cartilage defects and bone marrow lesions (BMLs) and six tibiofemoral and six patellofemoral subregions to score osteophytes (Hunter et al., 2011). Meniscal lesions were scored separately for the medial meniscus and lateral meniscus and divided into anterior, posterior, and central subregions. Cartilage defects were graded from 0 to 3 based on size (percentage of the surface area relative to each subregion) and depth (percentage of the lesion relative to full thickness). Osteophytes were graded from 0-3 according to size based on how far they extended from the joint. Meniscal tears were described as absent or present and by type (vertical, horizontal, or complex). Meniscal maceration was described as absent or present and by type (partial, complete, or

progressive). Meniscal extrusion was described by size on a scale from 0-3. Hoffa fat pad synovitis was also graded form 0-3 (Chapter 3 for more details of scoring).

7.2.4 Definition of Worsening OA Features

Subregions were combined into three compartments: patellofemoral (patella and trochlea), medial tibiofemoral (medial femur: central and posterior; medial tibia: anterior, central, and posterior), and lateral tibiofemoral (lateral femur: central and posterior; lateral tibia: anterior, central, and posterior). Worsening of MOAKS features in each compartment was defined as any increase in the score (in any corresponding subregions for that compartment). Therefore, either progression of an existing feature (increase in defect severity) or a new feature (from no defect to present defect) from baseline to follow-up was classified as worsening. This definition is reliable and sensitive to changes in ACL-injured patients and other populations at high risk for OA (Runhaar et al., 2014, van Meer et al., 2016).

7.2.5 Motion Analysis Data Collection

Data were collected at the John MacIntyre motion Laboratory of Applied Biomechanics (mLAB) at Acadia University following the baseline MRI. Participants completed the testing in their personal indoor footwear typically used for training or competition, compression shorts and a tight-fitting shirt. Participants' height and weight were measured using an electronic scale (Health-o-meter professional, McCook, IL, USA), followed by measuring maximum calf and thigh circumference for both legs using a standard tape measure. Foot width was measured using a Rosscraft caliper (Campbell, USA) from the head of the first metatarsal to the head of the fifth metatarsal.

41 retro-reflective markers (14 mm) were attached to the participant's lower extremities to collect three-dimensional position of the pelvis, thigh, shank and foot and to estimate the location of the hip, knee, ankle and metatarsal-phalangeal (MTP) joints. Single markers were attached with double sided tape to anatomical bony landmarks and marker clusters, rigid square plastic plates with four fixed markers at each corner, were attached by Velcro to Fabrifoam compression wraps at the shank and thigh. Marker

clusters were secured to the legs using athletic tape. Triad marker plates were positioned at each heal and secured using duct tape (Figure 3.2).

A 12-camera motion capture system (Qualisys Oqus 4) was used to capture the three-dimensional position of the retro-reflective markers during each trial at a sampling rate of 250 Hz. Ground reaction forces were measured by three floor-embedded AMTI force plates (Advanced Mechanical Technology, Inc., Watertown, MA), at a sampling rate of 2000 Hz. Qualisys Track Manager (QTM) software (Qualisys, AB, Sweden) simultaneously captured force and marker position data.

Participants completed five successful trials (clean foot strike on a force plate) for each foot, of self-selected speed over-ground walking and over-ground running at 4 m/s +/-5%. Speed was monitored using Smart Speed timing gates (Fusion Sport, Brisbane, Australia).

7.2.6 Data Analysis

Net external knee joint moments during the stance phase of running and walking were calculated in Visual3D (C-motion, Inc., Rockville, MD), using an inverse dynamics approach. The foot, shank, thigh and pelvis were each modeled as a rigid body with a local coordinate system located at the segment's center of mass. Net resultant knee joint moments were projected onto the joint coordinate system (Grood and Suntay, 1983). Subject's ensemble average, time and mass normalized waveforms were projected onto the mLAB Principal Component (PC) model (Chapters 3 and 4) to calculate PC scores for the 22 participants. The first three PCs for each knee moment during each movement were retained for analysis to retain approximately 90 percent of the variance in the data (Jackson, 1993).

Chi-Square analysis was used to determine if the difference in baseline MRI scores for each sub-region were significant between sports. Generalized estimating equations (GEEs) were used to determine if PC features of knee joint moments while walking and running were related to worsening signal on an MRI and if there was an interaction between sport and worsening. SPSS was used for statistical analyses and P values <0.05 were considered statistically significant.

7.3 Results

All but one (BB) participant had at least one signal abnormality on their baseline MRI that persisted throughout the season. The most prominent signal abnormalities at baseline were related to the meniscus. Six XC runners and four basketball players had medial or anterior extrusion of the medial meniscus. Six runners and four basketball players also had irregularities in meniscus morphology including intrasubstance signal (5 XC, 2 BB) and tears (1XC, 2BB), half of which were the same athletes that had meniscal extrusion. Many periarticular features were abnormal at baseline for participants from both sports (Table 7.3).

Table 7. 2 Subject characteristics of the worsening and non-worsening groups

	Worsening (N=8)		Non-Worsening (N=14)		P-value
	Mean	SD	Mean	SD	
Sport (XC:BB)	5:3		7:7		
Age (years)	20.8	2.3	19.9	1.6	0.33
BMI (kg/m^2)	22.6	3.5	23.6	4.6	0.61
Height (m)	169.7	7.4	168.7	6.8	0.74
Walking Speed (m/s)	1.4	0.2	1.4	0.3	0.78
RPE at 4m/s (/20)	16.0	2.1	14.8	2.0	0.20

*RPE: rating of perceived exertion on a BORG scale from 6-20

Eight participants (five cross-country and three basketball players) had worsening of at least one MRI feature from baseline to follow-up. These participants were not different from the non-worsening cohort on any demographic variable (Table 7.2). The specific features that showed worsening at follow-up were not consistent between the eight participants: one patellar BML (BB), one osteophyte (XC), two patellar tendon (1BB, 1XC), one pes anserine bursitis (XC), one popliteal cyst (XC), one infrapatellar bursa (XC), one prepatellar bursa (BB).

Table 7. 3 Baseline MRI findings for XC and BB

MRI detected OA features	XC Baseline /12 (%)	BB Baseline /10 (%)	Chi-Square
Cartilage defect (grade ≥1, full or partial-thickness			
Patellofemoral	0 (0)	0 (0)	N/A
Medial tibiofemoral	0 (0)	0 (0)	N/A
Lateral tibiofemoral	0 (0)	0 (0)	N/A
Bone marrow lesion (grade≥1)			
Patellofemoral	0 (0)	0 (0)	N/A
Medial tibiofemoral	0 (0)	0 (0)	N/A
Lateral tibiofemoral	0 (0)	0 (0)	N/A
Osteophyte (grade ≥1)			
Patellofemoral	0 (0)	1(10)	0.26
Medial tibiofemoral	3 (25)	1(10)	0.36
Lateral tibiofemoral	4 (33)	2 (20)	0.48
Meniscal Extrusion			
Medial	6 (50)	4 (40)	0.86
Lateral	0 (0)	0 (0)	N/A
Meniscal lesion (grade ≥1)			
Medial tibiofemoral	4 (33)	3 (30)	0.87
Lateral tibiofemoral	2 (17)	1 (10)	0.65
Hoffa fat pad synovitis (grade ≥1)	2 (17)	0 (0)	0.18
Patellar tendon	2 (17)	1 (10)	0.65
Pes anserine bursitis	1 (8)	0 (0)	0.35
Iliotibial band signal	4 (33)	4 (40)	0.94
Popliteal cyst	2 (17)	3 (30)	0.46
Infrapatellar bursa signal	2 (17)	1 (10)	0.65
Prepatellar bursa signal	1 (8)	0 (0)	0.35

There were no significant interaction effects between sport and worsening MRI features for any kinetic variable (Table 7.4). Three variables had a main effect of MRI worsening: Walk-KFM PC2, Walk-KRM PC1, and Run-KAM PC1. All three

characterized the worsening group with lower knee joint moments (Table 7.4, Figure 7.1).

Five PCs had a main effect of sport, three walking gait PCs and two running gait PCs. XC had higher KAM and KRM magnitude features and greater range of KFM compared to BB (Table 7.4, Figure 7.2).

Table 7. 4 Generalized Estimating Equations Results for Knee Joint Moment Features

	Interaction	Worsening	Sport	Direction of Worsening	XC relative to BB
Walking					
KFM PC2	0.702	**0.007**	**0.005**	Lower; less range	Higher
KAM PC1	0.302	0.262	**0.010**		Higher
KRM PC1	0.683	**0.025**	**0.003**	Lower, lower magnitude	Higher
Running					
KAM PC1	0.967	**0.024**	**<0.001**	Lower, lower magnitude	Higher
KRM PC1	0.670	0.442	**0.044**		Higher

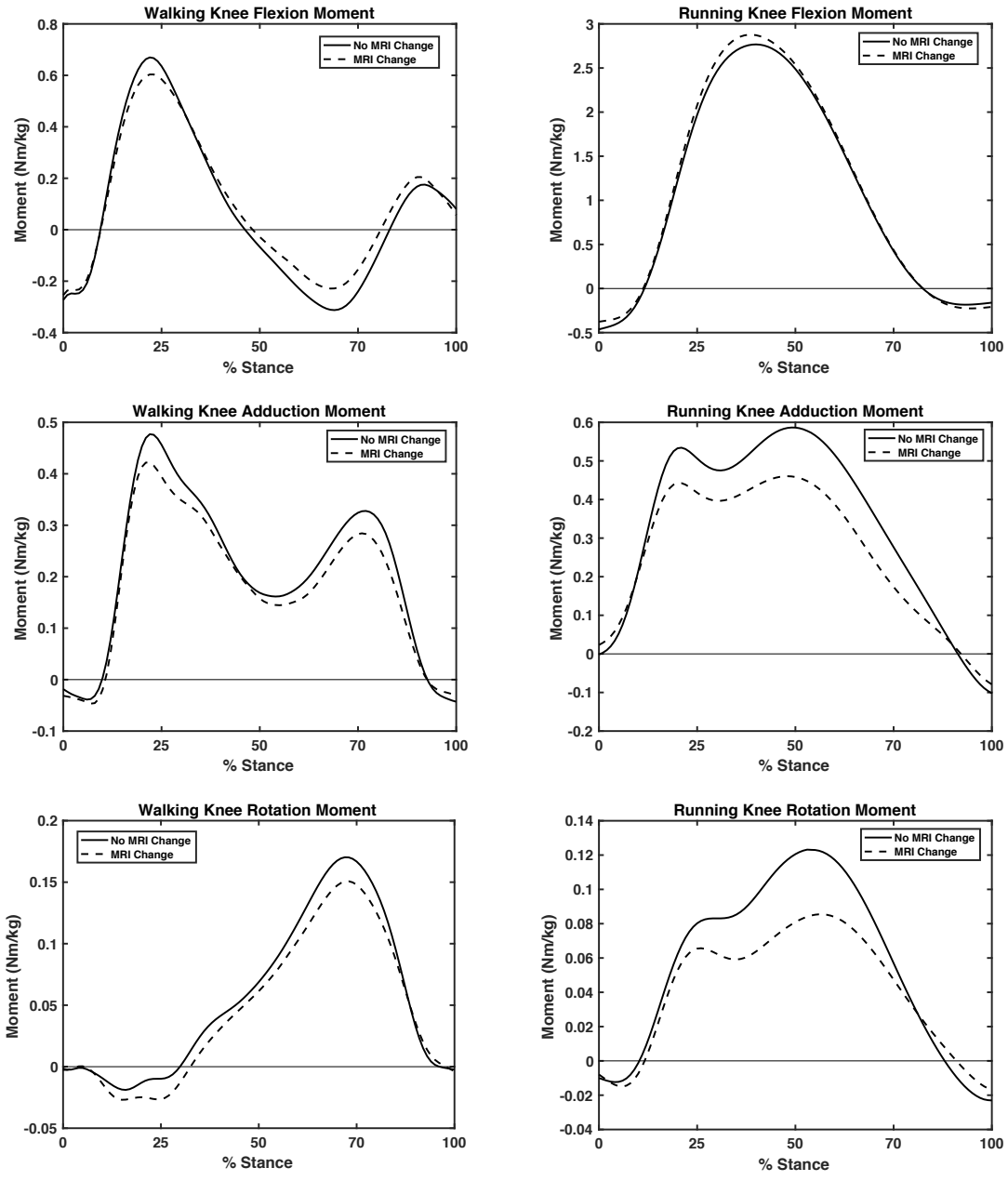


Figure 7. 1 Mean Knee Joint Moment Waveforms during Walking (Left) and Running (Right) for MRI-Worsening and Non-Worsening Groups

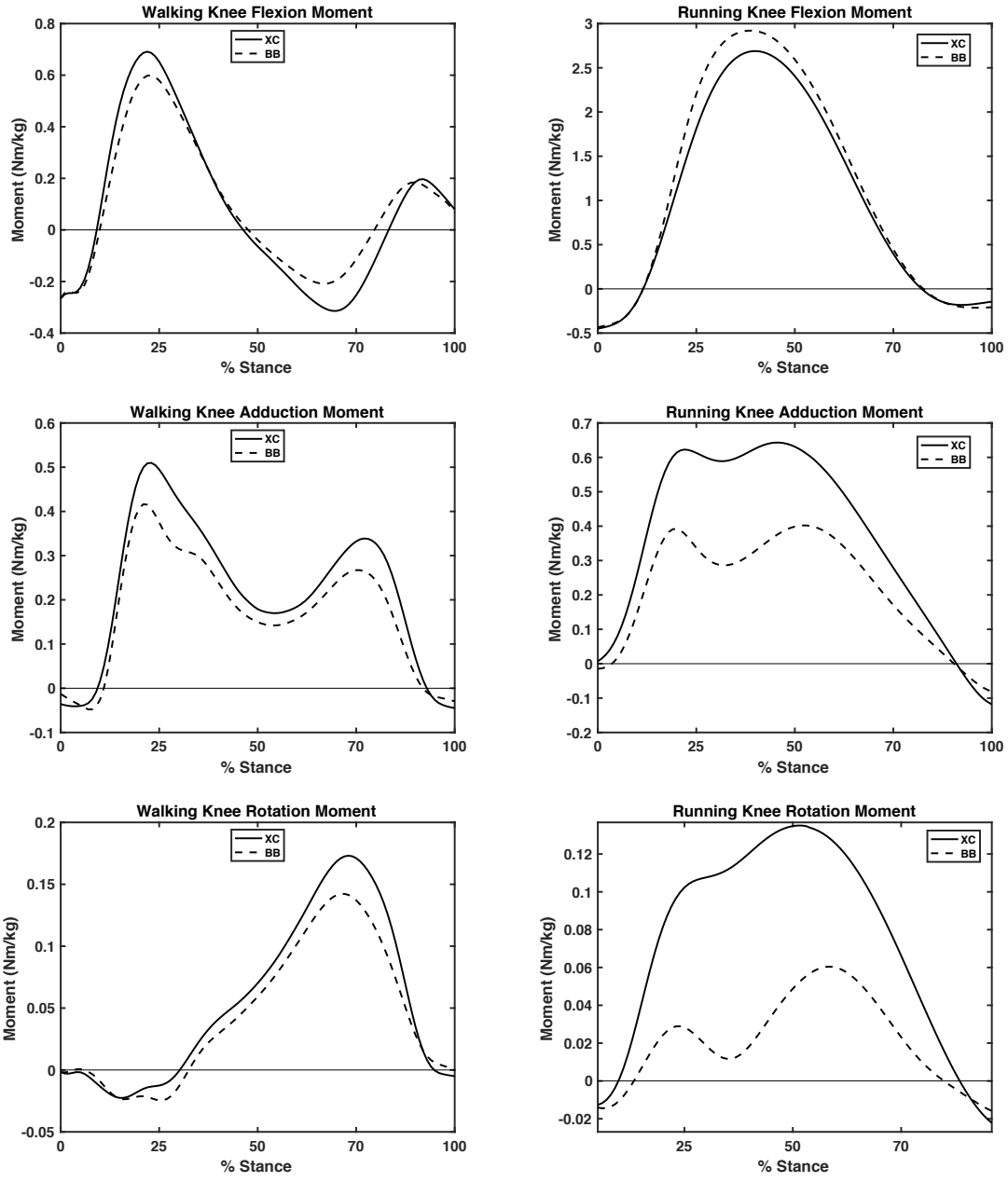


Figure 7. 2 Mean Knee Joint Moment Waveforms during Walking (Left) and Running (Right) for BB and XC Groups

7.4 Discussion

This is the first study to model the relationship between MRI signal change and joint level mechanics in asymptomatic collegiate level female athletes. By using a multi-

feature joint assessment, the relative functional integrity of the knee was scored in a semi-quantitative manner and compared against the most relevant magnitude and pattern features of joint kinetics. While the small sample size of this pilot limits strong conclusions, this study sheds new insight into the relationship between knee joint mechanics and joint level changes after a large dose of physical activity. This preliminary data suggests that BB is not worse in terms of one season of MRI joint tissue change compared with XC and that high magnitude features of joint moments were not related to knee joint worsening.

All but one participant had at least one signal abnormality on their baseline MRI that persisted throughout the season. This is similar to a recent study on male and female collegiate basketball players (Pappas et al., 2016). The most prominent location of signal abnormalities at baseline were in the meniscus, located primarily in the anterior-medial compartment. This was not unexpected in a population of elite basketball and cross-country athletes. In a previous study of male and female National Collegiate Athletic Association (NCAA) basketball athletes, most meniscal changes were localized to the medial meniscus with a trend toward increasing meniscus signal following one season of basketball participation (Pappas et al., 2016). In a study of male professional basketball players, Kaplan et al. (2005) reported meniscal abnormalities in 8 of 40 knees (20%), with seven of the eight lesions in the medial meniscus. Walczak et al. (2008) reported higher rates of degenerative changes in the menisci (54%) of NBA players. Shellock (1991) reported meniscal tears in nine percent of runners while 45% had grade one or two signal abnormalities. A study of asymptomatic non-athletes found a 25% rate of meniscal signal abnormality (Kornick et al., 1990). Cross-country runners in this study had a higher but non-statistically significant rate of meniscal signal abnormalities at baseline, against the hypothesis that the knees of basketball players would have more signal irregularities due to the type of movements performed.

Patellar tendinopathy was found in two runners at baseline, with a third runner developing this during the season. Similarly, one basketball player at baseline and one additional basketball player developed this in season. We hypothesized that basketball players would have a greater occurrence of signal abnormalities in the patellar region due to the increased stress during jumping (Ferretti, 1986), however this was not supported by

the baseline results of this study. All three changes in the BB group were, however, related to the patella. The rate of patellar involvement is similar to the rates previously found in MRI studies of basketball players performed in the preseason, Walczak et al. (2008) and Major and Helms (2002) reported patellar tendinopathy in 39% of professional and 24% of collegiate knees, respectively. In contrast, Pappas et al. (2016) found much higher rates, reporting MRI signal consistent with patellar tendinopathy in 83% and 90% of basketball athletes in the preseason and postseason, respectively.

Only one XC participant had joint effusion at baseline, which was no longer present in the follow-up images. Previous studies reported 8% effusions in NBA players (Walczak et al., 2008) and 29% of collegiate basketball athletes (Pappas et al., 2016). Only one participant (BB) had a bone marrow lesion, which developed during the season (lateral patella). This incidence is far less than previously reported. Pappas (Pappas et al., 2016) identified bone marrow edema in 75% of players in the preseason and 86% at the end of the season. Walczak et al. (2008) and Major and Helms (2002) reported a preseason prevalence of bone marrow edema in 25% of professional and 41% of collegiate knees, respectively. Meniscal pathology typically precedes BMLs in knee osteoarthritis (Lim et al., 2013) and although this cohort of young athletes had high rates of meniscal signal abnormalities, they may not have progressed to signal change in the bone. Strenuous physical activity independently predicted an increase in BML size in middle-aged adults (Foong et al., 2014). There is weak evidence to suggest that BMLs in younger populations are modifiable (Antony et al., 2016). In a study of professional runners, almost all asymptomatic athletes showed BMLs, with more than half of the lesions fluctuating during the season (Kornaat and Van de Velde, 2014). An incidental finding of a BML on MRI of a professional athlete is not always related to clinical complaints (Kornaat and Van de Velde, 2014). More data is needed to understand the relationship between MRI identified lesions and future joint degeneration.

Surprisingly, there were no articular cartilage findings for either the XC or BB participants at baseline or follow-up. Previous studies have found about a 50% prevalence of articular cartilage injuries in college and professional basketball players (Kaplan et al., 2005, Walczak et al., 2008), however this is not a consistent finding. Major and Helms (2002) found no tears in 34 knees of college basketball players, but

found signal abnormalities in 41% of the MRIs. Soder (2011) reported no cartilage abnormalities in adolescent soccer players. Boeth (2017) found cartilage lesions in 56% of the adult volleyball athletes (mean age 46.8 years) but found none in the adolescent cohort (mean age 16 years). Many of these studies did not control for prior knee injury or surgery, which increases the risk of cartilage lesions (Nepple et al., 2012). The most commonly used MRI pulse sequences for examining articular cartilage are fat-suppressed, T1-weighted, 3D gradient-echo, and fat-suppressed T2-weighted (Peterfy et al., 2004). This study used a combination of 2D T2 weighted fat saturated (saturation is one method to suppress fat) sequences and 3D gradient-echo, and so the lack of cartilage findings is not likely an issue with the image sensitivity but could rather be due to the young and healthy nature of the knees that were imaged. Differences in sequences and magnets could be a factor in the variability of results between studies, in addition to the sample populations.

The incidence of MRI worsening was not significantly different for XC and BB (41% and 30% respectively). This was against the hypothesis that BB would have more signal irregularities and worsening due to the type of movements performed and the differential rates of knee OA reported (Buckwalter and Lane, 1997b). The results of the statistical analysis revealed no interaction effect between sport and MRI worsening. The three variables with a main effect of MRI-worsening represented lower moment range (Walk-KFM PC2), and lower magnitudes (Walk-KRM PC1, Run-KAM PC1), against the hypothesis that higher joint moments would be related to MRI worsening. Both higher and lower joint moments have been associated with negative changes on MRI. Lower peak vertical ground reaction force and lower knee flexion moments at six months were associated with increased T1ρ values from baseline to three years in a cohort of ACL reconstruction participants (Shimizu et al., 2019). Higher KAM during walking has also been associated with MR relaxation times in medial knee compartments (Kumar 2014; Kumar 2018). More research is clearly needed to reveal dominant trends in the relationship between joint moments and MRI changes over time.

The waveform patterns were very different between XC and BB, especially for running frontal and transverse plane moments (Figure 7.2). No studies have directly compared the running mechanics of these two types of athletes. BB had significantly

lower frontal and transverse moments (PC1 features) during walking and running. Basketball involves many movements with predominant motion in the frontal (side-cutting) and transverse plane (pivoting). These athletes may have developed neuromuscular strategies to control the knee in these planes, thereby generating lower net torques, compared to runners during running and walking. Because of the small study sample and small sub-sample of those that had MRI signal change, it was not possible to analyze the within sport mechanics related to worsening, and the variability between sports may have limited this analysis. Future research should be completed to increase the power through a larger sample of athletes.

Further study is warranted to determine whether MRI findings in asymptomatic knees are associated with increased risk for future injury or degenerative change. In theory, morphological defects of the meniscus visualized on clinical MRI sequences are likely preceded by early degeneration of the biological matrix, including effects on proteoglycan metabolism, collagen composition, and water content (Stehling et al., 2011). Future work should include male and female cohorts to improve our understanding of sex specific biomechanics and tissue changes to better understand mechanisms that might lead to disproportionate OA and injury in females. Although Stehling et al. (2011) found no difference in the total score between marathon runners and control subjects using a similar semi-quantitative scoring system (WORMS), the addition of sedentary or non-athlete controls to this study design would provide a context to the baseline scores and contrast the physical activity incurred by athletes.

7.5 Conclusion

This prospective study on basketball and cross-country athletes provided an interesting framework to study the response of the knee joint to an extreme dose of loading. Surprisingly, both sports resulted in similar incidence of baseline signal abnormalities and signal change on the MRI after one season. Significant differences in joint level mechanics were linked to MRI signal worsening with unexpected links to lower frontal and transverse plane moments when running and walking. This short-term pilot study showed the efficacy of incorporating medical imaging into biomechanical

analysis of athletes as a surrogate for joint health and uncovered questions about the role of the pattern of joint moments in relation to changes in the knee joint.

CHAPTER 8
Conclusion

8.1 Summary of Findings

Knee osteoarthritis (OA) is a complex interaction between joint mechanics and biology affecting the structure and function of the joint. This thesis used biomechanics, the science of the intersection of biology and mechanics, to study knee OA with a focus on early disease processes to improve the understanding of the role of biomechanics and activity on causation. While there are multiple pathways that can lead to knee OA, the focus of this thesis was the relationship between abnormal knee joint loading and changes to the structure joints with and without OA. The goal of this thesis was to test the hypothesis that magnitude and pattern features of knee loading during gait could stress the diseased joint leading to knee OA structural progression and have a role in the micro-injuries that could lead to knee OA development in a healthy joint. Three studies were used to address the four primary aims of this thesis, where external knee joint moments and muscle activation patterns served as surrogates to the load imposed on the joint and medical images as surrogates for joint health.

8.1.1 Three-Year Progression Study

In 2002, a seminal paper linking higher frontal plane knee moments to knee OA structural progression was published (Miyazaki et al., 2002); a six-year prospective study of medial compartment knee OA progression. The Three-Year Progression Study in this thesis aimed to determine if mechanical factors related to the shorter timeframe of radiographic progression were the same as what was previously found in the frontal plane, and if additional features of the sagittal and transverse plane moments and muscle activation patterns were also related to the disease process. This more comprehensive look at joint and muscle mechanics in relation to structural OA progression was intended to provide a more complete picture of the altered loading environment that precedes knee OA progression. The replication of the finding of higher fontal plane moment magnitude and knee OA progression is an important contribution to the literature. Prospective

longitudinal studies are rare due to the time, cost and methodological requirements; however, replication is a cornerstone of the scientific process and critical for scientific progress. Greater frontal plane loading has been repeatedly related to knee OA progression and is robust across different patient populations and when using both radiographic defined OA progression and MRI defined progression (Bennell et al., 2011, Chang et al., 2015).

The novel findings of Aim 1 in the transverse plane and greater lateral muscle activation in the first half of stance phase are new signals related to knee OA structural progression. The muscle activation findings in this study were in conflict with the 2016 results of Hodges et al., (Hodges et al., 2016) who reported greater medial site muscle activation with knee OA progression. Biceps femoris (lateral hamstring) is bi-articulate and has a role in hip extension in addition to knee flexion. Because of the combined results of lateral gastrocnemius and lateral hamstrings, it is likely that this difference in muscle activation has a stabilizing role at the knee joint, however it could also signal mechanical changes at the hip. Future work should include an analysis of hip and ankle mechanics to further explain the mechanisms that are seen at the knee.

The Three-Year Progression Study included asymptomatic participants who had medial joint space narrowing in the progression group, one of whom was diagnosed with clinical knee OA during the study, and therefore was not just progression of existing OA. While these asymptomatic progressors made up a small proportion of this group, qualitatively, this subset had different knee moment patterns and muscle activation patterns than the OA-progressors. The separation of OA initiation from progression is an important piece of the pathomechanics of knee OA and future studies should include more detailed assessments of the control or asymptomatic cohorts (both biomechanically and related to the relative disease state of the joint) in an effort to capture early changes related to knee OA. This study was originally designed to do this, however incidence of KL grade two radiographic severity in the asymptomatic group was very high at baseline, limiting the analysis of radiographic knee OA initiation. With this in mind, future studies would require the inclusion of a younger cohort in parallel, followed over a longer period of time with more frequent radiographs.

8.1.2 Three-Year Changes in Gait

The mechanical cause and effect of knee OA progression is difficult to distinguish. The novelty of the Three-Year Progression Study design was the inclusion of both radiographic and biomechanical data at baseline and follow up, facilitating the study of gait changes in concert with knee structural worsening. Although no group by time interaction effects were found in Aim 2, there were multiple main effects of time. The increases in joint loading from baseline to follow-up were two to three times greater for the progression group than the non-progression OA group and the asymptomatic group. The small sample sizes in each group may have been a factor in the inability to detect statistically significant interactions, however the trends warrant further investigation. The joint moment and muscle activation pattern changes suggest that the gait of the OA group was affected by the disease over the three years and that, potentially, gait was more sensitive to the disease process than the standard radiograph.

8.1.3 Puberty and Gait

There is a general consensus in the OA research community that prevention of knee OA is the greatest opportunity to lessen the disease burden. The efficacy of reducing the external KAM through gait modifications and the subsequent slowing knee OA progression has not been well established (Lewinson and Stefanyshyn, 2016). Due to the association between abnormal frontal plane knee biomechanics and the sex disparity of joint injuries (Myer et al., 2015), and OA development, focusing on the sex-specific maturation of running and walking gait is a foundational piece to understanding relative mechanical predisposition. Extending the use of walking gait as the model of joint loading from the adult knee OA population to the young adolescent athlete was done in an attempt to link mechanical features between these two cohorts and to provide the basis for a sub-maximal functional assessment of joint mechanics.

Walking and running gait were both characterized by significant sex and puberty differences in all three planes. While there were no sex and puberty interaction effects for the frontal plane moment features during walking, both the magnitude and pattern of the running KAM had a significant interaction effect. Later puberty stages had higher frontal and transverse plane moments when walking and altered patterns of frontal and

transverse plane moments when running, adding evidence to the importance of the dynamic pattern of joint loading in addition to magnitude features. Discriminant models using the patterns of knee moments during walking gait were as good at classifying participants based on puberty status and sex as running models and may be a useful tool in young athlete monitoring in the future. Further research is needed to link features of joint loading during walking gait to future injury and OA risk.

8.1.4 Female Athlete Joint Health Study

Sport has often been used in the discussion of the over-load theory of knee OA initiation and the role of load type on the differential risk between sports. Current evidence suggests that participation in sports that involve discrete movements at high intensity and at an elite level increases the risk for idiopathic knee OA. The lack of connection between running and increased rates of knee OA is seemingly in direct conflict with this theory, however the majority of research on this topic is retrospective and often confounded by selection bias. There was therefore a clear motivation for studying the variance in joint level mechanics among young female athletes prospectively and to measure changes in the joint resulting from participation in sport. The use of university student-athletes as a high-load-dose model worked on a few different levels. The general lifestyle of the student athletes, due to similar academic schedules and sport specific commitments, was fairly consistent and reduced the need to monitor specific daily dose of physical activity. While activity monitoring was considered for this study, early compliance was very low, and it became clear that this was beyond the scope of the current study design. The contrast of basketball and cross-country athletes was chosen with the goal of achieving a similar load volume accumulated through very different load types.

The use of a semi-quantitative MRI score to measure changes in the knee joint was both pragmatic and purposeful. The semi-quantitative scores captured all of the possible morphological changes in the knee, therefore broadening the scope of the study from a cartilage centric view, to a total knee joint view. The sequences captured could allow for different processing in the future, however after reviewing the initial MOAKS results, the added-value of quantitative MRI in this sample due to the low incidence of

change did not seem to warrant the additional analysis. Quantitative MRI to measure cartilage volume or T2 relaxation times is sensitive to the proximity of physical activity to the acquisition of the images (Kim et al., 2019; Karanfil et al., 2018). Both the availability of the MRI for research and student-athlete free-time was limited, and therefore extensive control around the MRI was not possible in the current study.

Although a pilot study by design, this was the first study to compare MRI changes between female basketball and cross-country athletes prospectively and relate knee joint loading to MRI signal changes. Contrary to our hypotheses, we found that one season of basketball was no more injurious to the knee joint (as defined by worsening MOAKS score) than cross-country running and that higher magnitude features of joint moments were not associated with increased MOAKS scores. Cross-country running does involve more maneuvering on uneven terrain and elevation changes than road or track running, and it is possible that cross-country puts greater strain on the knee joint. These two cohorts are also training and performing at an elite level, which has been previously shown to increase risk of knee OA compared to non-elite athletes in the same sports. Similar to the Three-Year Progression Study, more timepoints and a longer duration are needed to truly measure the longitudinal relationship between mechanics and joint health. The addition of a non-athlete control group and male-athlete cohorts would improve the interpretation of results and facilitate the identification of sport-related and female-specific relationships. Other researchers have proposed using alternative surrogates to monitor knee joint loading, such as inertial measurement units (Karatsidis et al., 2017, Besier, 2019) which may add value by quantifying cumulative loading during training and competition.

8.2 Research Limitations and Future Directions

The study of knee OA is iterative and cross-disciplinary and complicated by the human body; its underdetermined mechanical nature, its constant evolution from birth to death, and its uniqueness at an individual level. The time-course of osteoarthritis is slow, and therefore the study of its pathogenesis is also slow, which is juxtaposed by the rapidly increasing burden (physically and fiscally) on the global population. The progression of knee OA can be monitored by the increase in disease severity (structure),

the increase in the illness (symptoms) and the loss of function of the joint which is related to both the changing structure and worsening symptoms. Decreased function is most notable during the end stages of the disease where the joint is insufficient in transferring forces, supporting the body and aiding in locomotion, culminating in total "joint failure" (Loeser et al., 2012). Early functional declines measured through joint level mechanics may help to identify susceptible individuals or those that are already early in the disease process.

The objective assessment of joint function as a signal of disease progression is not trivial. Individuals with knee OA often report difficulty walking (Ling et al., 2003) and knee joint mechanics and muscle activation patterns during walking have been shown to differ with the level of severity of knee OA (Astephen et al., 2008a, Astephen Wilson et al., 2011). As a result, the manner in which someone walks, and more specifically, walking with a biomechanical style of a healthy and asymptomatic adult population, is commonly used as a model of normal joint function. The failure to discriminate between "average" and "normal" is a major limitation in knee OA research. Statistical averages do not acknowledge the uniqueness of the individual. Solit (1962) proposed that only a relative normal exists—that each individual represents the most economical performance of their own body, and therefore an individual can only be compared to their own potential, not to other individuals and groups. By the time a patient seeks treatment for knee pain, contact mechanics have already changed due to degradation of articular cartilage, subchondral bone and the formation of osteophytes which are coupled with neuromuscular impairments resulting in a change in gait mechanics. To compare a patient to their own "normal", measurement and monitoring of an individual's biomechanics, joint morphology and composition would be required early in life and repeated frequently throughout.

While cross sectional research has improved our understanding of the mechanical differences of an osteoarthritic knee joint from an asymptomatic knee joint, it is only through longitudinal research that we can appreciate the biomechanical changes that occur in concert with structural changes. Two timepoints is not enough to make strong conclusions about the stability of gait and how joint mechanics fluctuate with changes in the disease. Continuous monitoring of patient function and structure would result in the

ideal dataset to answer these questions. While in theory inertial measurement units (IMUs) provide an answer to laboratory constraints and open up the possibility for more frequent measurements of joint kinematics and surrogates for joint kinetics (Nedergaard, 2017), we may be further away from continuous data than expected. In the Female Athlete Joint Health Study, IMUs were distributed to the participants to be worn on their shoes during training and competition. The compliance was very low, with certain participants declining to use the small device due to the green color, the sound of their laces hitting it, not wanting to be "monitored", losing it, forgetting it, along with other person-specific reasons. As we enter the 5G enabled internet of things, passive collection of data without the need for conscious participation from the participants will be possible, however the tension between our personal privacy and the potential advancements in preventative medicine is already evident. The groups that control most of the medical data today are insurance companies and there is a perceived or potentially real harm of personal data disfavouring coverage of care in countries like the United States of America. The benefit of more data driven and evidence-based solutions in research and healthcare is clear, but how we get there is not.

The discordance between clinical trial approved monitoring standards for knee OA (joint space narrowing on a radiograph) (Dougados, 2004) and current available technology is frustrating. The reliance on crude three-point scales to monitor disease progression is not sufficient or necessary. The exclusion of four participants in the Three-Year Progression Study (Chapters 4 and 5) who had a baseline joint space narrowing score of three was due to the ceiling effect of this scale. By definition, they were unable to progress structurally and so these participants would have defaulted to the OA-non-progression group regardless of the change in the relative severity of the disease. Five participants in the Three-Year Progression Study had a one-point decrease in medial joint space narrowing score at follow-up. The definition of structural worsening as a dichotomous factor: progression and no-progression (Ornetti et al., 2009a), follows the definition of OA as a progressive disease. This well accepted decision to not consider anti-progression in knee OA research has made us blind to this potential aspect of knee OA (and knee OA research) and reiterates the need for better tools to increase the

resolution of the changing disease state and the involvement of other tissues in the disease process.

The non-ionizing modality and high-resolution images of an MRI should make this technology the clear gold standard for joint health and knee OA diagnosis and monitoring. The high cost is the largest barrier, which stems from the reliance on helium to cool the magnet. There has been substantial improvement in methods to cool superconducting magnets for MRI machines without the need for a continuous supply of liquid helium (Iwasa, 2017), and companies like Cryogenic Limited (Cryogenic Ltd., London, UK) are already manufacturing these devices. This could be the technological advancement that brings MRI into the biomechanics laboratory and musculoskeletal clinic, helping to bridge the gap from biology to morphology to mechanics. There is a concern that MRI may measure smaller and more insignificant or reversible structural changes and therefore not provide as stable of a metric for the progress of knee OA. More data is needed on the plasticity of these measurements including the effect of time of day, menstruation, the day to day fluctuation with activity, and the micro-injury/repair cycle. More frequent studies using MRI will help to fill the gaps in our understanding of the limits of detection, the stability of various features related to knee OA, and the identification of confounding factors to the appearance and intensity of these MRI signals.

8.3 Final Thoughts

This thesis aimed at identifying the type of loading that is harmful to the knee joint in terms of type, magnitude, and pattern of loading with and without knee OA. Both radiographs and MRIs were used to measure the global biological response to these loads. While we can only speculate the mechanisms linking the load to the degenerative response, the results of these studies suggest that the mechanical factors related to knee OA progression are not related to sport induced MRI signal changes in healthy asymptomatic female athletes. Most of the interesting signals throughout each study were in the frontal and transverse plane and more effort should be placed on the comprehensive analysis of joint moment waveforms and muscle activation patterns in biomechanics research.

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APPENDIX A

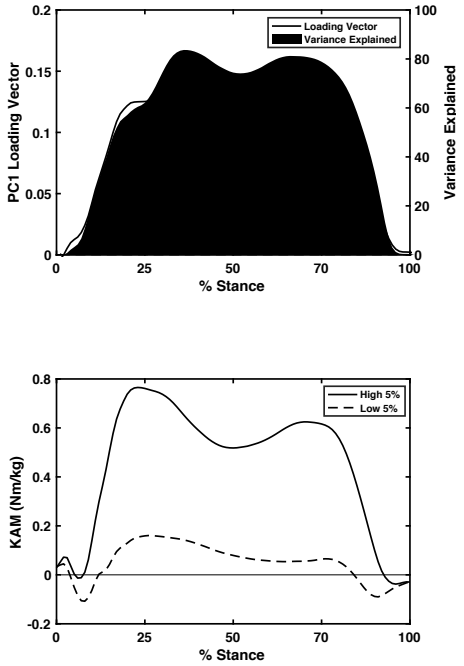
Description and Figures of Principal Components

A PC score for each subject was calculated for each principal component. PC scores describe how far that subject is from the mean for that feature of variation. The subject with the highest PC score exhibits the greatest amount of variation. By plotting the waveforms corresponding to the maximum and minimum PC scores, PC features can be interpreted (Jones and Rice, 1992).

There are three typical interpretations of principal components of gait waveforms: magnitude, difference operators and skewness. Magnitude features indicate that the greatest variation in the waveform is in the y direction. A difference operator also describes variability in the y direction, however, describes the total range. Skewness describes the position/timing of peaks often interpreted as a phase shift along the x-direction.

A.1 Three-Year Progression Study Walking Knee Moment PCs

KAM PC1



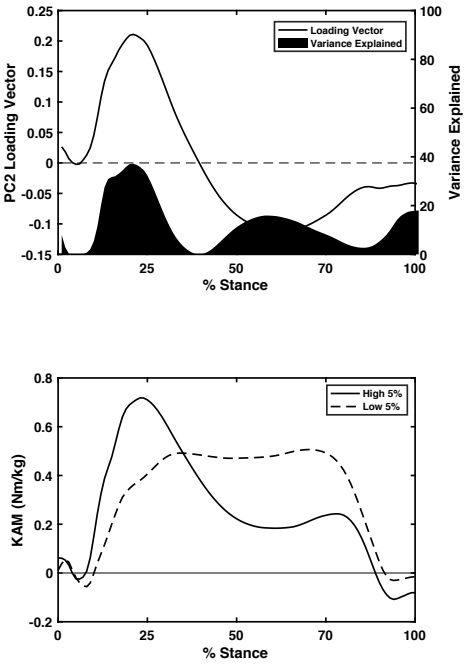
Variance Explained:
67.2%

Description:
Overall magnitude features where high scores have greater overall KAM

High scores have less abduction moment in early and late stance, and greater adduction moment throughout stance

Figure A.1 Walking KAM PC1 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom).

KAM PC2



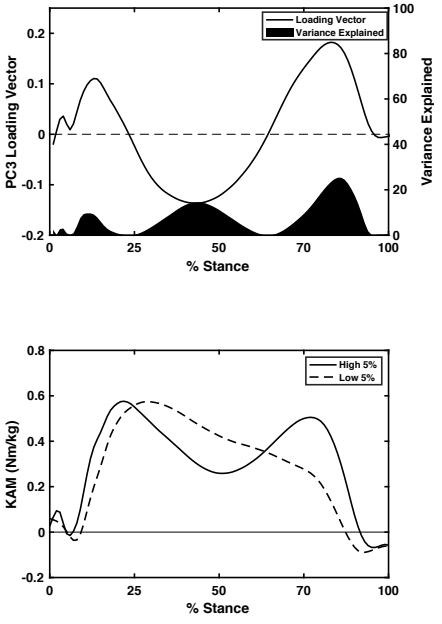
Variance Explained:
14.8%

Description:
Difference between early stance and mid- to late-stance.

High scores have a greater difference between early and mid- to late-stance.

Figure A.2 Walking KAM PC2 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom).

KAM PC3



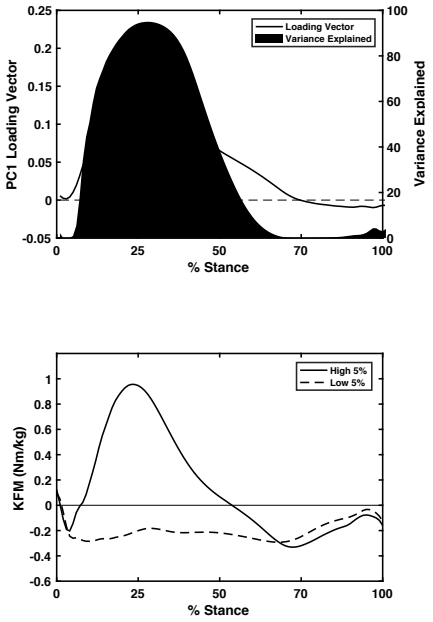
Variance Explained:
7.5%

Description:
Greater difference between mid-stance and late stance

High scores have greater moments in late stance (a defined second peak)

Figure A.3 Walking KAM PC3 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom)

KFM PC1



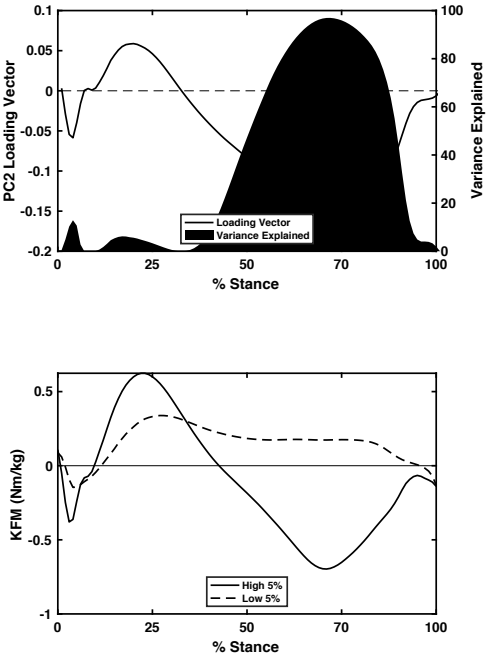
Variance Explained:
49.4%

Description:
Magnitude of flexion moment in first half of stance phase

High scores have greater magnitude knee flexion moments.

Figure A.4 Walking KFM PC1 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom).

KFM PC2



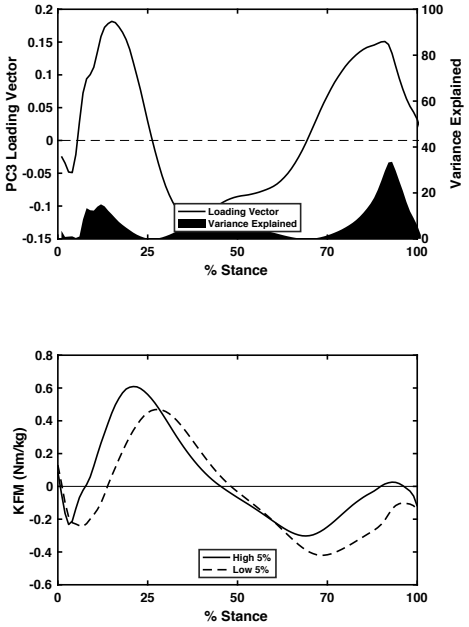
Variance Explained:
26.8%

Description:
Difference between moment in first half compared to second half of stance phase. More variance is explained in the second half of stance (knee extension moment)

High scores have greater range of moment: higher knee flexion moments in first half of stance, and higher extension moments in second half of stance.

Figure A.5 Walking KFM PC2 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom).

KFM PC3



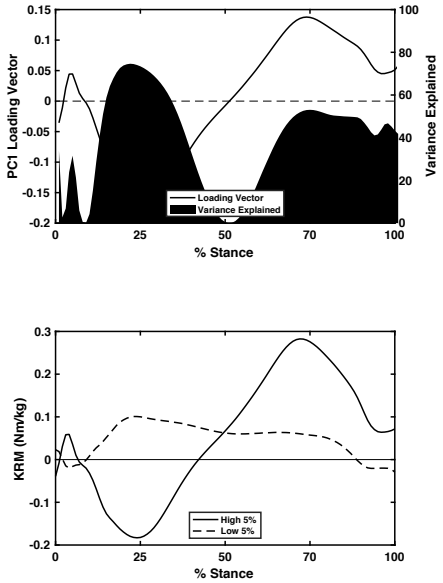
Variance Explained:
4.4%

Description:
Phase shift to the left (earlier in stance phase).

High scores have an earlier peak flexion moment

Figure A.6 Walking KFM PC3 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom).

KRM PC1

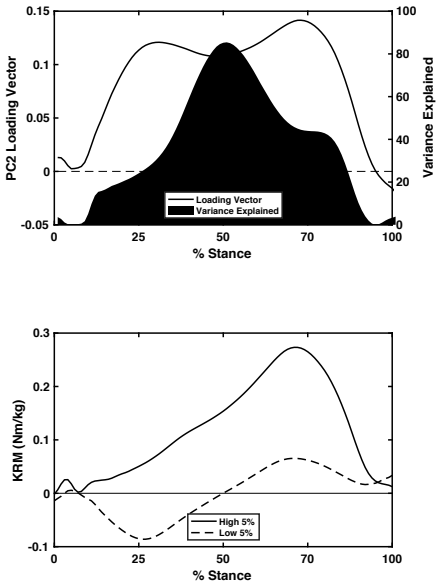


Variance Explained:
49.3%

Description:
Greater external to internal rotation moment difference

Figure A.7 Walking KRM PC1 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom).

KRM PC2

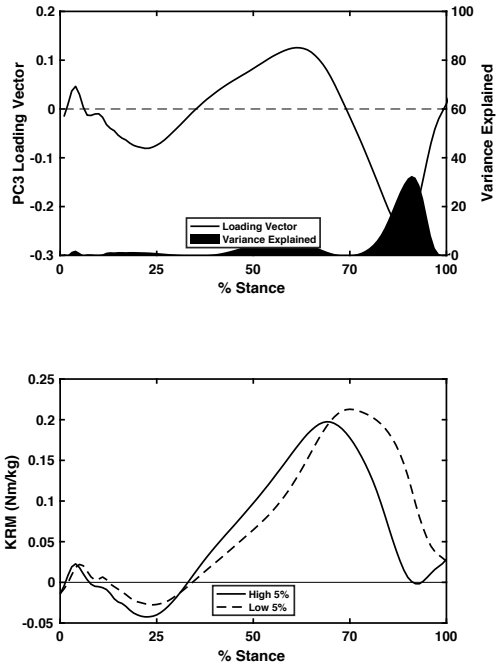


Variance Explained:
39.2%

Description:
Greater overall mid- to late-stance internal rotation magnitude

Figure A.8 Walking KRM PC2 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom).

KRM PC3



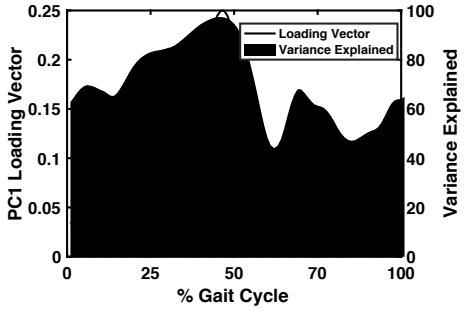
Variance Explained:
3.7%

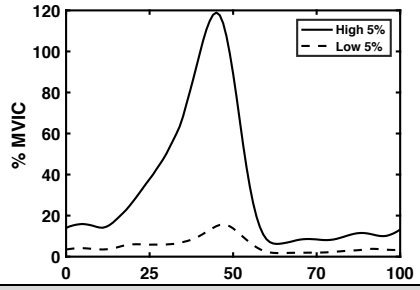
Description:
Phase shift to earlier peak internal rotation moment in mid- to late-stance

Figure A.9 Walking KRM PC3 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom).

A.2 3-Year Progression Study Walking EMG PCs

Gastrocnemius PC1





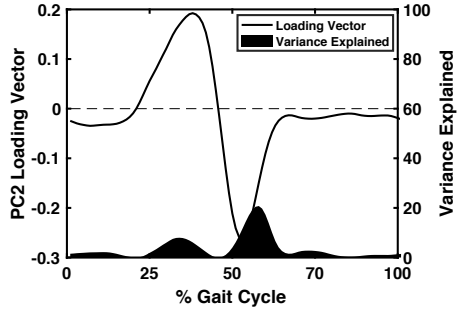
Variance Explained:
89.8%

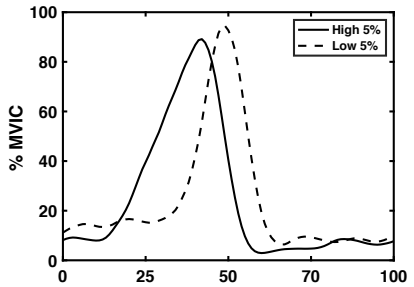
Description:
Higher overall magnitude

High scores have greater gastrocnemius activation throughout the gait cycle

Figure A.10 Walking Gastrocnemius PC1 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom).

Gastrocnemius PC2





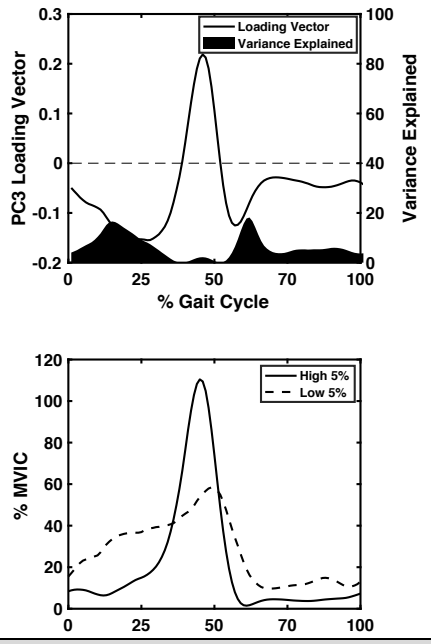
Variance Explained:
4.1%

Description:
Phase shift – earlier in gait cycle

High scores have earlier onset of peak activation.

Figure A.11 Walking Gastrocnemius PC2 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom).

Gastrocnemius PC3



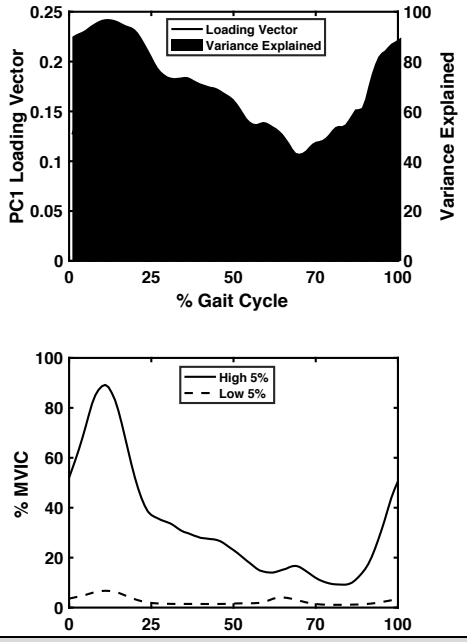
Variance Explained:
2.7%

Description:
Difference between early stance and swing baseline activation and late-stance peak

High scores have a greater difference (more prominent burst of activity in late-stance).

Figure A.12 Walking Gastrocnemius PC3 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom).

Quadriceps PC1



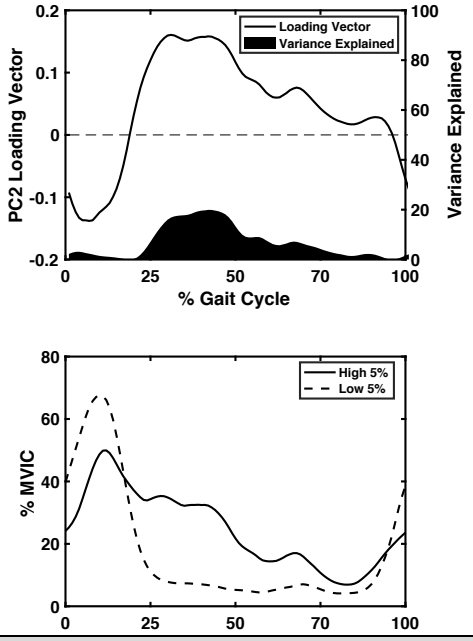
Variance Explained:
87.1%

Description:
Overall magnitude

High scores have greater magnitude of muscle activation throughout the gait cycle

Figure A.13 Walking Quadriceps PC1 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom).

Quadriceps PC2



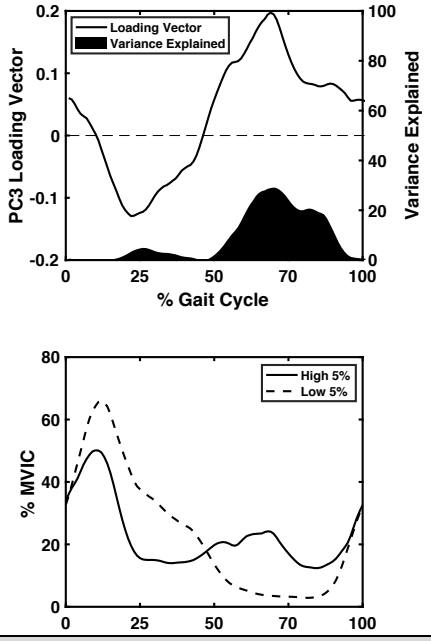
Variance Explained:
4.1%

Description:
Greater mid-stance activation compared to early stance activation (more prolonged activity)

Higher scores have more prolonged muscle activation throughout the gait cycle.

Figure A.14 Walking Quadriceps PC2 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom).

Quadriceps PC3



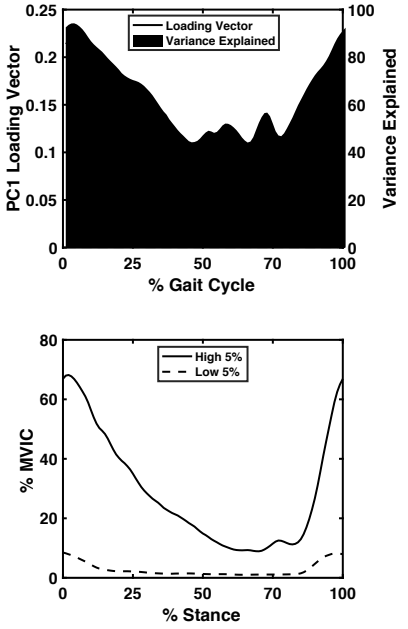
Variance Explained:
2.5%

Description:
Difference between mid-stance and early swing magnitude

High scores have lower mid-stance and greater early swing activation

Figure A.15 Walking Quadriceps PC3 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom).

Hamstrings PC1



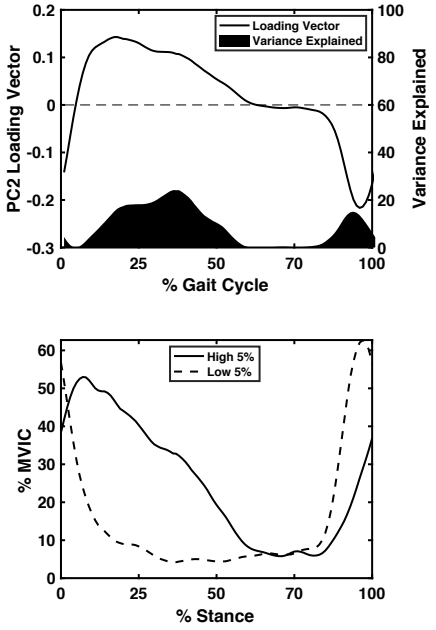
Variance Explained:
80.9%

Description:
Overall magnitude

High scores have greater muscle activation throughout the gait cycle.

Figure A.16 Walking Hamstrings PC1 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom).

Hamstrings PC2

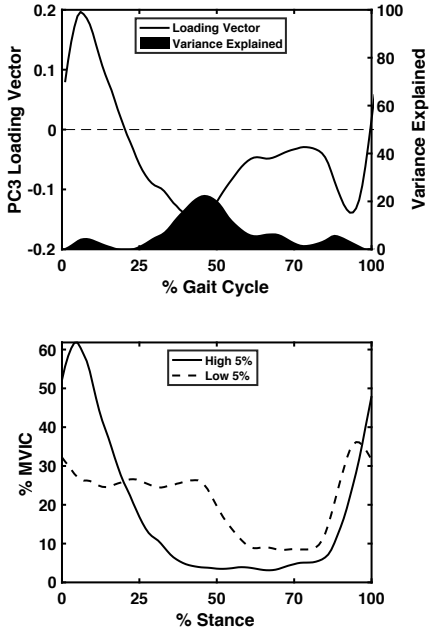


Variance Explained:
8.9%

Description:
Phase shift: peak activation after touch down and prolonged throughout stance phase

Figure A.17 Walking Hamstrings PC2 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom).

Hamstrings PC3



Variance Explained:
3.5%

Description:
Magnitude and duration of activation in stance

High scores have greater peak activation and lower late-stance/early swing activation.

Figure A.18 Walking Hamstrings PC3 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom).

A.3 mLAB Adolescent Biomechanics Walking Knee Moment PCs

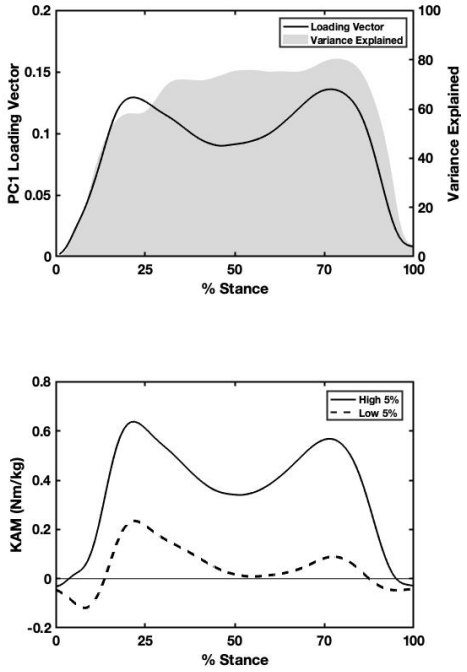
KAM PC1	
	**Variance Explained:** 66.9% **Description:** Overall magnitude features where high scores have greater overall KAM High scores have less abduction moment in early and late stance, where the highest scores do have an abduction moment.

Figure A.19 Walking KAM PC1 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom).

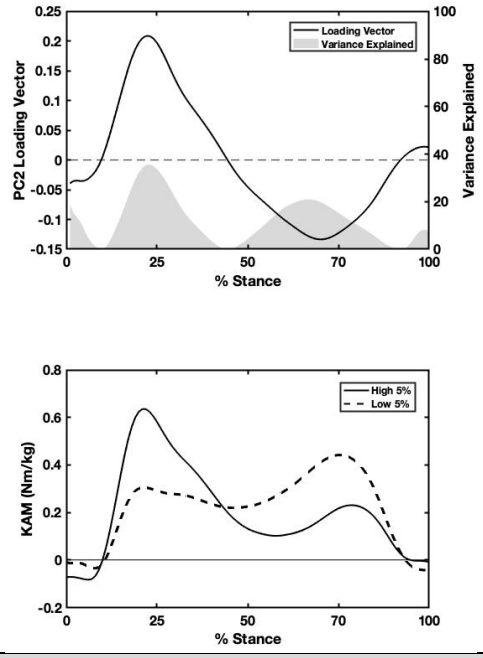
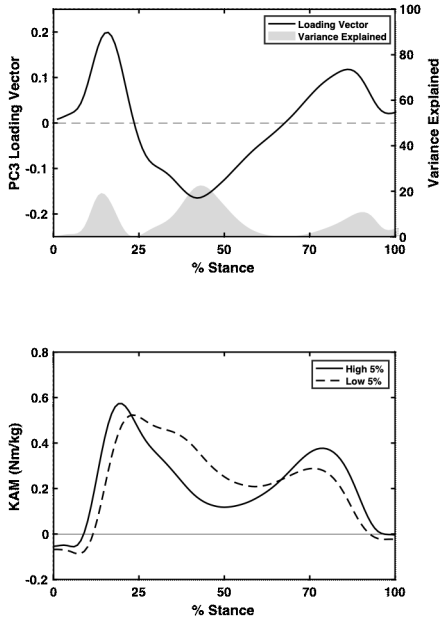
KAM PC2	
	**Variance Explained:** 15.6% **Description:** Difference between early stance and mid- to late-stance. High scores have a greater difference between early and mid- to late-stance.

Figure A.20 Walking KAM PC2 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom).

KAM PC3



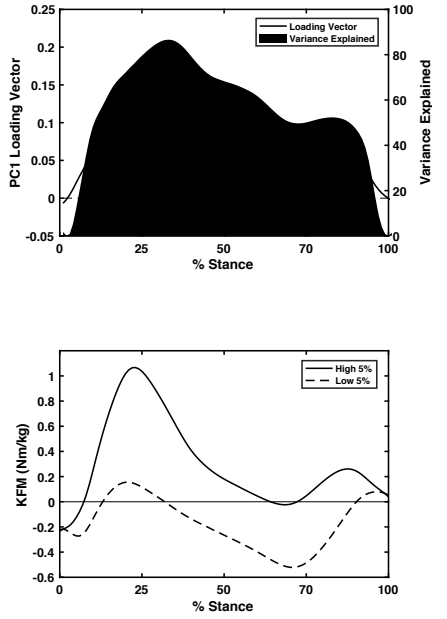
Variance Explained:
7.5%

Description:
Greater difference between mid-stance and late stance

High scores have greater moments in late stance (a defined second peak)

Figure A.21 Walking KAM PC3 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom)

KFM PC1



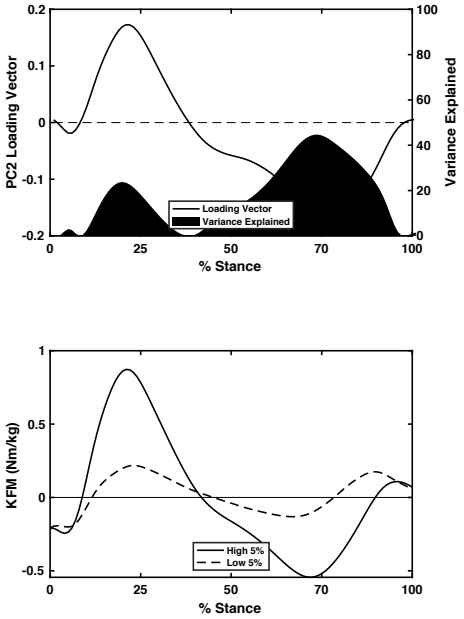
Variance Explained:
66.1%

Description:
Magnitude feature (overall shift towards flexion moment)

High scores have greater flexion moment in early stance and lower extension moment in late stance

Figure A.22 Walking KFM PC1 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom)

KFM PC2



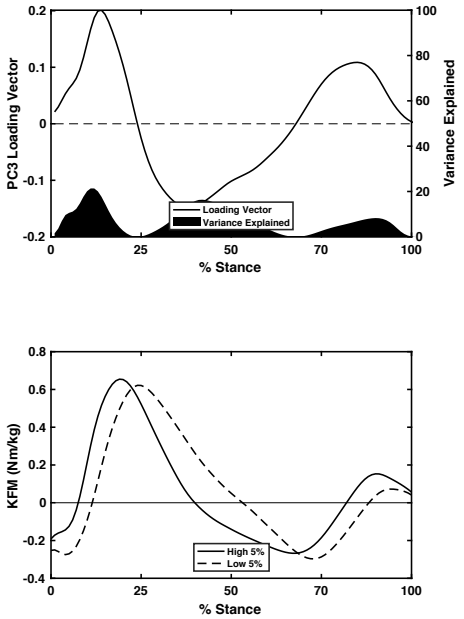
Variance Explained:
20.3%

Description:
Greater range

High scores have greater early stance flexion moment and greater late stance extension moment

Figure A.23 Walking KFM PC2 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom)

KFM PC3



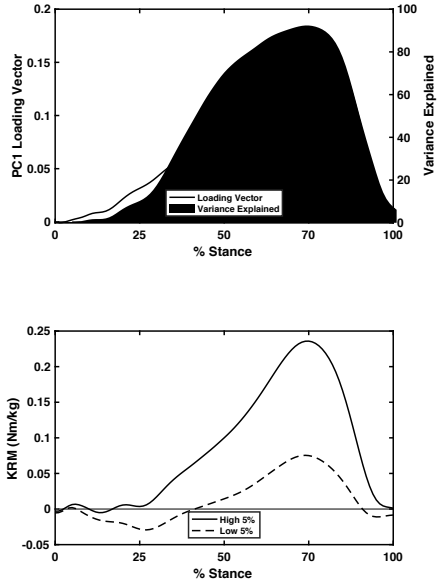
Variance Explained:
6.1%

Description:
Phase shift

High scores reach peak flexion moment earlier in stance phase

Figure A.24 Walking KFM PC3 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom)

KRM PC1



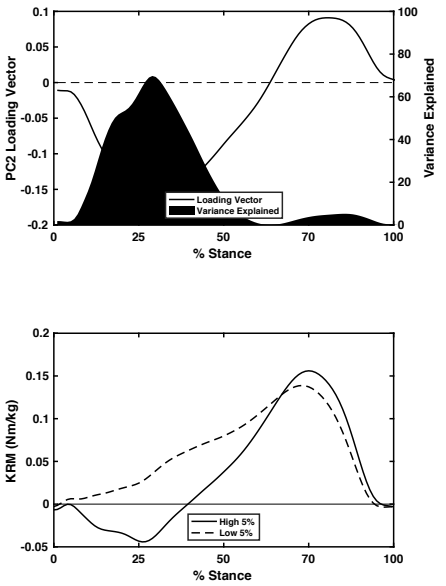
Variance Explained:
68.3%

Description:
Magnitude feature

High scores have greater internal rotation moment in late stance

Figure A.25 Walking KRM PC1 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom)

KRM PC2



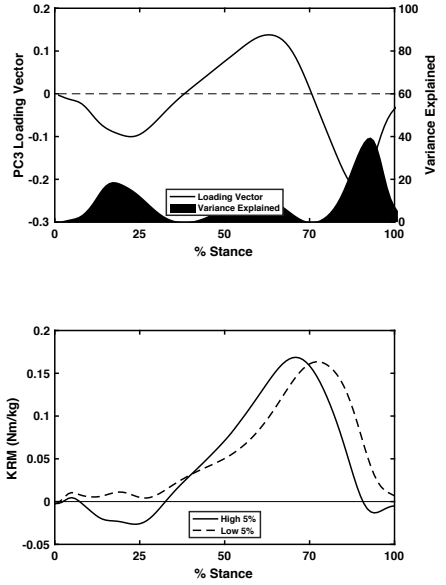
Variance Explained:
13.4%

Description:
Difference between early stance external rotation moment and late stance internal rotation moment with most variance explained in first half of stance (greater external rotation moment)

High scores have greater difference between early stance external rotation magnitude

Figure A.26 Walking KRM PC2 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom)

KRM PC3



Variance Explained:
9.0%

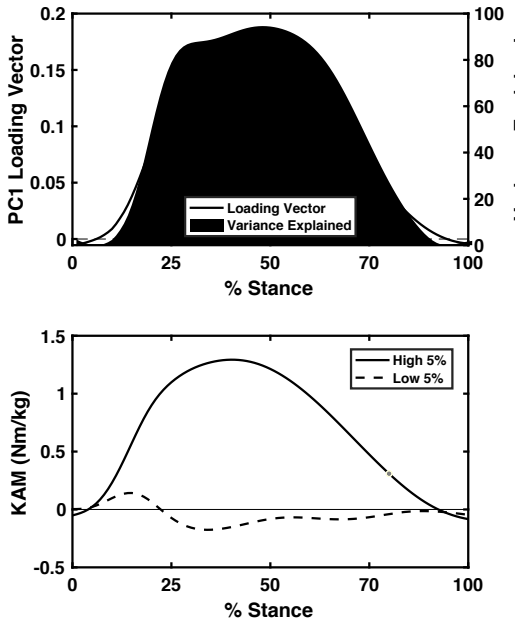
Description:
Phase shift to earlier in mid- to late-stance

High scores have earlier peak internal rotation moment

Figure A.27 Walking KRM PC3 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom)

A.3 mLAB Adolescent Biomechanics Running Knee Moment PCs

KAM PC1



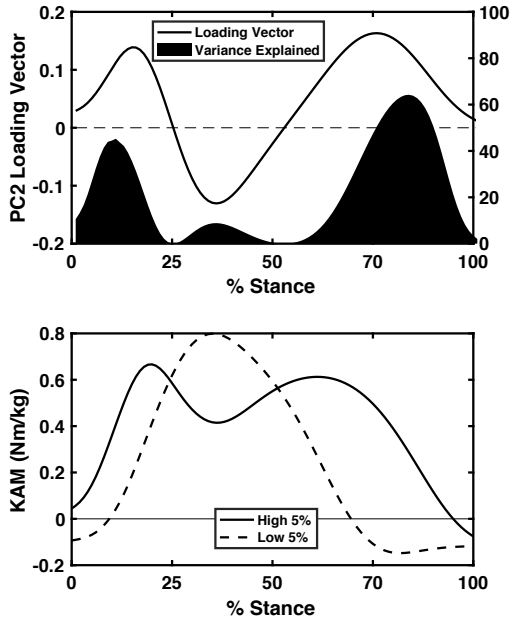
Variance Explained:
76.3%

Description:
Overall magnitude features where high scores have greater overall KAM

High scores have less abduction moment in early and late stance, where the highest scores do have an abduction moment.

Figure A.28 Running KAM PC1 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom).

KAM PC2



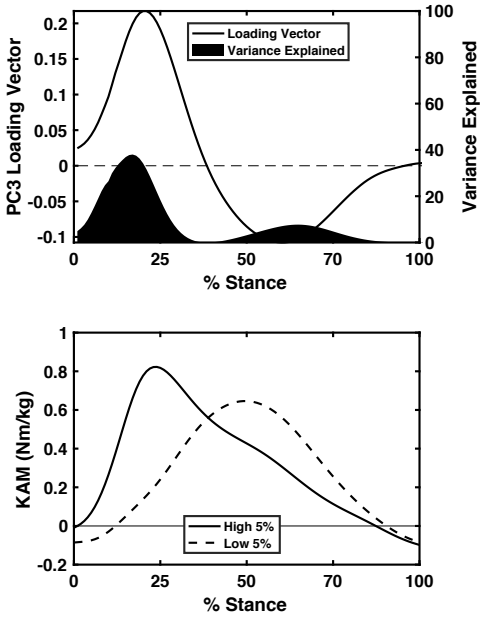
Variance Explained:
11.1%

Description:
Bi-modal profile: mid-stance unloading

High scores have a two-peak waveform: higher early and late stance moment and low mid-stance moment.

Figure A.29 Running KAM PC2 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom).

KAM PC3



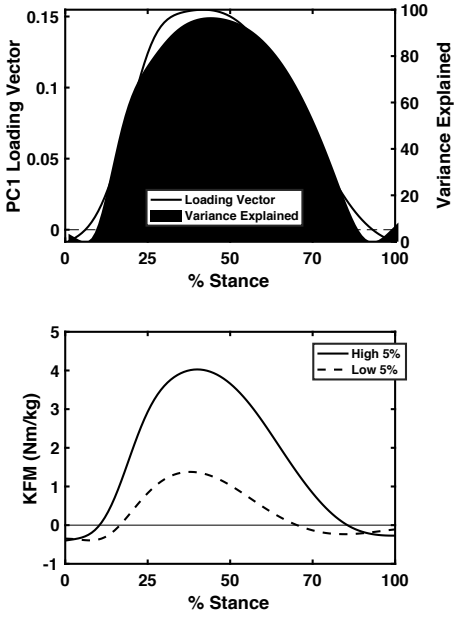
Variance Explained:
7.5%

Description:
Phase shift

High scores have earlier peak KAM

Figure A.30 Running KAM PC3 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom)

KFM PC1



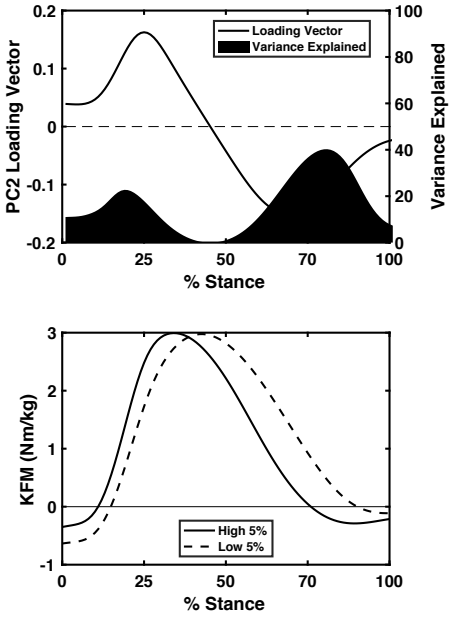
Variance Explained:
80.6%

Description:
Overall magnitude

High scores have greater knee extension moment

Figure A.31 Running KFM PC1 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom)

KFM PC2



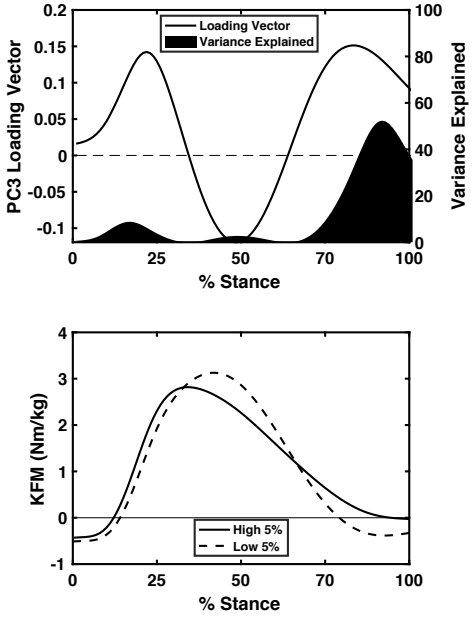
Variance Explained:
11.1%

Description:
Phase shift

High scores have earlier peak flexion moment

Figure A.32 Running KFM PC2 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom)

KFM PC3



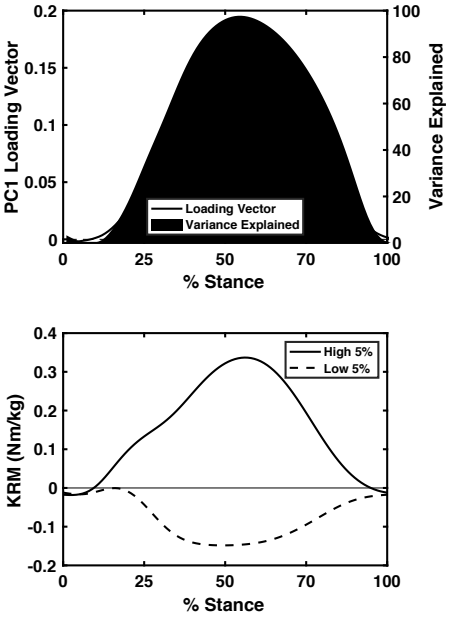
Variance Explained:
3.6%

Description:
Skewness

High scores have an earlier peak and a more prolonged moment to the end of stance phase

Figure A.33 Running KFM PC3 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom)

KRM PC1



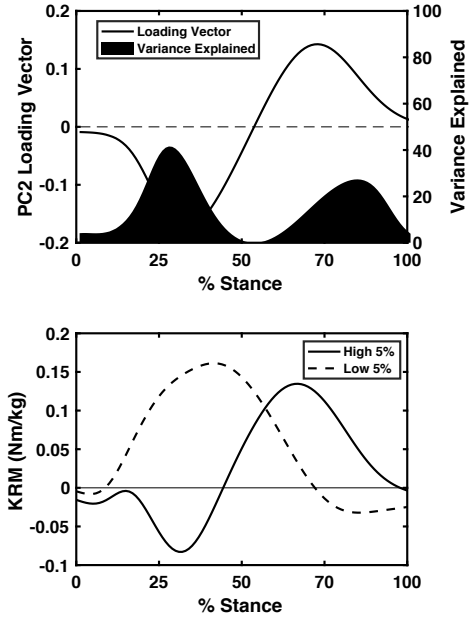
Variance Explained:
81.1%

Description:
Overall magnitude

High scores have greater internal rotation moment

Figure A.34 Running KRM PC1 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom)

KRM PC2



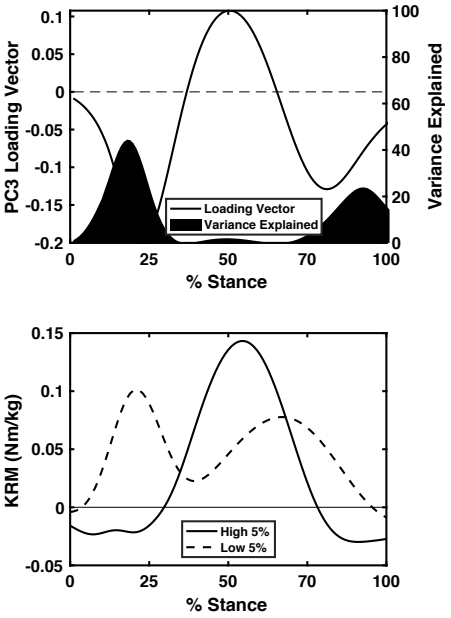
Variance Explained:
12.4%

Description:
Difference between early stance external rotation moment and late stance internal rotation moment

High scores have greater difference between early-stance external rotation moment and late stance internal rotation moment

Figure A.35 Running KRM PC2 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom)

KRM PC3



Variance Explained:
12.4%

Description:
Single peak internal rotation moment in mid stance versus high peak in early and late stance with mid-stance unloading

Figure A.36 Running KRM PC3 loading vector and variance explained (top) and 5th and 95th percentile waveforms (bottom)

APPENDIX B

Linear Discriminant Function – MRI Study

The Linear Discriminant Functions from Chapter 6 were used to calculate a "maturation-score" (discriminant score) for each of the participants in the MRI study of female athlete joint changes after one season of sport participation (Chapter 7).

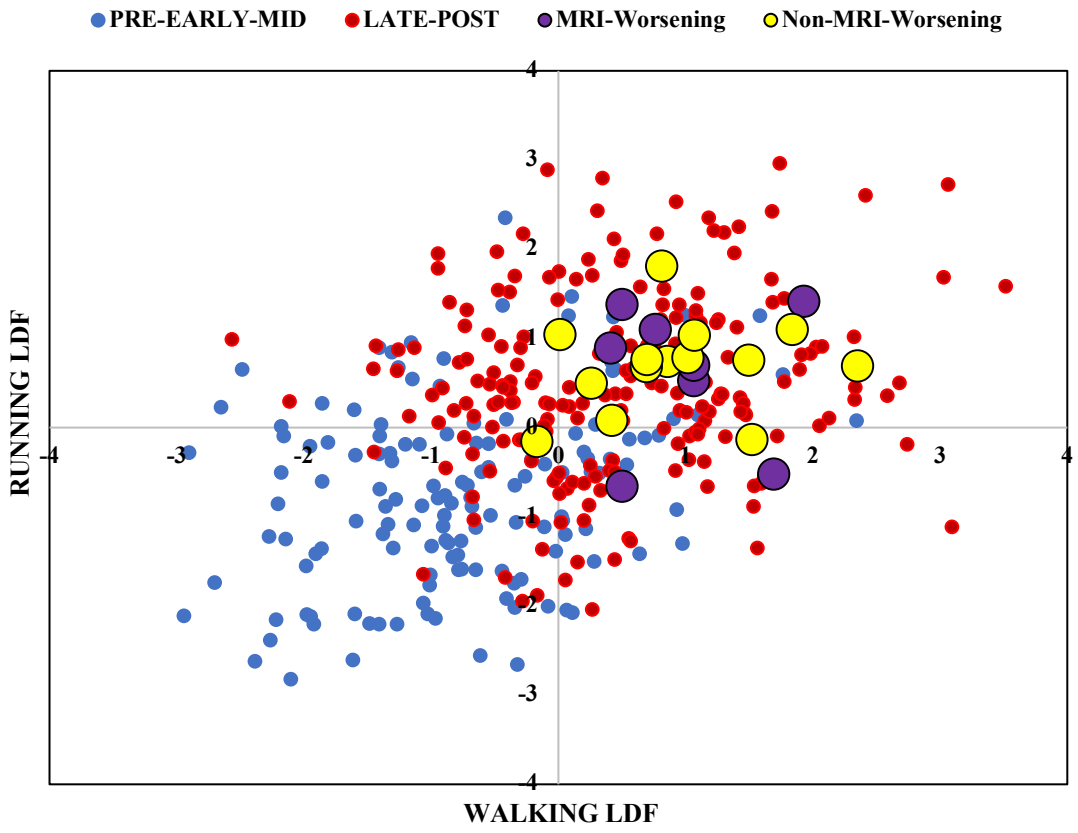


Figure B.1 MRI-Worsening and Non-MRI-Worsening participants Running and Walking LD-scores relative to the early and later puberty groups.

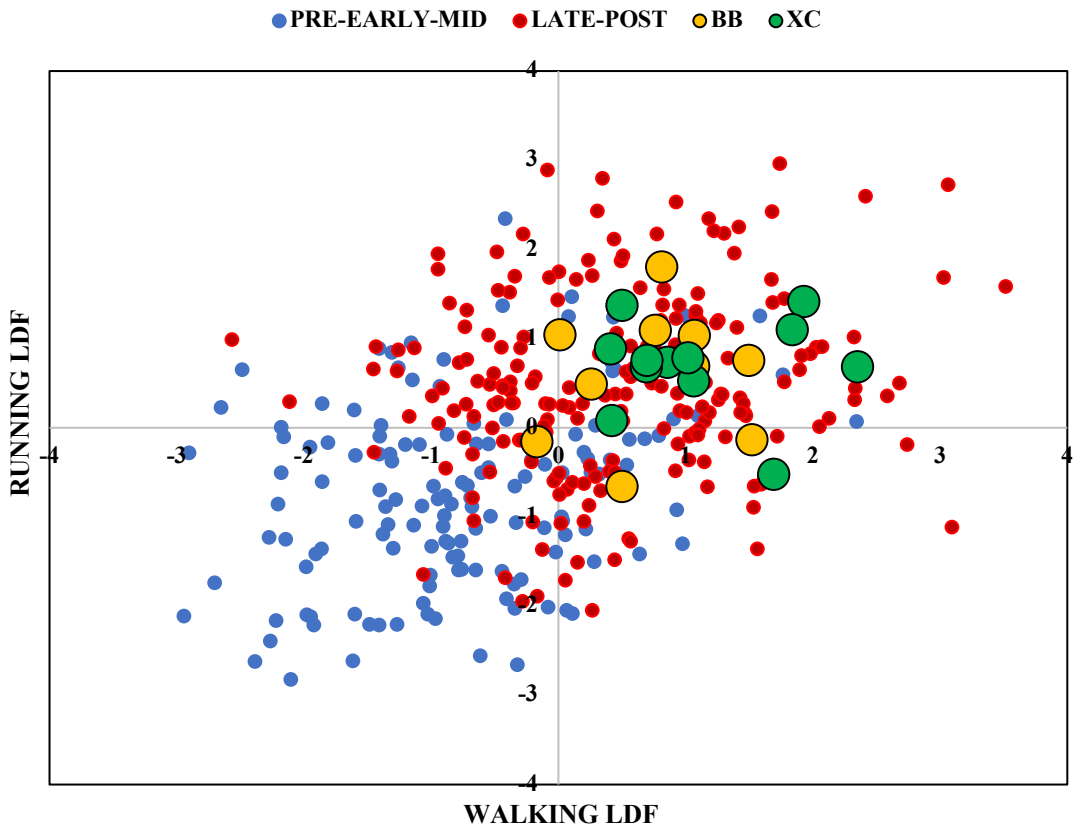


Figure B.2 Basketball (BB) and Cross-Country(XC) participants Running and Walking LD-scores relative to the early and later puberty groups.

APPENDIX C
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Chapter 4: Longitudinal Evidence Links Joint Level Mechanics and Muscle Activation Patterns to 3-Year Medial Joint Space Narrowing

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