Overall Knee Joint Loading Exposure And Clinical Progression Of Knee Osteoarthritis

by

Kerry Elizabeth Costello

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

at

Dalhousie University
Halifax, Nova Scotia
August 2018

Dedicated to my family

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Abstract

Objective: Mechanical loading has been implicated in osteoarthritis but the relationships between the many components of joint loading in vivo and clinical progression of knee osteoarthritis has not been fully explored. The goal of this thesis was to better understand how features of the knee joint loading environment are related to clinical progression of medial tibiofemoral knee osteoarthritis.

Methods: Five studies were undertaken to address this goal. Using principal component analysis to extract patterns of variation in knee moment and electromyography waveforms, the first two studies explored differences in baseline gait features associated with structural and clinical osteoarthritis progression and the relative contributions of moment and electromyography data to discriminating between those who do or do not progress clinically at follow-up. The next two studies investigated factors influencing joint loading frequency using accelerometers. Last, correlations between joint loading magnitude/duration variables (from gait) and joint loading frequency (from accelerometers) were investigated and differences in these variables between individuals who do or do not progress clinically at follow-up were identified.

Results: The patterns of electromyography waveforms were important to clinical progression, and combining moment and electromyography features better discriminated clinical progression versus no progression than either alone. Differences in habitual joint loading frequency between groups were identified using a single week of accelerometer data but individual variations over a year were high. Differences in joint loading frequency were also found between women and men but depended on whether individuals had symptomatic or asymptomatic osteoarthritis. Gait, but not joint loading frequency, differences were present at baseline in those who progressed clinically at short-term follow-up but individuals with the lowest frequency levels exhibited gait patterns that have been linked to clinical progression.

Conclusions: Given the large burden of osteoarthritis on patients and the healthcare system, addressing patterns of prolonged muscle activation in those at risk of clinical progression may provide alternative treatment opportunities. While joint loading frequency was not related to clinical osteoarthritis progression over a short follow-up, the gait patterns seen in individuals with low frequency levels suggest that these individuals are especially in need of intervention.

List Of Abbreviations

3D	Three-dimensional
ANOVA	Analysis of variance
ASYM	Asymptomatic
BMI	Body mass index
BML	Bone marrow lesion
CCR	Correct classification rate
CI	Confidence interval
CPM	Counts per minute
EMG	Electromyography
GLM	General linear model
HTO	High tibial osteotomy
ICOAP	Intermittent and Constant Pain
ICCs	Intraclass correlation coefficients
JSN	Joint space narrowing
KAM	Knee adduction moment
KEM	Knee extension moment
KFM	Knee flexion moment
KL	Kellgren-Lawrence
KRM	Knee rotation moment
LG	Lateral gastrocnemius
LH	Lateral hamstring
LPA	Light intensity physical activity
MET	Metabolic equivalent of task
MG	Medial gastrocnemius
MH	Medial hamstring
mJSN	Medial joint space narrowing
MRI	Magnetic resonance imaging
MVIC	Maximum voluntary isometric contraction

MVPA	Moderate to vigorous intensity physical activity
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OR	Odds ratio
PA	Physical activity
PCA	Principal component analysis
PCs	Principal components
PF	Patellofemoral
RF	Rectus femoris
ROC	Receiver operating characteristic
SED	Sedentary behavior
TJR	Total joint replacement
TKA	Total knee arthroplasty
VL	Vastus lateralis
VM	Vastus medialis
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Acknowledgements

"If I have seen further, it is by standing on the shoulders of giants."
Isaac Newton, 1676

Getting to where I was today is more than just the effort of myself and more even than just the last five years of work. I would not be where I am today without the support of countless people along the way.

My journey to where I am today started a long time ago and there are many, many people to thank for their support. My parents ***Thomas*** and ***Christina***, my sisters ***Pamela*** and ***Maureen***, and my family for teaching me to be a good person and encouraging me to strive for my best, sharing in my achievements and boosting me up when things didn't work out as I hoped. All the teachers and mentors I had growing up, through school, sports, and other extracurricular activities, for teaching me that I could do anything I set my mind on. During my undergraduate at Duke, I had wonderful opportunities to explore how my education could benefit others, like Engineers Without Borders, through which I got to work with ***David Schaad***, ***Kenneth Kasule***, Central Buganda University, and the village of Kasaka. I also had the incredible experience of playing on the Duke women's lacrosse team under ***Kierstin Kimel*** and a wonderful coaching and support staff from whom I learned accountability, dedication, goal-setting, and working to "deserve it" (our team motto for 2004 – 2005). I also got introduced to research through working in ***Nimmi Ramanujam's*** optical spectroscopy lab and at the Cardeza Foundation at Jefferson Hospital, and of course, the Pratt Fellows program where ***Farsh, Tim,*** *and* ***Lori*** got me started in OA research. Farsh then introduced me to ***Maarten*** at the Vrije Universiteit in the Netherlands, where I first experienced research with human participants and learned the importance of collaboration and work-life balance. To Maarten, ***Matthie***, ***Menno***, ***Johan*** and my colleagues at the VU, bedankt! After a few more research opportunities working with ***Mike Madigan*** and SBES at Virginia Tech (watched over by ***Tess***) for my master's and learning the sports medicine side of research alongside a great colleague, ***Chris,*** in Vail, Colorado, I finally reached the most recent chapter but brought with me all the lessons I learned along the way.

There were many students who offered both research and moral support at Dalhousie University (***Elise, Kathryn, Elysia, Jereme, Gillian, Adam, Aishwarya, Kristin, Pouya, Ian, Kat, Sean, Saad, Dan, Trish, Matt, Sarah, Michelle, Josh, Jasmin, Emile*** and many more). ***Dianne*** – I don't think I could have ever been able to navigate the DOHM database without you! ***Diane Cox*** helped rekindled my love for teaching and mentoring and the ***PREP*** program provided meaningful professional development opportunities. Thanks to the ***OARSI community*** for supporting me in my crazy idea to start an OA research podcast and the ***IMPACT research group*** for lots of interesting discussions and useful feedback at cabals. Thank you also to ***Geoff***, ***Sandra***, and the rest of the ***BME department*** at Dalhousie.

To my committee: ***Jason*** – although we first met playing field hockey, it was great being able to see the other side of you and learn from your expertise in OA, especially coming from a different area of research than me. You always kept me on my toes! ***Dr. Stanish*** – I knew things were going to be okay between us from the moment we met at your retirement party and you said, "hey Duke, let me buy you a drink!" - your manner of offering clinical insights in an encouraging way with a smile on your face was always appreciated and kept me motivated to keep working hard. I also would like to thank ***Dr. Rebecca Moyer*** for serving on my examining committee and ***Dr. Katherine Boyer*** for serving as my external examiner. And last but not least, the research crew would not be complete without the leadership of my co-supervisors, ***Janie*** and ***Cheryl***. Cheryl – your passion for this research was always obvious and it was great to watch you get excited about the results I shared with you. Janie – your quick feedback on my work and organized approach to research were always appreciated.

Being in a new country and (at least slightly) different culture, I also appreciated all the people who welcomed me to Halifax including all the people mentioned above but also ***JP, Drew, Mario, Pat, Linda, Mike, Paul, Cooper, Mal*** and all the wonderful people I met through field hockey.

Paul, thanks for always helping me to keep things in perspective with your patience, eternal happiness, and enthusiasm for adventures big and small. You kept me smiling with jokes like "I think PhD actually stands for: Powered by Hot Drinks"

Of course I have to thank my cats, ***Dwayne*** and ***Poncho***, who provided warm laps while writing and an extra weight on my back to make my stress-relieving yoga practice even more challenging.

And a thank you to my family again for bearing with me while I lived abroad for over 5 years and missed special family events and activities. Thanks to Whatsapp and Google hangouts for making the distance seem a little less far! In this time we added ***Pat*** and ***Margaret*** (and ***Willy*** too)!

Last, I would like to acknowledge the funding sources that allowed me to pursue this the work contained in this thesis (a ***Killam Predoctoral Fellowship, the Nova Scotia Health Research Foundation, Dalhousie University, and the Canadian Institutes for Health Research***), *the* ***staff and students of the DOHM laboratory*** who assisted with participant recruitment and data collection, ***James Warren*** who shared his valuable expertise on bootstrapping, and ***the study participants*** without whom none of this would be possible.

I feel incredibly lucky to have had all these experiences and the support of so many wonderful people throughout this journey. This thesis is not just a product of my own efforts but also reflects the support and encouragement I have received from all these wonderful people and organizations over the years. You have all allowed me to believe in myself and achieve things I never would have dreamed of.

Chapter 1. Introduction

1.1 Motivation

There are an estimated 250 million people worldwide living with knee osteoarthritis (OA) (T. Vos et al. 2012) and this number is expected to grow due to population trends in aging and obesity (R. C. Lawrence et al. 2008, A. G. B. D. Obesity Collaborators: Afshin et al. 2017). This high prevalence of knee OA combined with the high prevalence of co-morbid conditions in individuals with OA (F. C. Breedveld 2004, G. M. van Dijk et al. 2008) collectively represents a huge burden on individual patients and the healthcare system.

This burden is made worse by the fact that there is no cure for OA. The current model of care consists of symptom management (e.g. long-term pain medication) until "end-stage" disease, when a patient may be recommended for surgical intervention, such as total knee arthroplasty (TKA), following failure of more conservative management strategies (R. Speerin et al. 2014). This model of care is problematic for a few reasons. For patients with comorbidities, certain medications to ease the symptoms of OA may be contraindicated (F. C. Breedveld 2004). Long-term pharmaceutical use can also come with undesirable side effects (F. C. Breedveld 2004) and can be costly (M. Hiligsmann et al. 2013). Total joint replacement (TJR) costs are also high (whether they are borne by the patient, private insurers, or public healthcare system) (M. Hiligsmann et al. 2013) and in Canada, the already extensive wait lists for TJR (Canadian Institute for Health Information 2014) are another cause for concern in light of the growing prevalence of OA. Furthermore, even after TJR, as many as 1 in 5 patients are dissatisfied with the outcome (O. Robertsson et al. 2000, R. B. Bourne et al. 2010). The most important concern with the current model of care for OA, however, is that it does not treat the underlying disease and thus is unable to slow, stop, or reverse joint damage and OA symptom progression (C. R. Chu et al. 2014). To improve the current model of care and address this growing burden of knee OA, a better understanding

of the factors involved in knee OA progression is needed so that interventions can be developed to slow or stop this process.

Mechanical insults to the joint are thought to disrupt the balance between anabolic and catabolic processes in joint tissues, leading to the cartilage degradation, osteophytes, subchondral bone sclerosis, and synovitis characteristic of OA (J. W. J. Bijlsma et al. 2011, D. J. Hunter 2011). There is a discordance, however, between the degree of structural damage in the joint (the disease) and the severity of OA symptoms (the illness) (K. Barker et al. 2004), which has created challenges in understanding the relationships between joint loading and OA progression. Objective pathoanatomical measures of structural change (e.g. radiographic joint space narrowing (W. W. Scott, Jr. et al. 1993)) can be collected with relative ease, but changes in OA symptoms, or clinical status, are more relevant to OA patients and the healthcare system as they are a better representation of the burden of OA on these stakeholders (Y. Zhang and J. Niu 2016). To improve the current model of care and thus improve quality of life for individuals living with the symptomatic illness of knee OA, a focus on understanding factors related to clinical OA progression is needed.

To date, research on mechanical loading associated with the progression of knee OA in humans has mainly focused on structural progression in the joint. Specifically, multiple gait analysis studies have found that features of the knee adduction moment (KAM), considered a surrogate of the ratio between medial and lateral tibiofemoral compartment joint loading (D. E. Hurwitz et al. 1998), were associated with structural knee OA progression at 1-6 year follow-up (T. Miyazaki et al. 2002, A. Chang et al. 2007, K. L. Bennell et al. 2011, J. D. Woollard et al. 2011, E. F. Chehab et al. 2014, A. H. Chang et al. 2015, N. M. Brisson et al. 2017). The loading environment of the knee, however, is more complex than this single feature. The knee experiences multi-dimensional loads (M. W. Creaby 2015) and loads resulting from activation of musculature around the knee (K. B. Shelburne et al. 2006), and thus the three-dimensional (3D) joint moments (including the knee flexion moment (KFM) and knee rotation moment (KRM) in addition to the KAM) and muscle activation (which can be estimated with electromyography (EMG)) should also be

explored further in relation to OA progression as they have received little to no attention to date (E. F. Chehab et al. 2014, A. H. Chang et al. 2015, P. W. Hodges et al. 2015).

The only research on joint moments and clinical OA progression to date showed that while a higher magnitude of the KAM was related to clinical OA progression (defined by a TKA endpoint), similar to the results in structural OA progression, the dynamic patterns of both the KAM and KFM were also important (G. L. Hatfield et al. 2015b, G. L. Hatfield et al. 2015a). Specifically, reduced unloading between early and mid-stance KAM and a smaller difference between early stance KFM and late stance knee extension moment were found in those who progressed clinically at 8-year follow-up (G. L. Hatfield et al. 2015b). Similarly, both the magnitude and pattern of muscle activation were important to clinical OA progression in another study in the same cohort, where more specifically, higher overall activation of the gastrocnemii, quadriceps, and hamstrings and prolonged quadriceps and hamstrings activation through mid-stance were associated with clinical OA progression (TKA endpoint) at 8 year follow-up (C. L. Hubley-Kozey et al. 2013a). Although structural and clinical progression might be different steps along the same pathway rather than distinct pathways (F. M. Cicuttini et al. 2004, O. Bruyere et al. 2005), a better understanding of the joint loading features related to clinical OA progression, and whether these are different than those associated with structural OA progression, may identify targets for OA interventions that are more effective at reducing the clinical burden of OA.

Recent research (C. L. Hubley-Kozey et al. 2018) reported significant correlations between the patterns of prolonged muscle activation through mid-stance, found by Hubley-Kozey et al. (C. L. Hubley-Kozey et al. 2013a), and patterns of joint moments, specifically, the KAM and KFM features found by Hatfield et al. (G. L. Hatfield et al. 2015b). Thus, while both muscle activation and joint moments have been associated with clinical OA progression, it is unclear what the relative contributions of moment and muscle activation data are to discriminating between those who do or do not progress clinically. Understanding these contributions could provide greater direction for intervention targets in the knee OA population.

The joint moments and muscle activation features derived from gait data provide surrogate metrics of joint loading magnitude and duration during an average step, however, they do not describe how often the joint experiences this loading magnitude/duration, i.e. joint loading frequency. Daily step count, quantified from objective measures of physical activity (PA) using accelerometers, has been proposed as a surrogate metric of joint loading frequency (M. R. Maly 2008). While PA, including specific exercise programs, have been shown to improve OA symptoms (M. Fransen et al. 2015), step count has only recently been studied in relation to knee OA progression and in this study it did not help explain variance in structural progression over 2.5 years (N. M. Brisson et al. 2017). To determine the relationships between joint loading frequency and either structural or clinical OA progression, it is important to be able to quantify a baseline "habitual" level of step count, as PA more generally is thought to vary over time around a true mean (P. Bergman 2018), and to identify whether factors like sex or clinical symptoms, that have been shown to affect PA levels more generally (D. D. Dunlop et al. 2011, J. Song et al. 2018), also affect step count. These factors could be relevant to the design of studies investigating joint loading frequency and OA progression and could affect the results of studies like that of Brisson et al. Furthermore, the relationships between joint loading magnitude/duration variables (from gait) and joint loading frequency (step count) and the relationships between step count and clinical OA progression have not been explored and warrant further study.

In summary, there are gaps in our understanding of how the overall loading environment of the knee joint is related to clinical knee OA progression. First, while structural OA disease progression has been studied more often, clinical progression is likely more relevant to individual patients, clinicians, and the healthcare system as it affects the patient experience, clinician responsibilities, and healthcare costs more directly, but it is unknown whether the same loading features are related to both structural and clinical knee OA progression, which has implications on identifying appropriate targets for interventions. Second, while the literature has clearly demonstrated that there is a mechanical loading component in OA disease processes, a thorough understanding of all aspects of joint loading, including

dynamic 3D joint moment and muscle activation patterns along with joint loading frequency, and how each contributes to clinical OA progression is still lacking. It is unknown what factors influence joint loading frequency, including how many sessions of data collection are needed over the course of a year to capture "habitual" joint loading frequency or what effects sex and clinical symptoms have on joint loading frequency. Last, it is unknown whether joint loading frequency is related to joint loading magnitude/duration or whether joint loading frequency at baseline is related to future clinical OA progression. Understanding the relationships between all aspects of overall joint loading and clinical OA progression may provide guidance regarding appropriate targets for interventions and an opportunity to improve the current model of care.

1.2 Thesis Aim And Objectives

The overall aim of this thesis was: ***To better understand how features of the knee joint loading environment are related to clinical progression of medial tibiofemoral knee OA.*** This aim was addressed by three specific objectives. The motivation, approach, and hypotheses for each objective are described below.

OBJECTIVE 1: To determine differences in baseline three-dimensional knee joint moment and EMG waveform features between progression and no progression groups using both a structural and a clinical progression definition within the same cohort

The discordance between structural changes and OA symptoms suggests that there may also be discordance between joint loading features associated with structural and clinical OA progression. Understanding how joint loading is related to progression when using a clinical progression definition and how that differs when using a structural progression definition will help situate this work within the current body of literature that mainly focuses on structural progression while also moving towards understanding variables that could be more relevant to improving the current clinical model of care.

To address this objective, baseline gait characteristics (3D knee moment and EMG features) were compared between individuals who did or did not progress at 7-year follow-up by separately using two different definitions: 1) a structural progression definition and, 2) a clinical progression definition. A qualitative comparison was then made between the features associated with each of the two progression definitions.

For objective 1, it was hypothesized that progression would be related to increased magnitude of joint moment and EMG waveform features when using a structural progression definition, and to less dynamic patterns of moment waveforms and prolonged muscle activation when using a clinical progression definition.

OBJECTIVE 2: To compare the ability of baseline knee joint moments, EMG waveform features, and demographic and clinical covariates, both alone and in combination, to discriminate between individuals who do or do not progress clinically at follow-up

Joint moments have been more frequently studied in the literature in relation to OA progression, but muscle activation patterns also impart loads on the joint. Thus, muscle activation patterns could provide additional information to understanding OA progression and potential opportunities as alternative or concurrent targets for interventions aimed to slow progression. It is unclear whether including muscle activation patterns (EMG waveform features) in a model for clinical OA progression will improve correct classification of progression and no progression groups compared to models based on joint moments or EMG only, or how these models compare to models including demographic and clinical covariates.

To address this objective, correct classification rates, sensitivity, specificity, and odds ratios for progression were compared among models of clinical progression at 5-10 year follow-up developed from moment features only, EMG features only, covariates only, or a combination. The robustness and generalizability

of the models was also tested through leave-one-out cross-validation and bootstrapping.

Objective 2 was focused on model creation and qualitative comparison of model performance using the metrics described above rather than specific hypothesis testing, although it was hypothesized that models incorporating more data types would qualitatively have higher correct classification rates.

OBJECTIVE 3: To understand whether joint loading frequency alters the relationships between gait metrics and clinical OA progression

The influence of joint loading frequency on OA progression outcomes has not received much attention, but joint loading frequency is a part of the overall exposure of the joint to loading and thus, could be relevant to understanding clinical OA progression. Three sub-objectives were developed to address this objective. The first two sought to better understand the factors that affect joint loading frequency in the OA population. The last sub-objective then built upon these two to explore whether joint loading frequency data contributed to our understanding of clinical OA progression.

Sub-Objective 3A: To determine whether between-group differences in joint loading frequency that were identified when averaged data from two or three weeks during a year was used could also be identified using a single, one-week session of data

While accelerometer-derived measures of PA and inactivity, including sedentary behavior (SED), light-intensity PA (LPA), and moderate-to-vigorous physical activity (MVPA), have shown high day-to-day reliability over 3-5 consecutive days, PA fluctuates over time due to seasonal and symptom variations, among other factors. In order to confidently use step count derived from accelerometer data to establish a baseline level of "habitual" joint loading frequency to relate to long-term OA outcomes, it is important to understand whether variations in these accelerometer-derived metrics like step count during a given year necessitate averaging data from multiple data collection sessions.

To address this sub-objective, step count and time spent in light intensity PA (LPA), moderate to vigorous intensity PA (MVPA), and sedentary behavior (SED) were extracted from accelerometer data collected during three one-week data collection sessions (baseline and approximately 6 and 12 months follow-up). Using OA and asymptomatic groups as a model, the effects of group, number of sessions of data averaged, and their interaction on step count and PA variables were explored in order to understand whether multiple sessions were needed to identify group level differences in habitual PA or joint loading frequency. The limits of agreement between using a single session or an average of two or three sessions were also examined to gain insight into the possible error associated with using a single session to estimate habitual joint loading frequency or PA at an individual level.

For sub-objective 3A, the hypothesis was that measurements from a single session would not differ from the average measurement across multiple sessions in any of the variables tested.

Sub-Objective 3B: To determine whether clinical status (symptomatic or asymptomatic) or sex (women or men) affect joint loading frequency in individuals with structural signs of knee OA

Both OA symptoms and sex have been related to decreased levels of PA, with individuals with OA, especially women, not meeting PA guidelines, and individuals with higher pain having lower PA. Exploring whether joint loading frequency and PA are affected by clinical status and sex will help inform future study design and may provide insight into why these individuals do not meet recommended PA levels.

To address this sub-objective, in a group of individuals who all had structural signs of knee OA, the effects of sex, clinical status (asymptomatic or symptomatic), and their interaction on step count (joint loading frequency) and PA were explored.

It was hypothesized that women would have lower overall PA and joint loading frequency compared to men and that there would be a greater difference between symptomatic and asymptomatic women than between symptomatic and asymptomatic men.

Sub-Objective 3C: To explore correlations between joint loading frequency and joint loading magnitude/duration variables that have been associated with OA progression and differences in joint loading frequency between individuals who later do or do not progress clinically

Finally, it is not known whether joint loading frequency contributes unique information to understanding clinical OA progression beyond that provided by joint loading magnitude/duration features from gait.

To address this sub-objective, two analyses were performed: 1) correlations between joint loading frequency and gait metrics (joint moment and muscle activation pattern features) that have been linked to OA progression were examined to determine whether joint loading frequency adds value in understanding the relationships between the overall joint loading exposure and clinical knee OA progression, and 2) baseline joint loading frequency, joint moments, muscle activation patterns, and demographic and clinical covariates were compared between those that did or did not progress clinically at 3.5-year follow-up.

It was hypothesized that joint loading frequency would not be correlated with gait variables linked to clinical OA progression, indicating that PA variables did contribute unique information to understanding clinical OA progression, but that joint loading frequency would not be different at baseline between those that do or do not progress clinically at short-term (3.5 year) follow-up.

1.3 Thesis Outline

Chapter 2 contains a review of background literature on mechanical loading and knee osteoarthritis progression. **Chapters 3-7** address the three thesis objectives and have been formatted as stand-alone manuscripts intended for publication in scientific journals. **Chapter 3** addresses *objective 1*, **Chapter 4** addresses *objective 2*, and **Chapters 5-7** address *objective 3*. **Chapter 5** addresses *objective 3a*, **Chapter 6** addresses *objective 3b*, and **Chapter 7** addresses *objective 3c*. **Chapter 8** presents a summary and discussion of the results of this thesis, along with clinical implications and proposed directions for future research. **References**

for all chapters in this thesis and **Appendices A, B,** and **C** (containing supplemental information for Chapters 3, 5, and 7, respectively) can be found at the end of this thesis.

Chapter 2. Background Literature

2.1 The Burden Of OA

2.1.1 OA Presentation, Prevalence, And Impact

The symptoms of OA can include joint pain, stiffness, reduced range of motion, crepitus, and joint inflammation (P. Dieppe and L. Lohmander 2005). In OA of hip or knee, these symptoms can cause significant activity limitations (A. A. Guccione et al. 1994) resulting in a loss of independence and reduced quality of life (F. Salaffi et al. 2005). Furthermore, the physical disability and related physical inactivity resulting from OA symptoms can lead to a range of comorbid conditions including type II diabetes, cardiovascular disease, and obesity, among others (G. M. van Dijk et al. 2008), further decreasing the overall health of individuals with OA and leading to even greater risk of disability (L. K. King et al. 2018).

The effects of OA are especially concerning due to both its already high prevalence (estimated at 8-16% of the population of developed nations in 2010 (R. Wong et al. 2010)) and the expected increase in prevalence due to recent trends in population aging and obesity (R. C. Lawrence et al. 2008, A. G. B. D. Obesity Collaborators: Afshin et al. 2017). In Canada, a 2001 study in British Columbia found 1 in 9 adults were diagnosed with OA (J. A. Kopec et al. 2007), and as many as 1 in 4 Canadians are expected to have OA by the year 2030 (C. Bombardier et al. 2011). The knee is one of the most commonly affected joints (S. K. Das and A. Farooqi 2008, R. C. Lawrence et al. 2008), particularly the medial tibiofemoral compartment (D. T. Felson et al. 2002) and worldwide, over 250 million people are estimated to be living with knee OA (T. Vos et al. 2012). Thus, knee OA, with all of its associated comorbidities, represents a huge and growing burden on the healthcare system.

This burden is a major concern for the healthcare system because there is no cure for OA. Furthermore, the current model of care is not sustainable for this growing population of individuals with OA. Current treatment consists of symptom management (e.g. long-term pain medication) until this conservative approach has

failed, at which time patients may be considered for "end-stage" surgical interventions, such as TKA, when appropriate (R. Speerin et al. 2014). In a population of patients who often have comorbidities, long term pharmaceutical use can be a concern due to contraindications (F. C. Breedveld 2004) and it can also be costly (M. Hiligsmann et al. 2013). TKA also comes with a high cost (whether it is borne by the patient, private insurers, or public healthcare system) (M. Hiligsmann et al. 2013) and as of 2013, only 76% of knee replacements and 82% of hip replacements across Canada were meeting the benchmark of 182-day wait times (Canadian Institute for Health Information 2014), highlighting that the current model of care can not keep up with the increasing need for interventions in individuals with OA. Furthermore, as many as one in five patients are dissatisfied following joint replacement (O. Robertsson et al. 2000, R. B. Bourne et al. 2010), suggesting that these interventions are not always meeting the needs of the patients. Most importantly, however, is that the current model of care does not treat the underlying disease, and thus is unable to slow, stop, or reverse joint damage and OA symptom progression (C. R. Chu et al. 2014).

To improve the current model of care for patients and address this growing burden of knee OA on the healthcare system, a better understanding of the factors involved in knee OA progression is needed so that interventions can be developed to slow or stop this process.

2.1.2 OA Etiology And Pathophysiology

OA involves an imbalance between anabolic and catabolic processes in joint tissues that leads to cartilage degradation, formation of osteophytes, subchondral bone sclerosis, and synovitis (J. W. J. Bijlsma et al. 2011, D. J. Hunter 2011). OA is thought to result from a combination of non-modifiable factors (e.g. age, genetics, anatomy) and modifiable factors (obesity, joint biomechanics: injury, instability, overload), that together result in both biomechanical and biochemical irregularities in the joint (P. Dieppe and L. Lohmander 2005). In contrast to other forms of arthritis with mainly inflammatory or autoimmune origins, OA was originally

thought to be solely a mechanical disease with "wear and tear" on the joint causing erosion of the articular cartilage, eventually leading to overall joint degeneration. Due to this original hypothesis of OA as a primarily mechanical disease, a large focus of research on OA initiation and progression has been on mechanical factors related to disease processes, and particularly those occurring in the articular cartilage. While there is now more evidence about the role of inflammation and involvement of other joint tissues in the OA disease process (F. Berenbaum 2013), data from tissue explant testing, animal models, and gait analysis in humans have linked mechanical loading with OA disease processes, in part supporting the original hypothesis. Furthermore, it has been hypothesized that mechanical insults to the joint may set off biochemical pathways leading to joint damage (P. Dieppe and L. Lohmander 2005). While it is believed that "moderate mechanical loading" is required to maintain healthy joint tissues (T. M. Griffin and F. Guilak 2005), non-physiological levels of loading may cause tissue damage leading to OA initiation, and physiological levels of loading applied to already damaged tissues may lead to OA progression (T. P. Andriacchi et al. 2004, T. P. Andriacchi 2009). Mechanical loading on the joints is a potentially modifiable risk factor for OA initiation and progression, thus a better understanding of how mechanical loading affects future joint damage and OA symptoms would aid in developing interventions for OA that could slow or stop the actual disease process.

2.2 Defining And Measuring OA Progression

2.2.1 Structural And Clinical Definitions Of OA

In order to understand the factors associated with OA progression, we need to be able to diagnose and monitor OA-related changes. Clinically, OA can be diagnosed with high specificity and sensitivity using a combination of physical symptoms and radiographic signs (R. Altman et al. 1986). For research purposes, OA severity is often catalogued using structural damage grading scales such as Kellgren-Lawrence (KL) grades (J. H. Kellgren and J. S. Lawrence 1957) and/or self-report measures of physical symptoms such as the Western Ontario and McMaster

Universities Osteoarthritis Index (WOMAC) (N. Bellamy et al. 1988). Discordance has been noted between the severity of OA symptoms and the degree of structural damage in the joint (M. T. Hannan et al. 2000, K. Barker et al. 2004, J. Bedson and P. R. Croft 2008), which has led to a distinction between *OA the disease*, related to the structural changes in the joint, and *OA the illness*, related to the symptomatic manifestation of OA (N. E. Lane et al. 2011, V. B. Kraus et al. 2015). The underlying disease can be found in the absence of symptoms (V. B. Kraus et al. 2015), and, perhaps not surprisingly, prevalence rates differ for radiographic OA (the disease) versus clinical OA (the illness) (e.g. 28% (radiographic OA) versus 16% (symptomatic OA) in a large cohort study conducted in the United States (J. M. Jordan et al. 2007)).

This discordance, and the fact that clinical symptoms are an important reason why patients seek clinical care (D. Coxon et al. 2015), has resulted in a recent shift towards studying the illness of OA, rather than the disease of OA (A. N. Bastick et al. 2015, Y. Zhang and J. Niu 2016). Clinical OA progression may also be more representative of the burden of OA on individual patients and the healthcare system than structural progression only. While there is some evidence that structural progression may be indicative of future clinical progression (F. M. Cicuttini et al. 2004, O. Bruyere et al. 2005), it is of interest to understand whether there are additional targets for intervention to prevent clinical progression that could be used in combination with or as alternatives to those developed for structural progression.

2.2.2 Structural And Clinical OA Progression

Historically, researchers have monitored OA progression by observing structural changes in the joint using imaging techniques (D. J. Hunter et al. 2015). While initially this involved scoring radiographs using ordinal scales or quantitative metrics (e.g. (J. H. Kellgren and J. S. Lawrence 1957, W. W. Scott, Jr. et al. 1993, R. D. Altman et al. 1995, R. D. Altman and G. E. Gold 2007)), newer technologies, such as magnetic resonance imaging (MRI), are gaining popularity for their ability to measure individual joint tissues and 3D structures (A. Guermazi et al. 2009, D. J.

Hunter et al. 2009, D. J. Hunter et al. 2011, D. J. Hunter et al. 2015, W. M. Oo et al. 2017, N. Hafezi-Nejad et al. 2018). While there is great promise in these newer technologies to identify earlier time-points in the disease process, which could be relevant to tracking OA initiation, metrics from radiographs, like joint space narrowing (JSN) (W. W. Scott, Jr. et al. 1993), which encompass changes in the articular cartilage, menisci, and other joint tissues, can provide a global metric of structural degradation in the joint, to measure structural OA progression. To date, both radiographic and MRI metrics of OA progression have been used to study the relationship between joint loading and structural changes in the joint.

Due to the discordance between OA structural damage and OA symptoms (M. T. Hannan et al. 2000, K. Barker et al. 2004), clinical progression may be more relevant to the individual patient experience and more reflective of the true burden on the healthcare system in terms of costs and provider time, as symptoms are what cause patients to seek care for OA (D. Coxon et al. 2015). Symptoms, however, can be difficult to measure. Often, measurements of OA symptoms rely on self-reports, such as WOMAC scores (N. Bellamy et al. 1988), and self-reports can be affected by a number of factors, including pain, strength, and depression (M. R. Maly et al. 2006), "good subject" bias (S. A. Adams et al. 2005), and pain catastrophizing (E. E. Helminen et al. 2016), among others. There are more objective tests for functional deficits (e.g. sit-to-stand task) but these are not specific to OA and may not be able to reflect deficits until the patient's symptoms are quite severe, as the metrics used (e.g. time to complete the task) might not capture compensatory strategies (e.g. (Y. Sagawa et al. 2017)). Thus, determining a clinically meaningful change in OA symptoms is a difficult task. An outcome measure that better captures the overall state of the patient may be more relevant.

Clinically, progression is monitored using a combination of patient self-reports symptoms including pain and function, along with imaging. Total joint replacement, such as TKA, has been suggested as a metric for determining clinical progression (J.-F. Maillefert and M. Dougados 2003), as the TKA decision-making process typically includes worsening OA symptoms in the presence of structural damage to the joint (A. Escobar et al. 2003, L. Gossec et al. 2011a). While the factors

for recommending a patient for TKA (L. Gossec et al. 2011b) and the reasons a patient does or does not undergo TKA (S. S. Bederman et al. 2012, L. Frankel et al. 2016) can vary, in a government-funded public healthcare system, such as that in Canada, there is likely a lower rate of unsubstantiated surgeries. Thus, a clinical progression metric using a TKA endpoint, which incorporates both the disease of OA (structural damage) and the illness of OA (worsening symptoms), will better represent the burden of OA on patients and the healthcare system.

2.3 Mechanical Loading And OA

2.3.1 Evidence From Tissue Explant And Animal Model Studies

Mechanical testing of tissue explants provides evidence that mechanical loading is involved in OA disease processes in joint tissues. The magnitude and duration of applied loads, both in compression and shear, and whether these loads are dynamic or static can all affect biochemical changes in joint tissues including inhibition of proteoglycan synthesis in cartilage (A. J. Grodzinsky et al. 2000, B. Fermor et al. 2001, M. S. Lee et al. 2002, A. D. Heiner and J. A. Martin 2004) and release of interleukin-11 in bone (K. Sakai et al. 1999). Proteoglycans are integral to the extracellular matrix that forms the cartilage structure (A. J. S. Fox et al. 2009) and interleukin-11 is involved in bone remodeling (N. A. Sims et al. 2005), thus mechanical loading on the joint has the potential to affect the structure and function of joint tissues and induce OA-related changes.

Animal models of OA provide further evidence for the involvement of altered joint loading in OA disease processes as changes in joint tissues have been induced in animals by direct application of loading at non-physiological levels (e.g. high magnitude (M. L. Roemhildt et al. 2013)), surgical destabilization of the joint (anterior cruciate ligament transection (F. Guilak et al. 1994, W. Herzog et al. 1998, J. Z. Wu et al. 2000) or meniscectomy (R. C. Appleyard et al. 2003, J. E. Beveridge et al. 2011)), and by creating transgenic animals with altered mechanical properties of their joint structures due to protein deficiencies (L. Ameye et al. 2002, J. M. Anderson-MacKenzie et al. 2005, K. Hu et al. 2006, L. M. Boyd et al. 2008). The

instability created in the surgical models can affect loads by altering the contact points between joint surfaces, thus subjecting certain tissues to loading at levels that are non-physiological for those specific tissues (T. P. Andriacchi et al. 2006, J. E. Beveridge et al. 2011), and initiating degenerative changes such as those seen in the animal models created with direct application of non-physiological levels of loading. In contrast, the altered material properties of the joint structures in the transgenic animals change how the joint structures respond to physiological levels of loading. For example, the decreased compressive modulus and uniaxial modulus in Col9a1 knockout mouse cartilage reduces the effectiveness of the cartilage to absorb and distribute loads across the joint, leading to early onset of cartilage degradation (K. Hu et al. 2006).

Thus, both tissue explant studies and animal models provide evidence that mechanical loading is a factor in OA disease processes in the joint.

2.3.2 Joint Loading Magnitude And Duration In OA

In humans, walking has been used as a model to study joint loading. Walking comprises the majority of PA done in the knee OA population (M. Sliepen et al. 2018) and many individuals with knee OA report walking disability (L. K. King et al. 2018). Thus, understanding the relationships between joint loading during walking and OA progression could help identify potential targets for interventions to slow or stop OA progression.

As described above, evidence from tissue explant and animal model studies shows that multiple aspects of mechanical loading can affect OA disease processes and thus have the potential to lead to OA progression. Both shear and compressive loads were related to these processes, implicating multi-dimensional loading in OA. In gait analysis, data from motion capture technology and force platforms is used to calculate 3D joint moment waveforms during an average step (C. L. Vaughan et al. 1992), from which features of the waveforms can be extracted and analyzed in comparison to OA outcomes. Discrete metrics extracted from the waveforms (e.g. first peak knee adduction moment, KAM (T. Miyazaki et al. 2002) or early peak knee

flexion moment, KFM (E. F. Chehab et al. 2014)), can be used as surrogate metrics of joint loading magnitude, although determining a surrogate metric of the duration of those loads becomes more challenging as they are time-varying waveforms. Alternatively, techniques such as principal component analysis (PCA) can extract the main patterns of variation in the waveforms (C. L. Hubley-Kozey et al. 2006, K. J. Deluzio and J. L. Astephen 2007), thus describing the dynamic nature of these loading waveforms and acting as a surrogate metric to describe the interaction between joint loading magnitude and duration.

The majority of knee OA gait biomechanics research has focused on the KAM, considered a surrogate measure of the ratio of medial to lateral tibiofemoral compartment loading (D. E. Hurwitz et al. 1998, D. Zhao et al. 2007), where a higher KAM magnitude (peak or impulse) has been associated with structural OA progression at 1-6 year follow-up up (T. Miyazaki et al. 2002, A. Chang et al. 2007, K. L. Bennell et al. 2011, J. D. Woollard et al. 2011, E. F. Chehab et al. 2014, A. H. Chang et al. 2015, N. M. Brisson et al. 2017) (see also **Chapter 3**, Table 3.1). Baseline KAM magnitude features have also been associated with clinical OA progression, using TKA as an endpoint, with both discrete metrics (KAM peak and impulse) (G. L. Hatfield et al. 2015a), and a pattern feature from PCA (describing a lack of KAM unloading in mid-stance relative to early stance) (G. L. Hatfield et al. 2015b) seen at baseline in individuals who progressed clinically at 8-year follow-up. Thus, features of the KAM appear to be involved in both structural and clinical OA progression.

Focusing on KAM features only does not fully describe the 3D loads in the joint that could be contributing to OA progression (M. W. Creaby 2015), however, only a few studies have examined the KFM or KRM in relation to OA progression. A higher peak KFM at baseline was associated with structural progression at 5-year follow-up (E. F. Chehab et al. 2014), although this result was not replicated in a large cohort study with a 2-year follow-up (A. H. Chang et al. 2015). Although peak KFM has not been examined in relation to clinical OA progression, a pattern feature from PCA (describing a smaller difference between early stance KFM and late stance knee extension moment at baseline) was associated with clinical OA progression (TKA endpoint) at 8-year follow-up but KRM features were not different between groups

(G. L. Hatfield et al. 2015b). Thus, there is evidence that joint loading in other planes is also a factor in OA progression.

While 3D joint moments do capture important aspects of the multidimensional loads experienced by the knee, they do not fully capture the contributions of muscle activation, which may be particularly relevant in a knee OA population where increased amplitude and changes in muscle activation patterns have been identified (C. L. Hubley-Kozey et al. 2006). This is due to the fact that co-activation of agonist-antagonist muscle pairs can produce moments that act in opposing directions (and thus sum to a small net moment), but the forces of these muscle pairs on the joint act in the same direction and thus collectively, can impart large compressive loads on the joint (K. B. Shelburne et al. 2006). Simultaneous collection of surface electromyography (EMG) data during gait data collection is used to provide insight into muscle activation and, by extension, muscle contributions to load and loading patterns. Surface EMG involves recording the electrical activity of underlying muscles using electrodes placed on the skin. The recorded signal, or interference pattern, is composed of superimposed motor unit action potentials from multiple motor units recorded from the muscle (S. Kumar 1996). After full-wave rectification, low pass filtering, and time- and amplitude-normalization, comparison of features extracted from this EMG waveform among muscles and participant groups can provide information about the relative amplitude and patterns of muscle activation (S. Kumar 1996). EMG does not directly translate into measures of muscle force because force can be affected by a number of other factors, including muscle size, length, and fiber type ratio and, in dynamic situations, muscle lengthening or shortening velocities (S. Kumar 1996). Despite this, EMG does provide insight into the load and loading patterns related to relative activation of different muscles acting at the knee that cannot be ascertained from net joint reaction moments.

Whether the information provided by EMG is relevant to understanding knee OA progression has not been well-explored to date, with only two studies examining differences in baseline muscle activation in relation to OA progression. Hodges et al. (P. W. Hodges et al. 2015) attempted to capture a discrete metric of the duration of

loading due to muscle activation by calculating the length of time that specific pairs of muscles were active above a certain threshold. From this they concluded that longer duration of medial muscle co-contraction was present in those that progressed structurally at 1-year follow-up compared to those that did not. Using PCA and the same sample as Hatfield et al. (G. L. Hatfield et al. 2015b), the other study found greater overall muscle activation in the gastrocnemii, quadriceps, and hamstrings and prolonged stance phase quadriceps and hamstrings activity were associated with clinical progression (TKA endpoint) at 8-year follow-up (C. L. Hubley-Kozey et al. 2013a). While both studies interpreted their findings as prolonged muscle co-contraction in those that progressed, these were the only studies on muscle activation in relation to OA progression.

Collectively, this literature presents evidence that joint loading magnitude/duration features during gait in humans are related to both structural and clinical OA progression with much of the work focused on KAM and structural progression. To determine whether the same targets for intervention are relevant to both structural and clinical OA progression, further research is needed to understand the relative contributions of all of these different aspects of joint loading in the knee to both structural and clinical progression, including dynamic loading patterns (using PCA) of the KAM, KFM, KRM, and gastrocnemii, quadriceps, and hamstrings EMG.

2.3.3 Joint Loading Frequency And OA

The overall loading environment of the knee is described not only by the magnitude and pattern of loading, but also by the frequency of loading. In humans, while gait analysis can provide surrogate metrics of joint loading magnitude and duration, alternate methods are needed to quantify joint loading frequency. Step count (steps/day), derived from accelerometer data, has been proposed as a surrogate measure of joint loading frequency (Monica R. Maly, 2008) but to date, there have been few studies that have used this metric to study OA progression (N. M. Brisson et al. 2017, H. Tateuchi et al. 2017).

While studies of accelerometer-derived PA metrics have shown high reliability during consecutive days (C. E. Matthews et al. 2002, T. L. Hart et al. 2011) and even consecutive weeks (E. Aadland and E. Ylvisaker 2015), both PA metrics (S. Levin et al. 1999, E. S. Pedersen et al. 2016) and step count (C. Tudor-Locke et al. 2004) have been shown to fluctuate over the course of a year. Measures of PA are believed to fluctuate around a true mean, or "habitual" level (P. Bergman 2018) but it is unknown whether a single one-week monitoring period, common in PA studies (C. E. Matthews et al. 2012), is able to capture a baseline of "habitual" step count. Understanding this will be relevant to study design when using step count as a surrogate metric of joint loading frequency.

Similarly, both sex and the presence of OA symptoms have been shown to affect PA levels, with research showing that both women and those experiencing higher levels of pain have lower PA (D. D. Dunlop et al. 2011, J. Song et al. 2018). The effect of these factors and their interaction on step count should be investigated more thoroughly to understand whether sex or clinical status (asymptomatic (OA disease) vs. symptomatic (OA illness)) should be accounted for in studies relating joint loading frequency to OA progression. Furthermore, understanding sex-based differences in PA and how they are related to clinical status may also be relevant to understanding the different rates of OA and OA progression in women versus men (V. K. Srikanth et al. 2005, S. N. Williams et al. 2015), or the overall low levels of PA reported in OA (D. D. Dunlop et al. 2011, J. Song et al. 2013).

Once a better understanding of how study methodology affects step count is obtained, further exploration into the relationships between step count and OA progression can be conducted. To date, there have only been two studies using step count as a surrogate metric of joint loading frequency to understand OA progression, one looking at structural progression in the hip (H. Tateuchi et al. 2017) and one looking at structural progression in the knee (N. M. Brisson et al. 2017). In the knee, Brisson et al. found that, despite a large range of step count within their sample (7786 ± 3876), step count did not help explain additional variance in cartilage volume change within a 2.5 year period over that explained by gait variables only (N. M. Brisson et al. 2017). The lack of additional variance

explained by step count may indicate that step count is dictated by gait patterns or vice versa, and thus is not contributing unique information to explain variance in OA progression. The relationships between OA symptoms and PA suggest that there could be a different relationship between step count and structural OA progression than there is between step count and clinical OA progression, but the relationship between clinical OA progression and joint loading frequency has not been investigated. Thus, whether step count contributes unique information to our understanding of the overall loading environment or whether step count is different at baseline between those who do or do not progress clinically at follow-up require further study. Understanding these relationships could help determine whether targeting PA levels or daily step count could be used as an intervention strategy to slow or stop clinical OA progression.

2.3.3 Interventions To Alter Joint Loading In OA

Gait biomechanics, muscle activation patterns, and PA levels are all potentially modifiable factors, and thus the goal of understanding the relationships between these factors and OA progression is to identify potential targets for non-invasive interventions that could improve the current model of care for knee OA. To date, biomechanical gait modifications have focused on reducing the peak KAM magnitude (N. D. Reeves and F. L. Bowling 2011), likely due to the large focus of structural OA progression research on KAM features (T. Miyazaki et al. 2002, A. Chang et al. 2007, K. L. Bennell et al. 2011, J. D. Woollard et al. 2011, E. F. Chehab et al. 2014, A. H. Chang et al. 2015, N. M. Brisson et al. 2017). By investigating the relationships between clinical OA progression and other joint moment features, including not only peak moments but also dynamic patterns of 3D joint moments, additional or alternative targets can be identified. Similarly, while the effectiveness of neuromuscular training on reducing the KAM has been previously evaluated (K. L. Bennell et al. 2014), understanding the relationships between muscle activation and clinical knee OA progression could provide more detailed targets for neuromuscular interventions. Last, PA is recommended in many OA guidelines (e.g. (T. E. McAlindon

et al. 2014)) and has been shown to reduce pain and improve function (M. Fransen et al. 2015), but a more thorough investigation of accelerometer-derived PA metrics and clinical OA progression could provide insight into the low levels of PA in OA (D. D. Dunlop et al. 2011) and potential targets for improvement in the OA population to help reduce clinical OA progression.

It also should be noted that treating OA pain can alter biomechanical loading on the joint in ways that may accelerate OA progression (reviewed in (K. A. Boyer 2018)). Thus, merely treating OA symptoms, as is done in the current model of care, may actually be detrimental to the joint. Identifying targets for interventions to alter joint loading will likely lead to higher success in altering clinical progression outcomes.

2.4 Summary

In summary, the current model of care for knee OA is not sustainable for the growing population of individuals with this illness and does not intervene in the underlying disease process. Biomechanical, neuromuscular, and/or physical activity based interventions for knee OA have been suggested as possible alternatives to the current model of care but the overall loading environment of the knee joint in relation to OA progression, and specifically to clinical OA progression (defined as reaching a total knee arthroplasty endpoint), has not been investigated in depth. Examining the relationships between the 3D moment magnitude and patterns, muscle activation magnitude and patterns, step count, and clinical OA progression will allow for a better understanding of appropriate targets for knee OA interventions that could improve the current model of care and reduce the burden of knee OA on individual patients and the healthcare system.

Chapter 3. Baseline Joint Moments And Muscle Activation Patterns Associated With Knee Osteoarthritis Progression Differ When Using A Clinical Versus Structural Progression Definition

3.1 Abstract

Objectives: Clinical knee osteoarthritis progression is relevant to patients and the growing clinical burden of osteoarthritis on the healthcare system, however, structural progression has been investigated more frequently. This study examined differences in baseline three-dimensional knee moment and muscle activation features between progression and no progression groups at 7-year follow-up when progression was defined using structural metrics and then, using the same sample, defined as those who reached a total knee arthroplasty endpoint.

Methods: Of 49 individuals with knee osteoarthritis who underwent baseline gait analysis, 32 progressed and 17 did not when using a structural definition (medial joint space narrowing) while 13 progressed and 36 did not when using a clinical definition (total knee arthroplasty). Key moment and electromyography waveform features were extracted using principal component analysis. Student's t-tests examined between-group differences in principal component scores and discrete metrics for each definition of progression.

Results: Using the clinical progression definition, those who progressed had prolonged quadriceps and lateral hamstrings muscle activation. Using the structural progression definition, those who progressed had greater baseline internal knee rotation moments during mid-stance.

Conclusion: These results provide preliminary evidence for the role of prolonged muscle activation in clinical progression, whereas structural progression may be related to loading magnitude. The implication is that muscle activation patterns

during walking could be a treatment target to slow clinical knee osteoarthritis progression.

3.2 Introduction

For end-stage knee osteoarthritis (OA), surgical interventions such as total knee arthroplasty (TKA), are indicated when conservative symptom management has failed (W. Zhang et al. 2008). While surgery can be effective (O. Robertsson et al. 2000), TKA is an invasive procedure with high costs to both patients and the healthcare system (D. J. Hunter et al. 2014) and these costs are expected to increase further as OA rates continue to rise (Arthritis Alliance of Canada 2011, D. Pereira et al. 2011). To ease this growing burden, a better understanding of the factors involved in OA progression is needed in order to develop earlier interventions to slow or stop this process.

OA progression to date has typically been measured by observing structural changes in joint tissues using imaging techniques (D. J. Hunter et al. 2015), i.e. *structural progression*, perhaps due to cartilage damage being historically considered a hallmark of the disease and the relative ease of obtaining objective pathoanatomical measures (e.g. radiographic scores (W. W. Scott, Jr. et al. 1993)). Subsequently, the focus of biomechanical interventions for knee OA has been on reducing the knee adduction moment (KAM) magnitude (N. D. Reeves and F. L. Bowling 2011), based on studies that identified higher baseline KAM magnitude features (peak or impulse) in individuals who exhibited *structural progression* at one to six year follow-up (T. Miyazaki et al. 2002, A. Chang et al. 2007, K. L. Bennell et al. 2011, J. D. Woollard et al. 2011, E. F. Chehab et al. 2014, A. H. Chang et al. 2015, N. M. Brisson et al. 2017) (Table 3.1). In addition to higher KAM, typically considered a surrogate metric for the ratio of medial to lateral tibiofemoral compartment loading, higher peak knee flexion moment (KFM), thought to indicate greater compressive loads on the joint, has also been associated with greater *structural progression* at 5-year follow-up (E. F. Chehab et al. 2014), although a large cohort study was not able to replicate this result over a two-year follow-up (A. H.

Chang et al. 2015) (Table 3.1). The knee rotation moment (KRM) has not received much attention in relation to OA progression but features of the KRM have been related to severity (J. L. Astephen et al. 2008, Janie L. Astephen et al. 2008) and the KRM may be an early indicator of change in the loading environment of the knee over time (E. M. Davis et al. 2017). Longer activation times of medial knee joint muscles, thought to indicate a greater duration of compressive loading on the joint, have also been associated with *structural progression* at 1-year follow-up (P. W. Hodges et al. 2015).

Measures of structural and symptomatic severity are not always well correlated in knee OA (K. Barker et al. 2004), however, and patients typically seek care due to worsening symptoms such as pain and functional disability (D. Coxon et al. 2015). Thus, a *clinical progression* metric that takes into account both structural damage and symptom worsening may better represent the burden of OA on patients, the increased strain on healthcare provider time related to OA, and the high cost of OA to the healthcare system (Y. Zhang and J. Niu 2016). Direct measurement of change in clinical symptoms is difficult due to subjective measurement tools and day-to-day symptom fluctuations (D. J. Hunter et al. 2008). TKA, in contrast, represents an appropriate and feasible endpoint to study *clinical progression* with both symptom severity and structural damage influencing decisions to recommend or undergo TKA (A. Escobar et al. 2003, L. Gossec et al. 2011a). Using this *clinical progression* definition (TKA endpoint), Hatfield et al. found higher KAM magnitude (overall magnitude, peak, and impulse) and reduced mid-stance KAM unloading (smaller difference between early and mid-stance KAM) (G. L. Hatfield et al. 2015b, G. L. Hatfield et al. 2015a), along with a smaller difference between early stance knee flexion moment (KFM) and late stance knee extension moment (KEM) (G. L. Hatfield et al. 2015b), in those with *clinical progression* of knee OA at 8-year follow up. In this same population, higher overall gastrocnemius, quadriceps, and hamstrings muscle activation, along with prolonged activation of the quadriceps and hamstrings through mid-stance, were found at baseline in those who progressed *clinically* at 8-year follow-up (C. L. Hubley-Kozey et al. 2013a) (Table 3.1).

While this literature collectively presents evidence that biomechanical features and OA progression are linked, what is absent is an understanding of whether the same features are related to both *structural* and *clinical progression*. Of the studies on *structural progression*, two were longer follow-up studies (5-6 years) that excluded individuals who progressed to TKA at follow-up (T. Miyazaki et al. 2002, E. F. Chehab et al. 2014), whereas the other three *structural progression* studies had shorter follow-ups (1-2 years) (K. L. Bennell et al. 2011, A. H. Chang et al. 2015, P. W. Hodges et al. 2015), and thus did not assess whether participants would progress to TKA over a longer 5-8 year time frame such as that seen in the other structural (T. Miyazaki et al. 2002, E. F. Chehab et al. 2014) and clinical (G. L. Hatfield et al. 2015b, G. L. Hatfield et al. 2015a) progression studies (Table 3.1). Although these two definitions of progression – *structural* versus *clinical* – may be different steps along the same pathway rather than distinct pathways, understanding the features associated with each could lead to more effective interventions to reduce the clinical burden of OA.

To date, no studies have examined the gait features associated with OA progression using both a *structural progression* definition and a *clinical progression* definition within the same population and same time frame. Our objective was to determine differences in baseline three-dimensional (3D) knee joint moment and electromyography (EMG) waveform features between progression and no progression groups using both a *structural* and a *clinical progression* definition within the same study population. Based on the results of previous progression studies, we hypothesized that progression would be related to increased magnitude of moment and EMG waveform features when using a structural progression definition, and to less dynamic patterns of moment waveforms and prolonged muscle activation when using a clinical definition of OA progression.

Table 3.1 Study designs, samples, and main outcomes of OA progression gait literature

Study design			Study sample					
Study	**Progression metric(s)**	**Follow up (yrs)**	**N (% female)**	**Age (yrs)**	**BMI (kg/m^2)**	**KL**	**Speed (m/s)**	**Features of progression group at baseline**
Structural Progression:								
Bennell et al. 2011	Change in medial tibial cartilage volume [MRI]	1	144 (56%)	64 (8)	28.6 (4.5)	2	1.3 (0.2)	• Peak KAM/(bw*ht) not different • KAM impulse/(bw*ht) higher
Brisson et al. 2017	Change in medial tibial cartilage volume [MRI]	2.5	52 (79%)	61 (7)	28.5 (5.7)	3	1.2 (0.2)	• Peak KAM/bm higher in higher BMI only • KAM impulse higher in higher BMI only
Chang et al. 2007	Increase in OARSI mJSN of 1+ grade(s) [radiograph]	1.5	56 (59%)	67 (9)	29.0 (4.2)	2	NR	• First peak KAM/(bw*ht) higher • Second peak KAM/(bw*ht) higher • Maximum KAM/(bw*ht) higher
Chang et al. 2015	Increase in medial tibiofemoral cartilage damage or BMLs of 1+ grade(s) [MRI]	2	391 knees (77%)	64 (10)	28.4 (5.7)	2	1.2 (0.2)	• Peak KAM/(bw*ht) higher • KAM impulse/(bw*ht) higher • Peak KFM/(bw*ht) not different
Chehab et al. 2014	Decrease in mean cartilage thickness or medial-to-lateral cartilage thickness ratio [MRI]	5	16 (63%)	60 (9)	28.3 (4.5)	2	1.3 (0.1)	• Peak KAM/(bw*ht) higher • Peak KFM/(bw*ht) higher
Hodges et al. 2015	Change in medial tibial cartilage volume [MRI]	1	50 (49%)	66 (8)	29.1 (4.6)	2	1.0 (0.0)	• Longer duration medial muscle co-contraction
Miyazaki et al. 2002	Increase in Altman mJSN of 1+ grade(s) [radiograph]	6	32 prog (88%) 42 no-prog (71%)	71 (6) 69 (9)	24.5 (4.3) 24.1 (3.2)	2	"nearest to 0.7"	• Peak KAM/(bw*ht) higher
Woollard et al. 2011	Loss of medial femoral cartilage volume > SEM [MRI]	1	13 (23%)	64 (11)	28.0 (4.0)	3	NR	• Peak KAM/bm higher

Study design			Study sample					
Study	**Progression metric(s)**	**Follow up (yrs)**	**N (% female)**	**Age (yrs)**	**BMI (kg/m²)**	**KL**	**Speed (m/s)**	**Main features of progression group at baseline**
Clinical Progression:								
Hatfield et al. 2015b	Total knee arthroplasty [surgical status]	8	26 TKA (27%) 28 no-TKA (32%)	60 (9) 58 (7)	30.9 (4.7) 31.5 (6.2)	3	1.2 (0.2) 1.3 (0.2)	• Increased KAM/bm amplitude • Smaller 1st peak to mid-stance KAM/bm difference • Decreased range of KFM/bm
Hatfield et al. 2015a	Total knee arthroplasty [surgical status]	8	26 TKA (27%) 28 no-TKA (32%)	60 (9) 58 (7)	30.9 (4.7) 31.5 (6.2)	3	1.2 (0.2) 1.3 (0.2)	• Peak KAM/(bw*ht) higher • Peak KAM/bm not different • KAM impulse/(bw*ht) higher • KAM impulse/bm higher
Hubley-Kozey et al. 2013	Total knee arthroplasty [surgical status]	8	25 TKA (24%) 25 no-TKA (32%)	59 (10) 58 (8)	30.6 (4.8) 30.8 (5.3)	3	1.2 (0.2) 1.3 (0.2)	• Increased gastrocnemius, quadriceps, and hamstrings activity • Prolonged stance phase activity in quadriceps and hamstrings

Data presented as mean (standard deviation), except for KL (median), and where otherwise noted. bm = body mass, BMI = body mass index, BML = bone marrow lesion, bw = body weight, ht = height, KAM = knee adduction moment, KFM = knee flexion moment, KL = Kellgren/Lawrence grade, mJSN = medial joint space narrowing, MRI = magnetic resonance imaging, NR = not reported, OARSI = Osteoarthritis Research Society International, SEM = standard error of the measurement.

3.3 Methods

3.3.1 Participants

The current study was a secondary analysis of data from participants in our database who had been diagnosed at baseline with medial compartment knee OA by a single high-volume orthopedic surgeon (WDS) using clinical and radiographic criteria (R. Altman et al. 1986), who had baseline gait and standard standing anterior-posterior and lateral view radiographic data available, and for whom we obtained follow-up surgical status and radiographic data at an average of 7 years post-baseline. Greater medial compartment involvement was determined by the presence of medial knee pain and medial joint space narrowing (mJSN) greater than or equal to lateral joint space narrowing (W. W. Scott, Jr. et al. 1993). All participants were considered moderate severity at baseline based on their functional level (self-reported ability to jog 5 meters, walk a city block, and climb stairs reciprocally), conservative treatment plan (clinical severity level indicated they were not candidates for TKA) (C. L. Hubley-Kozey et al. 2006), and having a mJSN score of less than three (maximal score possible) at baseline. Exclusion criteria were age under 35 years or any cardiovascular, neuromuscular, or musculoskeletal conditions other than knee OA that would affect gait or participant safety. In accordance with the Helsinki Declaration, all participants signed Nova Scotia Health Authority Research Ethics Board-approved informed consent before participating in this follow-up study. This resulted in a sample of 49 participants.

3.3.2 Gait Kinematics And Kinetics

At baseline, 3D motion and ground reaction forces of the most symptomatic limb were recorded using a standardized protocol during a six-meter self-selected speed walk (S. C. Landry et al. 2007). Individual infrared emitting diodes were placed on anatomic landmarks (lateral malleolus, lateral epicondyle, greater trochanter, and acromion) with rigid diode triads placed on the foot, shank, thigh, and pelvic segments. Eight virtual points (calcaneal tubercle, second metatarsal,

medial malleolus, tibial tuberosity, fibular head, medial epicondyle, and both anterior superior iliac spines) were digitized during a standing calibration trial. Marker motion was recorded at 100 Hz by two Optotrak 3020 cameras (Northern Digital Inc., Waterloo, Canada) and synchronized ground reaction forces were digitized at 2000 Hz by a force platform embedded in the floor (model BP400600, Advanced Medical Technology Inc., Watertown, USA). Four to seven trials were saved for analysis.

Biomechanics data were processed according to standardized protocols (S. C. Landry et al. 2007) using custom-written MATLAB programs (Mathworks Inc., Natick, USA). 3D joint angles, expressed in the joint coordinate system (E. S. Grood and W. J. Suntay 1983), were calculated from 3D diode positions using a least squares optimization routine (J. H. Challis 1995). 3D net external joint moments were calculated using inverse dynamics, time-normalized to the stance phase of the gait cycle, and amplitude normalized to body mass (C. L. Vaughan et al. 1982, P. A. Costigan et al. 1992, K. J. DeLuzio et al. 1993, J. Li et al. 1993).

3.3.3 Electromyography

According to a standard protocol (C. L. Hubley-Kozey et al. 2006), silver-silver chloride electrodes (10 mm^2) were placed in a bipolar configuration in line with the muscle fibers of the lateral (LG) and medial (MG) heads of the gastrocnemii, vastus lateralis (VL), vastus medialis (VM), rectus femoris (RF), biceps femoris (lateral hamstrings, LH) and semimembranosus (medial hamstrings, MH), with a single reference electrode placed over the tibial shaft. Raw EMG signals during walking were preamplified (500x), further amplified (AMT-8 EMG, Bortec™ Inc., Calgary, Canada; bandpass filter 10-1000 Hz, common mode rejection ratio = 115 dB at 60 Hz, input impedance = ~10GΩ), and then digitized at 2000 Hz, in synchrony with motion and force data. Offline, data were corrected for bias, converted to μV, full-wave rectified, and then low pass filtered (6 Hz) using a Butterworth filter in MATLAB. EMG waveforms were time-normalized to the gait cycle.

3.3.4 EMG Amplitude Normalization And Muscle Strength Testing

Following baseline gait data collection, eight maximum voluntary isometric contractions (MVICs) were performed according to standardized protocols (C. L. Hubley-Kozey et al. 2006, D. J. Rutherford et al. 2011) for the purposes of EMG amplitude normalization and strength assessment. Briefly, the exercises were: 1) plantar flexion in long sitting, 2) standing heel raise on one foot against manual resistance applied to the shoulders, 3) knee extension in sitting (knee at 45° flexion), 4) same as 3 with simultaneous hip flexion (hip at 90° flexion), 5) knee extension in supine (knee at 15° flexion), 6) knee flexion in sitting (knee at 55° flexion), 7) knee flexion in supine (knee at 15° flexion), and 8) knee flexion in prone (knee at 55° flexion). All exercises were held for three seconds and two trials were performed of each exercise. Consistent with recommended protocols, a practice trial was performed for each exercise, standardized verbal encouragement was provided during each trial, and rest periods were given between trials (M. D. Lewek et al. 2004). EMG waveforms were amplitude normalized to the highest activation amplitude (based on a 0.1-second moving window) for that muscle during the MVICs regardless of which exercise it came from (C. L. Hubley-Kozey et al. 2006).

Torque data were recorded simultaneously with EMG data for exercises 1, 3, 5, 6, 7, and 8 using a Cybex dynamometer (Lumex, New York City, USA). The highest torque for each muscle group was calculated as the highest amplitude steady state 0.5-second window (Nm) (C. L. Hubley-Kozey et al. 2006), regardless of which exercise it came from (D. J. Rutherford et al. 2011), and then normalized to body mass to calculate a relative strength measure for each muscle group (Nm/kg).

3.3.5 Key Moment And EMG Metrics

Principal component analysis (PCA) was applied to identify amplitude and temporal patterns (principal components, PCs) in the moment and EMG waveforms (C. L. Hubley-Kozey et al. 2006, K. J. Deluzio and J. L. Astephen 2007). These included PCs that capture overall magnitude (C. L. Hubley-Kozey et al. 2013a, G. L. Hatfield et al. 2015b), the relative difference between early and mid-stance KAM (G. L. Hatfield

et al. 2015b), the relative difference between peak KFM and late stance KEM (G. L. Hatfield et al. 2015b), and prolonged quadriceps and hamstrings muscle activation (C. L. Hubley-Kozey et al. 2013a).

PCs were extracted from a larger moderate OA dataset from the Dynamics of Human Motion database (n = 240 for moments, n = 231 for EMG; mean age: 58.7 ± 8.4 years, mass: 91.1 ± 17.5 kg, body mass index (BMI): 30.6 ± 5.1 kg/m^2, speed: 1.2 ± 0.2, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total: 28.1 ± 17.2, median mJSN: 2, median Kellgren-Lawrence (KL) grade: 3). Briefly, data for each moment was arranged in a separate matrix containing 101 columns (representing each percent of the gait cycle) and 240 rows (representing each individual from the larger database). For the EMG data, a separate matrix was created for each muscle group, thus, the gastrocnemii and hamstrings matrices were 462 rows (2 muscles for 231 participants) by 101 columns each and the quadriceps matrix was 693 rows (3 muscles for 231 participants) by 101 columns. For each moment and muscle group, PCA was applied to extract major patterns of variation among the waveforms (PCs), with extracted PCs cumulatively explaining greater than 90% of the variation in waveforms. For each variable, the covariance matrix (moments) or cross-product (muscle groups) of the original matrix was calculated and an eigenvector decomposition was performed to extract the eigenvectors, or PCs. Principal component scores (PC scores) were calculated for the average moment or EMG waveform (across trails) for each participant in the current study by multiplying the waveform by each eigenvector (C. Hubley-Kozey et al. 2008). These scores represent weighting coefficients describing how closely the participant's original waveform for each variable matches each extracted PC for that variable. Using a larger dataset allows extraction of more robust and generalizable PCs (J. W. Osborne and A. B. Costello 2004) and this method has been shown to have high test-retest reliability (C. L. Hubley-Kozey et al. 2013b, S. M. Robbins et al. 2013a).

To facilitate comparison with current literature, several discrete metrics were calculated: first peak KAM (T. Miyazaki et al. 2002), KAM impulse (K. L. Bennell et al. 2011), and early peak KFM (C. L. Hubley-Kozey et al. 2013a, G. L.

Hatfield et al. 2015b)., along with discrete metrics similar to PCs that have been identified from previous literature: KAM mid-stance minimum and KFM range (G. L. Hatfield et al. 2015b).

3.3.6 Classification Of Clinical OA Progression

The definition of clinical knee OA progression used in this study was that participants had undergone TKA on the study knee between baseline and follow-up or were on a waitlist to undergo TKA on the study knee at the time of follow-up (with follow-up occurring at an average of 7 years after baseline), based on self-reports. Self-reported TKA was confirmed on radiographs. Of the 49 participants in this study, 13 individuals progressed according to the clinical progression definition (TKA outcome) and 36 did not progress (Figure 3.1).

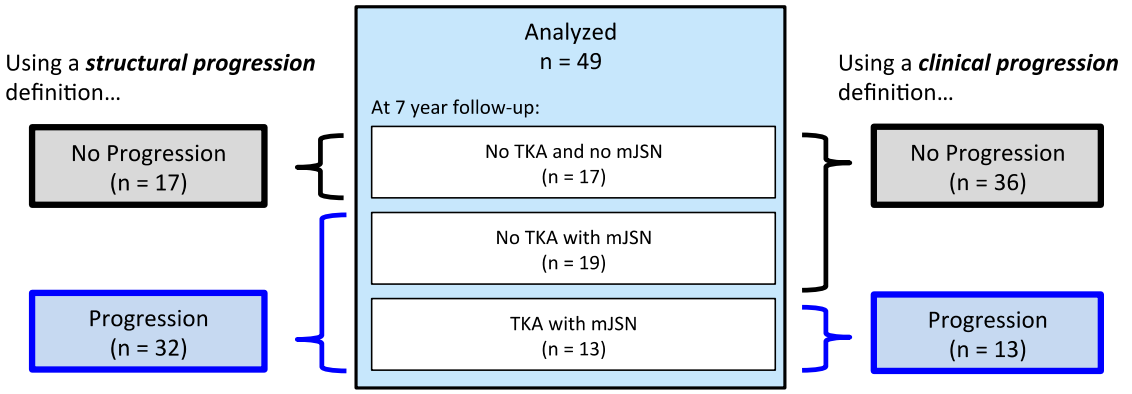

Figure 3.1 Group separation using the structural and clinical knee OA progression definitions

3.3.7 Classification Of Structural OA Progression

The definition of structural OA progression used in this study was a one grade or greater increase in mJSN score (W. W. Scott, Jr. et al. 1993) of the study knee from baseline to follow-up. Baseline and follow-up standard anterior-posterior and lateral view radiographs for each participant were scored for mJSN by two orthopedic surgeons (WDS, NU) with any disagreements regarding structural progression status resolved through adjudication (this occurred for 6 cases, or 12% of the total sample). For the subset of individuals who had undergone TKA, pre-

surgical radiographs were used as follow-up radiographs (average time from pre-surgical radiograph to TKA = 3.3 ± 3.7 months). For those who had not undergone TKA, radiographs from the preceding year were used as follow-up radiographs when available, or if not available, participants were sent for a radiograph. This resulted in 32 individuals that had progressed according to the structural progression definition and 17 that did not progress (Figure 3.1).

3.3.8 Statistical Analysis

Continuous variables were checked for normality using Shapiro-Wilk tests with logarithmic or Johnson transformations (N. L. Johnson 1949) applied in the case of non-normal distributions. If no transformation could be found, non-parametric testing was used. Chi square tests examined between-group differences in sex. Mann-Whitney U-tests examined between-group differences in ordinal radiographic scores and time to follow-up. A series of Student's t-tests were used to examine between-group differences in baseline demographics, clinical severity, knee moment and EMG PC scores, and discrete metrics. When Levene's tests for homogeneity of variance were not satisfied, Welch's t-tests were performed in place of Student's t-tests. Significance was set at $\alpha = 0.05$. All statistical analyses were performed in SPSS (IBM, Armonk, USA) with the exception of the Johnson transformations (Minitab Inc., State College, USA).

Table 3.2 Baseline group characteristics and time to follow-up for progression and no progression groups when using a structural or clinical definition of progression

	Structural progression definition			***Clinical progression definition***		
	No Prog (n = 17)	**Prog (n = 32)**	***P***	**No Prog (n = 36)**	**Prog (n = 13)**	***P***
Sex, women:men (%women)	3:14 (18%)	12:20 (38%)	0.15	11:25 (31%)	4:9 (31%)	0.99
Age (years)	55.9 (8.0)	58.0 (8.9)	0.42	56.9 (7.4)	58.1 (11.5)	0.69
Mass (kg)	94.2 (16.9)	96.5 (16.4)	0.65	96.1 (17.8)	94.4 (12.1)	0.86
Body mass index (kg/m^2)	30.5 (5.6)	32.4 (5.3)	0.17	32.1 (6.0)	30.7 (3.0)	0.70*
Radiographic Scores						
KL grade (1, 2, 3, 4)	1, 7, 9, 0	5, 10, 17, 0	0.56*	5, 13, 18, 0	1, 4, 8, 0	0.73*
Medial JSN (0, 1, 2, 3)	0, 5, 12, 0	3, 14, 15, 0	0.19*	3, 13, 20, 0	0, 6, 7, 0	0.51*
Lateral JSN (0, 1, 2, 3)	13, 4, 0, 0	24, 7, 2, 0	0.76*	29, 7, 0, 0	8, 4, 1, 0	0.15*
Patellofemoral JSN (0, 1, 2, 3)†	1, 7, 7, 0	6, 18, 6, 0	0.14*	6, 17, 9, 0	1, 8, 4, 0	0.65*
WOMAC						
Pain (/20)	7.3 (4.5)	6.7 (3.8)	0.99*	6.3 (4.1)	8.5 (3.2)	0.04*
Stiffness (/8)	3.6 (1.7)	3.7 (1.5)	0.53*	3.4 (1.6)	4.4 (1.0)	0.02*
Function (/68)	20.8 (15.0)	21.7 (11.4)	0.35*	19.7 (13.5)	26.0 (8.3)	0.06*
Strength‡						
Knee Extensor (Nm/kg)	1.32 (0.48)	1.25 (0.40)	0.59	1.30 (0.43)	1.19 (0.42)	0.40
Knee Flexor (Nm/kg)	0.69 (0.17)	0.64 (0.25)	0.43	0.67 (0.18)	0.61 (0.31)	0.53
Plantar Flexor (Nm/kg)	1.08 (0.50)	0.97 (0.33)	0.47	1.03 (0.41)	0.95 (0.37)	0.46§
Speed (m/s)	1.2 (0.2)	1.3 (0.2)	0.72	1.3 (0.2)	1.2 (0.2)	0.17
Time to follow-up radiograph (years)	7.1 (2.3)	6.8 (2.2)	0.79*	7.3 (2.0)	5.9 (2.6)	0.05*

All data are presented as mean (standard deviation), except where noted.

JSN = joint space narrowing, KL = Kellgren-Lawrence, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

† Patellofemoral JSN scores were unavailable for n = 2 no (structural) progression and n = 2 (structural) progression, and n = 4 no (clinical) progression

‡ Strength data was unavailable for n = 1 (structural) progression, and n = 1 no (clinical) progression

§ Welch's t-test performed due to a significant Levene's test result

* Mann-Whitney U-test performed

3.4 Results

3.4.1 Using The Clinical Progression Definition

There were no differences between no progression (n = 36) and progression (n = 13) groups defined using a clinical progression definition (TKA outcome) in sex or baseline age, mass, body mass index (BMI), radiographic scores, walking speed, or muscle strength, but the progression group did have higher WOMAC pain and stiffness scores (p = 0.04 and p = 0.02, respectively) with a trend towards a higher WOMAC function score (p = 0.06) (Table 3.2). There was also trend towards a shorter time to follow-up in the progression group (p = 0.05) (Table 3.2), as TKA had typically occurred prior to follow-up and time-to-TKA was used as time-to-follow up in those who had already undergone surgery.

When using a clinical progression definition, the progression group had higher overall lateral hamstrings activation (PC1, p = 0.01) with prolonged mid-stance activation in RF (PC2, p = 0.01) and LH (PC2, p = 0.01) (Table 3.4, Figure 3.4, Figure 3.5) compared to the no progression group. A higher KAM mid-stance minimum in the progression group (p = 0.04) was the only between-group difference in discrete metrics (Table 3.5). There were trends towards prolonged mid-stance activation in VL (PC2, p = 0.06) and a lower peak KFM (p = 0.07) in the group that progressed (Table 3.4). There were no significant differences in knee moment PC scores between progression and no progression groups with the only trend being a smaller difference between first peak KAM and mid-stance KAM (i.e. reduced mid-stance KAM unloading) in the progression group (KAM PC2, p = 0.06) (Figure 3.2, Table 3.3).

3.4.1 Using The Structural Progression Definition

There were no between-group differences for no progression (n = 17) and progression (n = 32) groups defined using a structural (radiographic (W. W. Scott, Jr. et al. 1993)) progression definition in sex, time to follow-up, or baseline age, mass, BMI, radiographic scores, WOMAC scores, walking speed, or muscle strength (Table 3.2). The progression group had a greater internal KRM through mid-stance (KRM

PC2, p = 0.01) along with trends towards a lower overall KFM magnitude (KFM PC1, p = 0.07) and a greater difference between the early stance external KRM and late stance internal KRM (KRM PC1, p = 0.06) compared to the no progression group (Table 3.3, Figure 3.2). While the progression group visually appeared to have a higher overall KAM, this was not a significant difference (KAM PC1, p = 0.12) (Table 3.3, Figure 3.2). The progression group had a trend towards higher overall magnitude of the gastrocnemii (both lateral p = 0.08 and medial p = 0.06 heads) and lateral hamstrings (p = 0.05) compared to the no progression group (Table 3.4, Figure 3.3, Figure 3.5) but there were no other muscle activation differences between groups. The discrete metric results for the structural progression definition were similar to those for the clinical progression definition. There were no differences in KAM impulse or first peak KAM between progression and no progression groups when using the structural progression definition but the progression group did have a higher mid-stance minimum KAM (p = 0.03) (Table 3.5, Figure 3.2). There was no difference in the range of the KFM but there was a trend towards a lower peak KFM in the progression group (p = 0.08) (Table 3.5, Figure 3.2).

Table 3.3 Baseline knee joint moments for progression and no progression groups when using a structural or clinical definition of progression

PCs		Description	*Structural progression definition*					*Clinical progression definition*				
			No Prog (n = 17)	**Prog (n = 32)**	**Mean Diff**	**95% CI**	***P***	**No Prog (n = 36)**	**Prog (n = 13)**	**Mean Diff**	**95% CI**	***P***
KAM	1	Overall magnitude	-0.51 (1.25)	0.03 (0.84)	-0.54	(-1.24, 0.16)	0.12§	-0.27 (1.02)	0.14 (1.01)	-0.37	(-1.02, 0.28)	0.26
	2	Early-, mid-stance difference	0.23 (0.65)	0.06 (0.42)	0.17	(-0.14, 0.48)	0.27	0.20 (0.54)	-0.11 (0.36)	0.31	(-0.01, 0.64)	0.06
KFM	1	Overall magnitude	0.47 (1.33)	-0.27 (1.31)	0.74	(-0.06, 1.54)	0.07	0.17 (1.31)	-0.53 (1.39)	0.70	(-0.17, 1.56)	0.11
	2	Flexion, extension moment difference	-0.10 (1.59)	0.13 (1.10)	-0.22	(-1.00, 0.56)	0.57	0.16 (1.38)	-0.27 (0.89)	0.43	(-0.40, 1.26)	0.30
KRM	1	External, internal rotation moment difference	0.20 (0.55)	-0.07 (0.41)	0.27	(-0.01, 0.55)	0.06	0.07 (0.50)	-0.09 (0.38)	0.15	(-0.16, 0.46)	0.33
	2	Mid-stance magnitude	-0.21 (0.37)	0.08 (0.34)	-0.29	(-0.50, -0.08)	0.01	-0.05 (0.38)	0.07 (0.35)	-0.12	(-0.37, 0.12)	0.32

All data are presented as mean (standard deviation), except where noted.

CI = confidence interval, KAM = knee adduction moment, KFM = knee flexion moment, KRM = knee rotation moment, PCs = principal components

§ Welch's t-test performed due to a significant Levene's test result

* Mann-Whitney U-test performed

Table 3.4 Baseline muscle activation patterns for progression and no progression groups when using a structural or clinical definition of progression

PCs		Description	*Structural progression definition*					*Clinical progression definition*				
			No Prog (n = 17)	**Prog (n = 32)**	**Mean Diff**	**95% CI**	***P***	**No Prog (n = 36)**	**Prog (n = 13)**	**Mean Diff**	**95% CI**	***P***
LG	1	Overall magnitude	174.9 (89.6)	209.8 (76.5)	-34.9	(-83.9, 14.1)	0.08	198.9 (85.6)	194.3 (74.6)	4.6	(-49.4, 58.6)	0.96
MG	1	Overall magnitude	170.9 (53.7)	210.6 (72.9)	-39.7	(-80.3, 0.9)	0.06	193.3 (59.5)	206.2 (94.1)	-12.9	(-59.4, 33.6)	0.58
VL	1	Overall magnitude	167.8 (96.2)	157.3 (103.6)	10.5	(-51.2, 72.3)	0.83	160.3 (107.0)	163.2 (83.1)	-2.9	(-69.3, 63.6)	0.56
	2	Mid-stance activation	-16.0 (40.5)	-15.1 (31.3)	-1.0	(-22.3, 20.3)	0.93	-21.3 (34.3)	0.1 (30.9)	-21.4	(-43.4, 0.6)	0.06
VM	1	Overall magnitude	166.6 (109.0)	163.1 (84.9)	3.5	(-55.0, 62.0)	0.91	167.7 (97.5)	154.8 (80.9)	12.9	(-50.4, 76.3)	0.68
	2	Mid-stance activation	-19.7 (34.5)	-15.2 (40.8)	-4.4	(-28.6, 19.8)	0.67	-21.9 (39.9)	-2.4 (30.9)	-19.5	(-45.1, 6.1)	0.15
RF	1	Overall magnitude	92.7 (45.2)	107.8 (48.4)	-15.1	(-43.8, 13.6)	0.30	98.1 (46.5)	114.2 (49.6)	-16.1	(-47.0, 14.9)	0.30
	2	Mid-stance activation	7.8 (24.0)	14.0 (28.9)	-6.3	(-22.8, 10.3)	0.42	5.5 (21.2)	28.9 (34.2)	-23.5	(-40.0, -7.0)	0.01
LH	1	Overall magnitude	123.7 (51.8)	163.8 (72.7)	-40.1	(-80.1, 0.0)	0.05	135.3 (58.4)	190.5 (79.5)	-55.2	(-97.2, -13.2)	0.01
	2	Mid-stance activation	-22.7 (29.7)	-4.6 (55.0)	-18.1	(-47.1, 10.8)	0.28	-20.9 (44.9)	16.7 (47.8)	-37.6	(-67.4, -7.9)	0.01
MH	1	Overall magnitude	99.2 (37.7)	115.4 (46.5)	-16.1	(-42.5, 10.3)	0.23	111.8 (43.4)	104.3 (46.9)	7.5	(-21.4, 36.3)	0.46*
	2	Mid-stance activation	-22.5 (28.2)	-28.6 (32.9)	6.2	(-12.8, 25.1)	0.52	-29.9 (34.4)	-17.1 (18.0)	-12.8	(-28.2, 2.5)	0.10§

All data are presented as mean (standard deviation), except where noted.

CI = confidence interval, LG = lateral gastrocnemius, LH = lateral hamstrings, MG = medial gastrocnemius, MH = medial hamstrings, RF = rectus femoris, VL = vastus lateralis, VM = vastus medialis, PCs = principal components

§ Welch's t-test performed due to a significant Levene's test result

* Mann-Whitney U-test performed

Table 3.5 Baseline discrete metrics for progression and no progression groups when using a structural or clinical definition of progression

	Structural progression definition					*Clinical progression definition*				
	No Prog (n = 17)	**Prog (n = 32)**	**Mean Diff**	**95% CI**	***P***	**No Prog (n = 36)**	**Prog (n = 13)**	**Mean Diff**	**95% CI**	***P***
KAM Impulse (Nm/kg*s)	0.17 (0.08)	0.20 (0.06)	-0.03	(-0.08, 0.02)	0.20§	0.18 (0.07)	0.22 (0.07)	-0.04	(-0.08, 0.00)	0.11*
KAM first peak (Nm/kg)	0.51 (0.21)	0.55 (0.13)	-0.04	(-0.16, 0.07)	0.46§	0.53 (0.17)	0.54 (0.14)	-0.01	(-0.12, 0.09)	0.84
KAM mid-stance minimum (Nm/kg)	0.23 (0.13)	0.30 (0.10)	-0.08	(-0.15, -0.01)	0.03	0.26 (0.12)	0.33 (0.10)	-0.08	(-0.15, 0.00)	0.04
Max peak KFM (Nm/kg)	0.48 (0.30)	0.35 (0.22)	0.13	(-0.02, 0.28)	0.08	0.43 (0.27)	0.29 (0.17)	0.15	(-0.02, 0.31)	0.07
KFM range (Nm/kg)	0.71 (0.47)	0.68 (0.31)	0.04	(-0.19, 0.26)	0.74	0.73 (0.40)	0.57 (0.24)	0.17	(-0.07, 0.40)	0.19

All data are presented as mean (standard deviation), except where noted.

CI = confidence interval, KAM = knee adduction moment, KFM = knee flexion moment, KRM = knee rotation moment

§ Welch's t-test performed due to a significant Levene's test result

* Mann-Whitney U-test performed

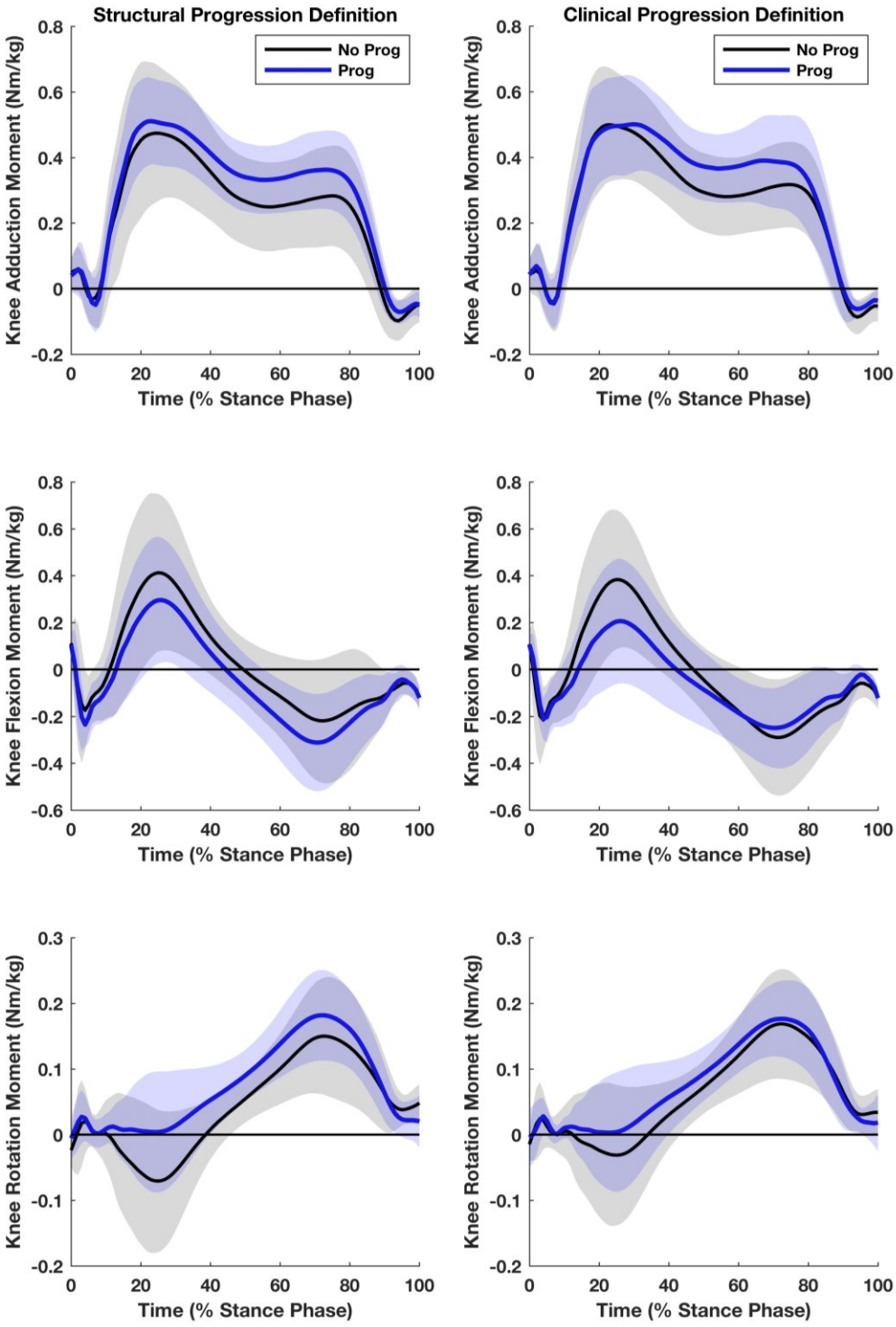

Figure 3.2 Knee moment waveforms for no progression and progression groups when using a structural progression definition (left panel) or a clinical progression definition (right panel).

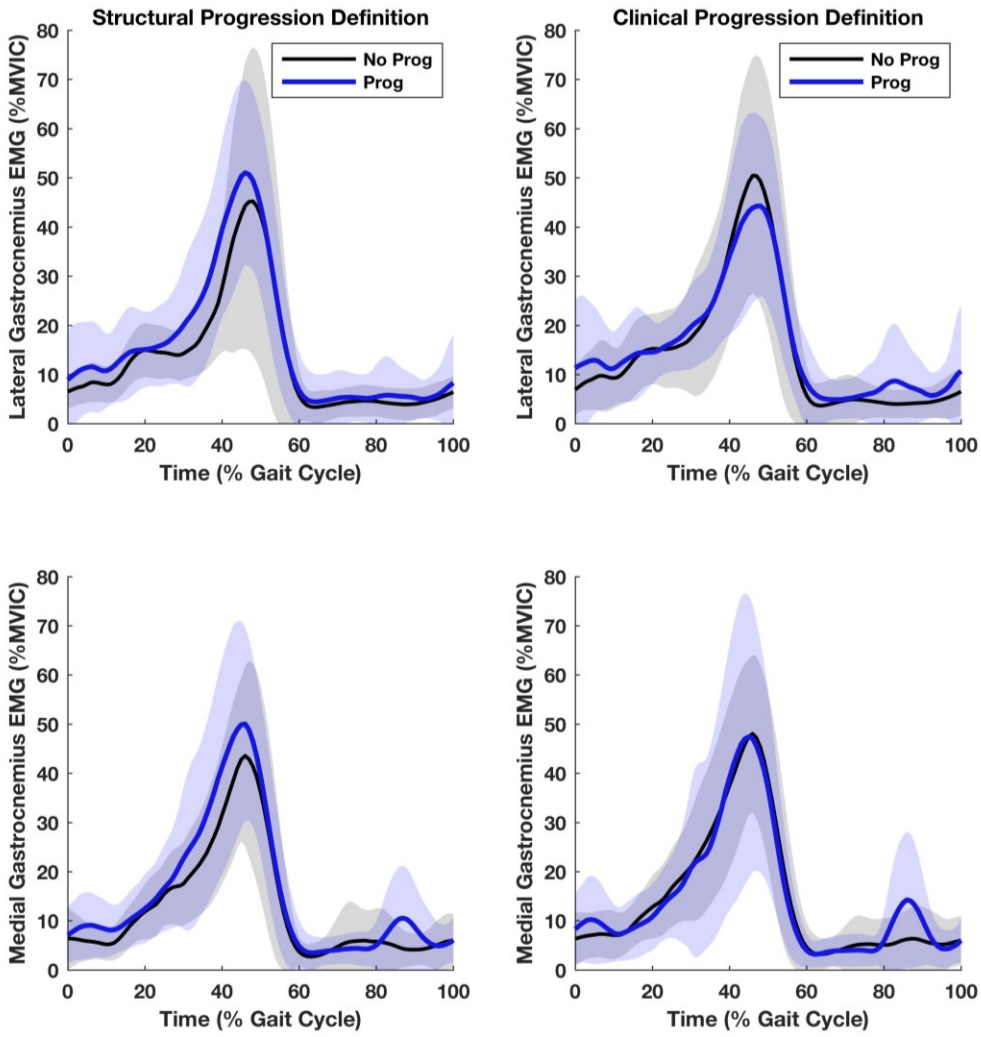

Figure 3.3 Gastrocnemius electromyography waveforms for no progression and progression groups when using a structural progression definition (left panel) or a clinical progression definition (right panel).

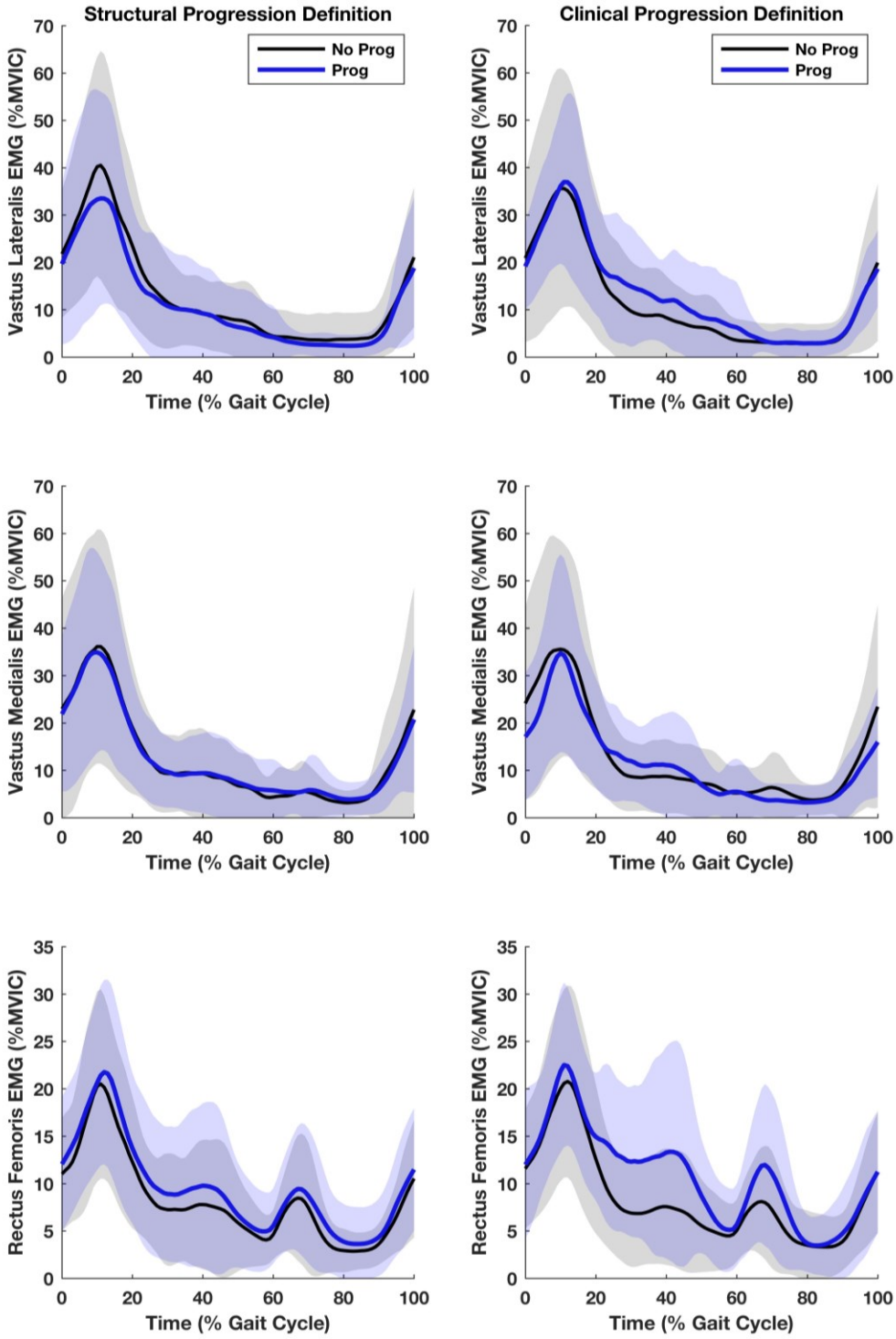

Figure 3.4 Quadriceps electromyography waveforms for no progression and progression groups when using a structural progression definition (left panel) or a clinical progression definition (right panel).

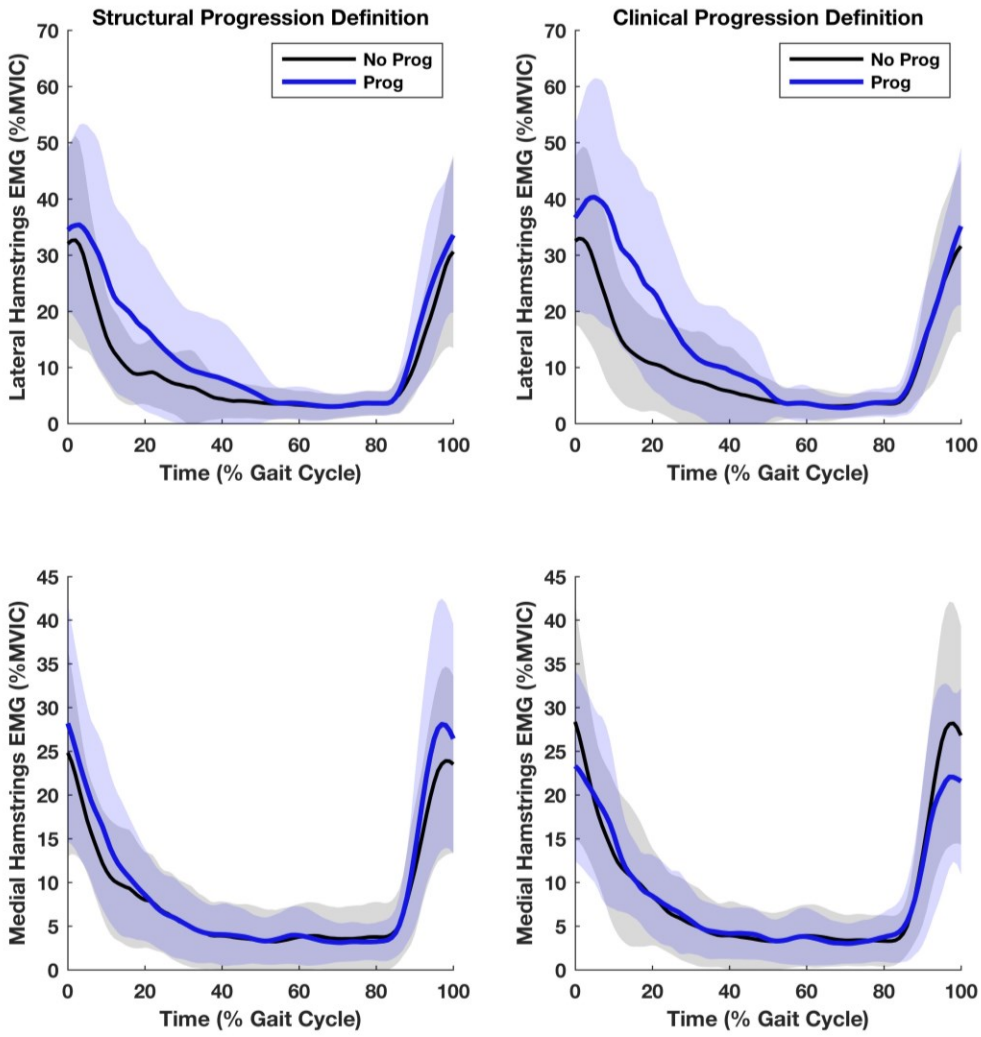

Figure 3.5 Hamstrings electromyography waveforms for no progression and progression groups when using a structural progression definition (left panel) or a clinical progression definition (right panel).

3.5 Discussion

The discordance between joint structure and clinical symptoms in knee OA (K. Barker et al. 2004), combined with the growing burden of knee OA on both individual patients and the healthcare system (O. Robertsson et al. 2000, Arthritis Alliance of Canada 2011, D. Pereira et al. 2011, D. J. Hunter et al. 2014), highlights the need for more effective treatments and a better understanding of the mechanisms associated with both structural and clinical OA progression. The current study aimed to provide a comprehensive evaluation of baseline 3D moment

and EMG features associated with OA progression, using both clinical and structural definitions of OA progression in the same population, in order to identify potential targets for biomechanical or neuromuscular interventions. Supporting our hypothesis, the majority of differences between progression and no progression groups when using the clinical progression definition were in the patterns of moment and EMG waveforms, in contrast to the overall magnitude differences between groups that were more prevalent when using a structural progression definition.

3.5.1 Using The Clinical Progression Definition

Key between-group differences identified when using the clinical progression definition included prolonged RF and LH (and a trend in VL) muscle activation through mid-stance in the group that progressed (TKA) compared to the no progression group (Table 3.4, Figure 3.4, Figure 3.5). Prolonged muscle activation can result in more sustained compressive forces on the joint (O. D. Schipplein and T. P. Andriacchi 1991, K. L. Bennell et al. 2008) and increased co-contraction has been linked to muscle fatigue (J. A. Psek and E. Cafarelli 1993), both of which could factor into the structural and symptomatic changes associated with TKA (A. Escobar et al. 2003, L. Gossec et al. 2011a). Strength and radiographic severity were not different between groups (Table 3.2), thus this prolonged muscle activation may be an attempt to control joint laxity (O. D. Schipplein and T. P. Andriacchi 1991), which was not measured in this study; a response to higher levels of pain (J. L. Astephen Wilson et al. 2011), which is supported by the higher baseline WOMAC pain scores in the progression group versus no progression group (using the clinical progression definition); or a causative factor for clinical progression. While the association between prolonged muscle activation and clinical progression is consistent with previous findings from our group (C. L. Hubley-Kozey et al. 2013a), the finding of prolonged muscle activation in the progression group when using a clinical, but not a structural (Table 3.4), definition of progression is novel.

In addition to prolonged quadriceps and hamstrings muscle activation through mid-stance, higher overall LH activity was also seen at baseline in the group

that progressed clinically at follow-up compared to the group that did not progress clinically (Table 3.4, Figure 3.5). This result is consistent with an earlier finding from our group showing higher overall muscle activation of the hamstrings at baseline in those who progressed clinically at follow-up (C. L. Hubley-Kozey et al. 2013a), although in the current study, only the LH activation was significantly different between groups, rather than the higher VL, VM, RF, LH, and MH activity seen by Hubley Kozey et al. This may indicate a lower severity level in the current study compared to this earlier work, as medial site muscle activation differences have been found in individuals with severe but not moderate knee OA (C. L. Hubley-Kozey et al. 2009). Differences in clinical severity between the current study and prior work may also explain the difference in findings between the current study (where higher and prolonged lateral muscle activation was found in the progression group) and a previous study by Hodges et al. (where a longer duration of medial muscle activation was found in the progression group) (P. W. Hodges et al. 2015), although the differences in progression metrics, study follow-up lengths, and muscle activation features examined could also explain this difference.

While there was a trend towards a between-group difference in a feature of the KAM when using the clinical progression definition, this feature (PC2) described the pattern, rather than the magnitude, of the KAM waveform (Table 3.3, Figure 3.2). The trend towards less mid-stance KAM unloading in the progression group is also consistent with an earlier finding from our group showing that individuals that progressed clinically at follow-up exhibited a smaller difference between the early stance and mid-stance KAM at baseline (G. L. Hatfield et al. 2015b) and with cross-sectional studies from our group showing that this feature is also associated with clinical OA severity (Janie L. Astephen et al. 2008). This result is also supported by the finding of a larger mid-stance minimum KAM ($p = 0.04$) but no significant difference in 1st peak of the KAM ($p = 0.84$) in the group that progressed clinically versus the group that did not progress clinically in the current study (Table 3.5).

There were also no significant differences in KFM or KRM between groups using the clinical progression definition although there was a trend towards a lower maximum peak KFM in the progression group at baseline (Table 3.5, Figure 3.2).

While the biphasic KFM pattern was qualitatively less prominent in the progression group versus no progression group when using the clinical progression definition (Figure 3.2), consistent with Hatfield et al. (G. L. Hatfield et al. 2015b), large variability in KFM range (Table 3.5) and PC2 scores (Table 3.3) can explain the lack of significant differences between groups in these metrics.

3.5.2 Using The Structural Progression Definition

The finding of greater internal KRM through mid-stance in the progression group compared to the no progression group when using the structural progression definition (Table 3.3, Figure 3.2) is novel as few OA progression studies have examined transverse plane rotation moments. Shear forces can lead to degenerative processes in osteoarthritic cartilage (M. S. Lee et al. 2002, M. S. Lee et al. 2003), thus a potential mechanism by which increased stance phase KRM magnitude could lead to structural progression is through increased shear in the joint. The lack of significant differences in KAM magnitude features (peak, impulse, and overall magnitude) was surprising based on earlier studies implicating KAM magnitude features in both structural (T. Miyazaki et al. 2002, K. L. Bennell et al. 2011, E. F. Chehab et al. 2014, A. H. Chang et al. 2015) and clinical progression (G. L. Hatfield et al. 2015b, G. L. Hatfield et al. 2015a). This may in part be explained by the lower radiographic severity (KL grades) in the current study compared to prior studies, because severity has been related to KAM features (J. L. Astephen et al. 2008, Janie L. Astephen et al. 2008, J. L. Astephen Wilson et al. 2011), as well as within-group variability in KAM PC1, impulse, and peak in the current study which may have resulted from the inclusion of individuals who later went on to TKA in contrast to other studies where these individuals were excluded (T. Miyazaki et al. 2002, E. F. Chehab et al. 2014, A. H. Chang et al. 2015) and could also explain why qualitative trends towards between-group differences in KAM magnitude features were not statistically significant (Fig. 3.2). The trend towards a lower max peak KFM (Table 3.5) and lower overall KFM (PC1) (Table 3.3) in the group that did not progress when using the structural progression definition (Figure 3.2) suggests that the magnitude of the KFM may also be relevant to structural OA progression. Although

there were no significant muscle differences between groups when using a structural progression definition, the few trends were associated with overall magnitude (higher overall LH, LG, and MG activation in the progression group) (Table 3.4, Figure 3.3, Figure 3.5), which differed from the clinical progression findings.

3.5.3 Structural Versus Clinical Progression

Many of the conservative management strategies for knee OA that have been explored to date have focused on changing the early or late stance peak KAM (N. D. Reeves and F. L. Bowling 2011). These interventions were mainly developed based on research showing higher magnitude loads at baseline in those who later progress using a structural progression definition (T. Miyazaki et al. 2002, A. Chang et al. 2007, K. L. Bennell et al. 2011, J. D. Woollard et al. 2011, E. F. Chehab et al. 2014, A. H. Chang et al. 2015, N. M. Brisson et al. 2017) (Table 3.1). The results of this study suggest that clinical progression may be better treated by addressing prolonged muscle activation and lack of dynamic loading patterns in knee moments, including the high mid-stance minimum KAM. It is unclear from the current study whether this prolonged muscle activation and lack of dynamic patterns are the result of instability, muscle inhibition due to pain, or some other underlying factor but merely treating pain may actually increase loading on the joints (K. A. Boyer 2018). Thus, other treatments that can alter the moment and EMG patterns seen in this study (such as bracing, which has been shown to decrease muscle co-activation (D. K. Ramsey et al. 2007) while also reducing pain (R. F. Moyer et al. 2015)), may have higher success in altering clinical progression outcomes. Furthermore, the patterns of muscle activation are highly correlated with the patterns of joint moments (C. L. Hubley-Kozey et al. 2018), thus treating the prolonged muscle activation patterns may also have an effect on the moment patterns.

One of the strengths of this study was the use of the same population to examine group differences using both structural and clinical definitions of progression, as it allowed for a comparison of features associated with progression between the two definitions of progression. There were a few between-group

differences that were found when using both the structural progression definition and when using the clinical progression definition, including higher LH overall magnitude and KAM mid-stance minimum, and a trend towards max peak KFM in the progression group. These findings support the hypothesis of a shared pathway between structural and clinical OA progression but could also reflect the overlap in individuals included in the progression group when using both definitions. Further analysis of the three distinct groups within the overall sample (n = 17 no structural or clinical progression, n = 19 structural but no clinical progression, and n = 13 structural and clinical progression) similarly showed magnitude differences related to structural progression and muscle activation pattern differences related to clinical progression (Appendix A).

Radiographic scoring is an accepted metric for structural progression (D. J. Hunter et al. 2015), although there are inherent limitations including image quality and experience of the readers. We used standard views, multiple experienced readers, and an adjudication process to improve our confidence in whether each participant progressed structurally (D. J. Hunter et al. 2015), and have previously reported excellent intra-rater (G. L. Hatfield et al. 2015b) and very good inter-rater reliability in mJSN scores (K. A. McKean et al. 2007). There are also confounding factors in TKA decisions including surgeon bias and patient willingness to undergo this elective procedure (S. S. Bederman et al. 2012, L. Frankel et al. 2016). Despite this, in a government-funded healthcare system (such as the one in the current study) the likelihood of standardized patient selection based on clinical and radiographic evidence is higher (i.e. fewer unsubstantiated surgeries) which may help reduce error around this metric. In this study, p-values were not adjusted for multiple comparisons so there is the potential for type I errors, however, this was the first study to comprehensively explore the 3D moment and EMG waveform features associated with OA progression at 7-year follow-up using both clinical and structural progression definitions. This provides valuable insight into the overall loading environment of the joint and its effect on both structural damage and clinical change. Although these results may be specific to those with clinically moderate knee OA at baseline and not generalizable to all individuals with knee OA,

we chose to focus on this group because intervening earlier in the disease process could help reduce the clinical burden of knee OA on both patients and the healthcare system.

In conclusion, this study found that dynamic waveform features, and in particular, prolonged muscle activation, were important to clinical OA progression while magnitude features were more often unique to structural progression of knee OA. This research suggests that to enact meaningful change in rates of clinical progression to ease the growing healthcare burden of OA, it may be helpful to address patterns of joint loading rather than just loading magnitude.

Chapter 4. A Comparison Of Modeling Clinical Knee Osteoarthritis Progression Using Knee Joint Moments, Muscle Activation Patterns, Covariates, Or A Combination

4.1 Abstract

Objective: Gait analysis has provided evidence to support biomechanical interventions aimed to slow knee osteoarthritis progression. While prior interventions have focused on reducing knee adduction moment magnitude features, three-dimensional loads, loading patterns, and muscle activation can all contribute to progression. The purpose of this study was to compare the ability of baseline joint moments, electromyography patterns, and covariates (demographics, clinical severity, etc.), either alone or in combination, to discriminate between individuals who did or did not progress clinically at follow-up.

Methods: Seventy-eight individuals with medial compartment knee osteoarthritis underwent baseline gait analysis. At 5-10 year follow-up, 30 progressed clinically (total knee arthroplasty) and 48 did not. Principal component analysis extracted major patterns of variation from gait waveforms. Student's t-tests identified variables for each data type (moments, electromyography, covariates) ($p<0.10$) that were included as variables in 5 discriminant analysis models: 1) moments only, 2) electromyography only, 3) moments and electromyography, 4) covariates only, and 5) moments, electromyography, and covariates. Leave-one-out cross validation and bootstrapping analyzed model stability. Receiver operating characteristic curve analysis and logistic regression evaluated the models' predictive ability.

Results: The combined moment and electromyography model had a better correct classification rate and higher odds ratio for progression than the single data type models, while the model combining all three data types had the highest correct classification rate and odds ratio. Minimal differences were found between leave-

one-out, bootstrapped, and original correct classification rates except for in the covariates only model, where bootstrapping indicated that this model was less robust.

Conclusions: Moment and electromyography variables contributed unique information to model clinical osteoarthritis progression, evidenced by the higher correct classification rate and odds ratio in combination versus alone. While the best classification was made with all three data types, a simpler model may be more relevant as a clinical screening tool. Addressing moment patterns or prolonged muscle activation may provide promising treatment avenues to slow clinical OA progression.

4.2 Introduction

Knee osteoarthritis (OA) affects 250 million people worldwide (T. Vos et al. 2012) and this number is expected to increase due to trends in population aging (R. C. Lawrence et al. 2008) and obesity (A. G. B. D. Obesity Collaborators: Afshin et al. 2017). To help address this growing burden on patients and the healthcare system, gait analysis research has investigated factors associated with OA progression to identify potential targets for disease modifying interventions (T. Miyazaki et al. 2002, A. Chang et al. 2007, K. L. Bennell et al. 2011, J. D. Woollard et al. 2011, C. L. Hubley-Kozey et al. 2013a, E. F. Chehab et al. 2014, A. H. Chang et al. 2015, G. L. Hatfield et al. 2015b, G. L. Hatfield et al. 2015a, P. W. Hodges et al. 2015, N. M. Brisson et al. 2017). The majority of this research has focused on the knee adduction moment (KAM) as it is considered a surrogate metric of medial to lateral tibiofemoral compartment joint loading ratio (D. E. Hurwitz et al. 1998). A number of studies have shown higher KAM magnitude (peak or impulse) at baseline is associated with increasing structural damage at 1-6 year follow-up (T. Miyazaki et al. 2002, A. Chang et al. 2007, K. L. Bennell et al. 2011, J. D. Woollard et al. 2011, E. F. Chehab et al. 2014, A. H. Chang et al. 2015, N. M. Brisson et al. 2017), with many interventions in turn focused on reducing the KAM magnitude (N. D. Reeves and F. L. Bowling 2011).

Discordance between structural damage in the joint and clinical OA symptoms reported by patients (K. Barker et al. 2004) has resulted in a recent shift towards studying clinical OA, versus structural OA alone, (A. N. Bastick et al. 2015, Y. Zhang and J. Niu 2016), particularly considering clinical symptoms are an important reason why patients seek clinical care (D. Coxon et al. 2015). Thus, clinical OA and clinical OA progression may be more representative of the burden of OA on the patient and the healthcare system than structural progression only. While there is some evidence that structural progression may be indicative of future clinical progression (F. M. Cicuttini et al. 2004, O. Bruyere et al. 2005), it is of interest to identify additional targets for intervention to prevent clinical progression that could be used in combination with or as alternative to those developed for structural progression.

Clinical progression at 8-year follow up (defined as reaching a total knee arthroplasty (TKA) endpoint) has also been associated with baseline joint moments, including higher baseline KAM magnitude features (peak, impulse, and overall magnitude) (G. L. Hatfield et al. 2015a, G. L. Hatfield et al. 2015b). In addition, through the use of principal component analysis (PCA), differences in the patterns of the moment waveforms between groups were also found at baseline. These included a smaller difference between early- and mid-stance KAM (lack of mid-stance KAM unloading) and a smaller knee flexion – extension moment difference (less dynamic knee flexion moment, KFM) in the group that went on to progress clinically (TKA endpoint) (G. L. Hatfield et al. 2015b). In this same population, the group that progressed clinically at 8-year follow-up exhibited higher overall muscle activation in the quadriceps, hamstrings, and gastrocnemii (quantified using surface electromyography), and prolonged muscle activation through mid-stance in the quadriceps and hamstrings compared to the group that did not progress (C. L. Hubley-Kozey et al. 2013a). While this suggests that addressing muscle activation patterns might also be helpful in slowing clinical OA progression, patterns of prolonged muscle activation through stance are highly correlated with patterns of joint moments (C. L. Hubley-Kozey et al. 2018), specifically, the KAM and KFM features found by Hatfield et al. (G. L. Hatfield et al. 2015b). Thus, it is unknown

whether joint loading due to prolonged muscle activation provides additional information for predicting or classifying clinical progression over moment data alone. Understanding the relative contributions of moment and muscle data could have implications on the design of complementary or alternative interventions for use in the knee OA population.

Furthermore, while biomechanical interventions based on previous OA progression studies (T. Miyazaki et al. 2002, A. Chang et al. 2007, K. L. Bennell et al. 2011, J. D. Woollard et al. 2011, C. L. Hubley-Kozey et al. 2013a, E. F. Chehab et al. 2014, A. H. Chang et al. 2015, G. L. Hatfield et al. 2015b, G. L. Hatfield et al. 2015a, P. W. Hodges et al. 2015, N. M. Brisson et al. 2017) are already being developed and evaluated (e.g. (N. D. Reeves and F. L. Bowling 2011)), little work has been done to understand the value of gait features in classifying those who are at greater risk for progression. Miyazaki et al. (T. Miyazaki et al. 2002) used logistic regression to understand the odds ratio for structural progression related to increased KAM peak and Hatfield et al. (G. L. Hatfield et al. 2015b) used discriminant analysis and logistic regression to understand the contribution of gait variables describing the magnitude and pattern of KAM and KFM to the odds ratio for clinical progression (TKA endpoint). Hatfield et al. (G. L. Hatfield et al. 2015b) then used leave-one-out cross-validation to check for overtraining (P. A. Lachenbruch and M. R. Mickey 1968), as no independent test set was available to run this model on. Other methods such as bootstrapping can be used to give a more robust estimate of correct classification rates (CCRs) in the absence of an independent test set (B. Efron and R. Tibshirani 1997) but have not been explored in the context of using gait features to classify future progression. More in depth validation would help expand upon the prior work and lend support to the use of gait interventions as a non-invasive therapy for knee OA.

The primary purpose of this study was to compare the ability of baseline knee joint moments, electromyography waveform features, and covariates (demographics, clinical severity, etc.), both alone and in combination, to classify clinical OA progression at 7-year follow-up by comparing the CCRs, sensitivity, specificity, and odds ratios for models developed using different combinations of

these data types. This information could help inform treatments by providing a better understanding of the relative contributions of these different factors in classifying clinical OA progression. The secondary objective of this study was to evaluate the robustness of these models by using bootstrapping to calculate CCRs and comparing those to the original and leave-one-out cross-validated CCRs.

4.3 Methods

4.3.1 Study Overview And Participants

A secondary analysis was performed on a subset of three-dimensional gait analysis data from two follow-up studies of gait in OA (G. L. Hatfield et al. 2015b, J. L. Astephen Wilson et al. 2016). Upon enrollment in the studies, participants signed Nova Scotia Health Authority Research Ethics Board-approved informed consent forms. Exclusion criteria included age of 35 years or younger, or any neurological, cardiovascular, or musculoskeletal issue other than OA that could affect gait or participant safety. Individuals from these two studies who had clinically moderate, medial compartment knee OA, complete baseline gait data, and a follow-up regarding their TKA status between 5 and 10 years after their baseline gait testing were candidates for the current study. Clinically moderate status was defined as not being a candidate for total knee arthroplasty (TKA) at the time of study enrollment and self-reported ability to walk a city block, jog 5 meters, and climb stairs in a reciprocal manner at study enrollment. All participants were diagnosed with knee OA at baseline using a combination of radiographic signs and symptoms according to the Altman et al. criteria (R. Altman et al. 1986) and had medial joint space narrowing (JSN) greater than or equal to lateral JSN (W. W. Scott, Jr. et al. 1993). Individuals who underwent a TKA within 3 years from baseline (n = 9) were excluded in order to focus on a more homogenous group. As our definition of moderate OA covered a range of severity, those who progressed to TKA in the shorter time frame may have represented a more severe group with whom there may be a lower chance of effective interventions. This resulted in a group of 30

individuals who reported having a TKA at 5-10 year follow-up and 48 who did not have a TKA in this time frame.

4.3.2 Gait Data Collection And Processing

The methods for gait data collection have been described in detail previously (C. L. Hubley-Kozey et al. 2006, S. C. Landry et al. 2007). Briefly, individuals walked across a six-meter walkway at self-selected speed while ground reaction forces (2000 Hz), three-dimensional (3D) motion of the lower limb (100 Hz), and electromyography (EMG) of 7 muscles surrounding the knee (2000 Hz) were collected simultaneously for the most symptomatic limb. Three-dimensional net external joint moments were calculated from the motion capture and force data using inverse dynamics with custom-written MATLAB programs (Mathworks Inc., Natick, USA), amplitude-normalized to body mass, and time-normalized to the stance-phase of the gait cycle. Recorded EMG signals from the lateral (LG) and medial (MG) heads of the gastrocnemius, vastus lateralis (VL), vastus medialis (VM), rectus femoris (RF), biceps femoris (lateral hamstrings, LH) and semimembranosus (medial hamstrings, MH) were corrected for bias, converted to μV, full-wave rectified, low pass filtered, and then time-normalized to the full gait cycle. As described by Hubley-Kozey et al. (C. L. Hubley-Kozey et al. 2006), following gait testing, eight maximal voluntary isometric contraction (MVIC) exercises (three knee extension, three knee flexion, and two plantar flexion) were performed for the purposes of muscle strength testing and EMG amplitude normalization. All exercises were performed twice following a practice trial with at least 1 minute of rest between trials and standardized verbal encouragement and feedback given during and after each trial. The EMG waveforms were amplitude-normalized to the highest activation amplitude (0.1-second moving window average) of the corresponding muscle during the 8 exercises regardless of which exercise it came from. Strength for each muscle group was calculated as the highest amplitude steady state 0.5-second window from the exercises, normalized to body mass (Nm/kg), regardless of which exercise it came from (D. J. Rutherford et al. 2011).

4.3.3 Covariates

Data on covariates was also collected as part of the original studies. These covariates included demographic variables (sex, age, body mass index (BMI)), muscle strength (as described above), gait speed, radiographic severity as measured by Kellgren-Lawrence (KL) grades (J. H. Kellgren and J. S. Lawrence 1957), and clinical severity as measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (N. Bellamy et al. 1988).

4.3.4 Waveform Feature Extraction

PCA was utilized to extract key features (principal components, PCs) of knee moment and EMG waveforms (C. L. Hubley-Kozey et al. 2006, J. L. Astephen Wilson et al. 2016) from a larger sample of individuals with moderate knee OA and asymptomatic individuals from the Dynamics of Human Motion (DOHM) laboratory database (n = 428 (207 women, 221 men) with mean age = 55.2 ± 9.4 years, mass = 84.3 ± 18.3 kg, BMI = 28.8 ± 5.3 kg/m^2, speed = 1.29 ± 0.20, WOMAC total = 17.5 ± 18.8, medial JSN (0:1:2:3) = 16:139:107:50, KL grade (1:2:3:4) = 25:138:101:46). Retained PCs cumulatively explained greater than 90% of the variability among waveforms. Principal component scores (PC scores) were calculated for each moment and EMG waveform for each participant in the current study, by multiplying the waveform by each PC (C. Hubley-Kozey et al. 2008). These PC scores representing weighting coefficients describing how closely the participant's original waveforms matched each extracted pattern from the larger database. Using a larger dataset to extract PCs is considered more robust (J. W. Osborne and A. B. Costello 2004) and has high test-retest reliability (C. L. Hubley-Kozey et al. 2013b, S. M. Robbins et al. 2013a). This list of retained PCs was then narrowed to include only those features that have been related to structural and/or clinical OA progression: overall KAM magnitude (PC1), the difference between early and mid-stance KAM (PC2), early stance KFM magnitude (PC1) and the difference between early stance KFM and late stance knee extension moment (KEM) (PC2) (G. L. Hatfield et al.

2015b), the difference between internal and external knee rotation moment (KRM) (PC1) (E. Davis et al. 2018), the internal KRM magnitude through mid-stance (PC2) (**Chapter 3**), higher overall activation of gastrocnemii, quadriceps and hamstrings (PC1), and prolonged quadriceps and hamstrings activation (PC2) (C. L. Hubley-Kozey et al. 2013a).

4.3.5 Statistical Analysis

Moment, EMG, and covariates that had been pre-selected based on literature showing they were associated with OA progression and/or OA severity were then tested for entry into the models using a chi square test (for sex), Mann-Whitney U-tests (for ordinal radiographic scores), or student's t-tests (for moment and EMG PC scores, and the remaining covariates). In cases where the Shapiro-Wilk test for normality or Levene's test for homogeneity of variance were not satisfied, Mann Whitney U-tests or Welch's t-tests, respectively, were used instead of t-tests. Variables with between-group differences at $p < 0.10$ from these tests were entered into stepwise discriminant analyses to identify the variable or combination of variables that best discriminated between TKA and no TKA groups. Five different stepwise discriminant analyses were performed (probability of F-to-enter: $p = 0.05$, probability of F-to-remove: $p = 0.10$) with the following types of variables entered into each model: 1) moments only, 2) EMG only, 3) moments and EMG variables, 4) covariates only, and 5) moment, EMG, and covariates.

CCRs were calculated for each model. Receiver operating characteristic (ROC) curve analysis was performed and a criterion value was selected to maximize sensitivity and specificity for each model. Logistic regression was used to calculate odds ratios for progression to TKA for each of the five models. Leave-one-out cross-validation (P. A. Lachenbruch and M. R. Mickey 1968) was performed to test for model overtraining.

Bootstrapping (B. Efron and R. J. Tibshirani 1993) was performed to further evaluate the robustness of the models. It mimics sampling multiple datasets from the population, which can reduce the variability of error rate predictions compared

to cross-validation (B. Efron and R. Tibshirani 1997). For each model, 1000 bootstrap datasets of n = 78 were generated using sampling with replacement and a stratification that maintained the distribution of TKA and no TKA groups from the original sample (n = 30 TKA, n = 48 no TKA). These datasets were used to train the coefficients for each of the five models using the same variables identified in the original stepwise discriminant analysis models. These models with new coefficients were then applied to the corresponding "test" dataset consisting of individuals from the original study sample that were not included in the "train" dataset (n ~= 28). CCRs for TKA and no TKA groups and overall CCRs were calculated for each train and test bootstrapped dataset for each model.

All statistical analyses were performed in SPSS 24 (IBM, Armonk, USA) except for the bootstrapping, which was performed in R 3.4.3 (R Core Team 2017) using the boot (A. C. Davison and D. V. Hinkley 1997, A. Canty and B. D. Ripley 2017), MASS (W. N. Venables and B. D. Ripley 2002), and TeachingDemos (G. Snow 2016) packages.

4.4 Results

4.4.1 Variable Identification For Stepwise Discriminant Models

Of the covariates, radiographic severity (KL grade, $p < 0.01$) and WOMAC stiffness ($p=0.09$) were identified for entry into the models according to a criterion of $p < 0.10$ for TKA versus no TKA groups (Table 4.1). The between-group difference in WOMAC stiffness was below a clinically relevant difference (i.e. less than 1) (A. Escobar et al. 2007), thus WOMAC stiffness was excluded from entry into the models. The overall KAM magnitude (KAM PC1, $p<0.01$), the overall KFM magnitude (KFM PC1, $p=0.08$), and the knee flexion/extension moment difference (KFM PC2, $p=0.07$) were entered into the stepwise discriminant models that included moment data (Table 4.2). Of the EMG variables, overall lateral hamstring magnitude (LH PC1, $p = 0.01$), prolonged LH mid-stance activation (LH PC2, $p = 0.05$), prolonged medial hamstring mid-stance activation (MH PC2, $p < 0.01$), overall lateral gastrocnemius activity (LG PC1, $p = 0.06$), and prolonged VL mid-stance activation (VL PC2, p =

0.08) were identified for entry into the models that included EMG data (Table 4.3). Thus, three variables (KAM PC1, KFM PC1, and KFM PC2) were entered in the moments only model, five variables (LG PC1, VL PC2, LH PC1, LH PC2, and MH PC2) were entered in the EMG only model, and a single variable (KL grade) was entered in the covariate only model. The remaining two models contained combinations of these variables according to the data types allowed in each model.

Table 4.1 Descriptive characteristics (covariates) for clinical progression (TKA) and no progression (no TKA) groups

	TKA (n = 30)	No TKA (n = 48)	Mean difference	95% CI	*P*
Women:Men (% Women)	9:21 (30%)	12:36 (25%)			0.63
Age (years)	55.5 (8.4)	57.3 (6.4)	1.7	-1.6, 5.1	0.31
Mass (kg)	89.2 (15.3)	93.5 (19.6)	4.4	-4.0, 12.8	0.30
Body mass index (kg/m^2)	30.2 (5.0)	30.5 (5.4)	0.3	-2.1, 2.8	0.84
Radiographic scores					
KL grade (1:2:3:4)	2, 5, 16, 7	4, 26, 18, 0			**<0.01**
Medial JSN (0:1:2:3)	2, 4, 13, 11	3, 18, 23, 4			**<0.01**
Lateral JSN (0:1:2:3)	14, 12, 2, 2	42, 5, 1, 0			**0.05**
Patellofemoral JSN (0:1:2:3)†	2, 14, 8, 2	10, 25, 10, 0			**<0.01**
WOMAC					
Pain (/20)	6.8 (3.3)	5.9 (4.1)	-0.9	-2.7, 0.8	0.18
Stiffness (/8)	3.6 (1.3)	3.1 (1.7)	-0.5	-1.2, 0.2	0.09
Function (/68)	20.8 (11.7)	18.5 (13.2)	-2.3	-8.3, 3.6	0.34
Strength (Nm/kg)					
Knee Extensors	1.33 (0.47)	1.43 (0.55)	0.10	-0.14, 0.34	0.57
Knee Flexors	0.74 (0.27)	0.74 (0.32)	0.00	-0.14, 0.14	0.77
Plantar Flexors	1.04 (0.39)	1.09 (0.45)	0.05	-0.15, 0.25	0.94
Speed (m/s)	1.25 (0.17)	1.27 (0.20)	0.02	-0.07, 0.11	0.67
Time to follow-up radiograph (years)	6.6 (1.6)	8.1 (1.9)	1.6	0.7, 2.4	**<0.01**

All data are presented as mean (standard deviation), except where noted. CI = confidence interval, KL = Kellgren-Lawrence, JSN = joint space narrowing, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index. †Patellofemoral JSN scores were unavailable for n = 4 individuals in the TKA group and n = 3 individuals in the No TKA group.

4.4.2 Stepwise Discriminant Models

In both the covariates only and EMG only stepwise discriminant analysis models, the model included a single term: KL grade for the covariates only model and prolonged MH mid-stance activity (MH PC2) for the EMG only model (Table 4.4, Figure 4.1). KAM PC1 and KFM PC2 emerged as terms in the biomechanics only model (Table 4.4, Figure 4.1). For the biomechanics and EMG model, KAM PC1, MH PC2, and LG PC1 emerged as terms (Table 4.4, Figure 4.1). The biomechanics, EMG, and covariates model included the same terms as the biomechanics and EMG model along with the addition of KL grade (Table 4.4). Generally, the CCR, specificity, sensitivity, and odds ratio for clinical progression increased as more terms were added to the models with the model including all three data types (biomechanics, EMG, and covariates) producing the highest CCR, sensitivity, specificity, and odds ratio (Table 4.4, Table 4.5, Figure 4.2).

Table 4.2 Knee moment differences between clinical progression (TKA) and no progression (no TKA) groups

PC		Interpretation	TKA (n = 30)	No TKA (n = 48)	Mean difference	95% CI	*P*
KAM	1	Overall shape and magnitude	0.93 (1.13)	0.09 (1.00)	-0.84	-1.33, -0.35	**<0.01**
	2	Early-, mid-stance difference	-0.05 (0.49)	0.01 (0.54)	0.06	-0.18, 0.31	0.60
KFM	1	Early stance flexion moment magnitude	-0.63 (1.11)	-0.13 (1.23)	0.50	-0.05, 1.05	0.08
	2	Early stance flexion moment- late stance extension moment difference	-0.07 (0.98)	0.36 (1.02)	0.43	-0.04, 0.89	0.07
KRM	1	External, internal rotation moment difference	0.08 (0.34)	0.13 (0.39)	0.06	-0.11, 0.23	0.63
	2	Overall mid-stance internal rotation moment magnitude	0.12 (0.48)	0.00 (0.37)	-0.13	-0.32, 0.06	0.19

All data are presented as mean (standard deviation), except where noted. KAM = knee adduction moment, KFM = knee flexion moment, KRM = knee internal rotation moment, PC = principal component, TKA = total knee arthroplasty.

Table 4.3 Electromyography differences between clinical progression (TKA) and no progression (no TKA) groups

PC		Interpretation	TKA (n = 30)	No TKA (n = 48)	Mean difference	95% CI	*P*
LG	1	Overall shape and magnitude	211.1 (87.9)	178.2 (81.2)	-33.0	-71.8, 5.9	0.06
MG	1	Overall shape and magnitude	190.6 (98.3)	203.3 (58.5)	12.6	-22.7, 28.0	0.17
VL	1	Overall shape and magnitude	151.0 (79.6)	144.7 (92.6)	-6.3	-47.1, 34.4	0.63
	2	Mid- to early-stance amplitude difference (mid-stance activation)	-3.2 (37.0)	-16.3 (26.9)	-13.1	-27.5, 1.4	0.08
VM	1	Overall shape and magnitude	159.4 (142.7)	163.9 (89.2)	4.5	-47.7, 56.7	0.27
	2	Mid- to early-stance amplitude difference (mid-stance activation)	-2.0 (34.8)	-13.5 (34.5)	-11.5	-27.5, 4.6	0.25
RF	1	Overall shape and magnitude	99.4 (51.8)	87.8 (43.3)	-11.6	-33.2, 10.1	0.29
	2	Mid- to early-stance amplitude difference (mid-stance activation)	17.4 (32.3)	7.6 (19.6)	-9.8	-21.5, 1.9	0.15
LH	1	Overall shape and magnitude	188.5 (111.3)	131.7 (68.9)	-56.8	-97.4, -16.2	**0.01**
	2	Mid- to early-stance amplitude difference (mid-stance activation)	17.9 (56.3)	-10.1 (36.0)	-28.0	-48.8, -7.2	**0.05**
MH	1	Overall shape and magnitude	111.3 (63.6)	108.7 (42.1)	-2.6	-26.5, 21.2	0.63
	2	Mid- to early-stance amplitude difference (mid-stance activation)	-4.0 (33.4)	-25.3 (28.0)	-21.3	-35.3, -7.3	**<0.01**

All data are presented as mean (standard deviation), except where noted. CI = confidence interval, LG = lateral gastrocnemius, LH = lateral hamstrings, MG = medial gastrocnemius, MH = medial hamstrings, PC = principal component, RF = rectus femoris, TKA = total knee arthroplasty, VL = vastus lateralis, VM = vastus medialis.

Looking across a range of sensitivity levels (60, 70, 80, or 90%), the moments, EMG, and covariates model gave the highest specificity of the five models (Table 4.5, Figure 4.2). At a desired sensitivity level of 60%, the moments only or EMG only models gave specificity of less than 70% but the moments and EMG model gave a specificity of greater than 90% (Table 4.5, Figure 4.2). While the EMG only model typically had the lowest specificity for each desired level of sensitivity, adding EMG to the moments only model (i.e. comparing the moments and EMG model to the moments only model), increased the model's specificity by at least 8% for all but the

80% sensitivity level, where the moments only model gave a slightly higher specificity (56.2% vs. 52.1%) (Table 4.5, Figure 4.2).

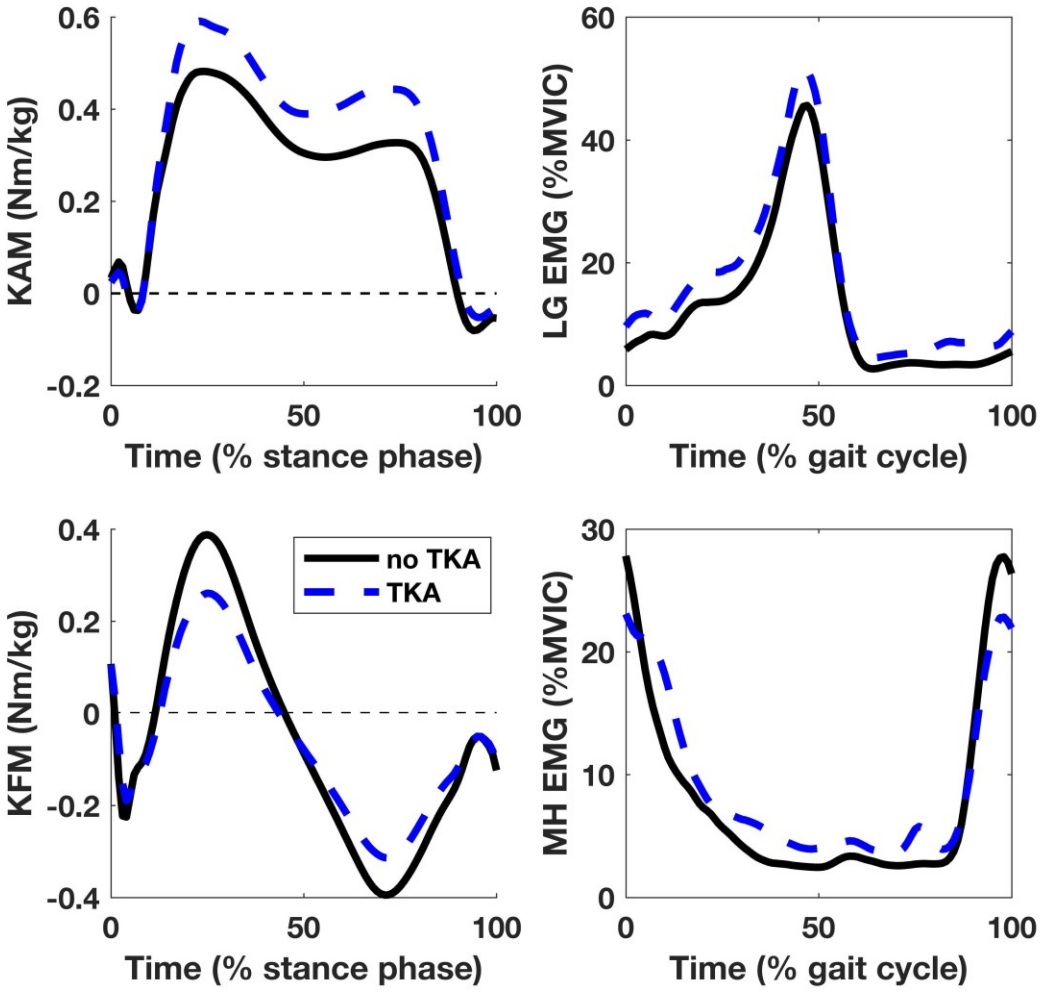

Figure 4.1 Group average waveforms of variables included in the discriminant models for TKA and no TKA groups.

Table 4.4 Discriminant analysis models

Model	Variables entered into the stepwise discriminant model	Variables in final model (std. coeff.)		Correct classification rates (in %) Original (n=78)	Leave-one-out cross-validated (n=78)	Bootstrap train set (n=78) §	Bootstrap test set (n~=28) §	OR for TKA (95% CI)
Moments only	KAM PC1, KFM PC1, KFM PC2	• KAM PC1 (0.929) • KFM PC2 (-0.623)	*Overall*	*70.5*	*69.2*	*71.9 (4.5)*	*69.3 (7.7)*	2.8 (1.5 – 4.9)
			TKA	46.7	46.7	47.9 (9.5)	45.4 (13.3)	
			No TKA	85.4	83.3	86.9 (4.5)	84.1 (10.9)	
EMG only	LH PC1, LH PC2, MH PC2, LG PC1, VL PC2	• MH PC2 (1.000)	*Overall*	*69.2*	*69.2*	*68.3 (4.2)*	*66.8 (7.1)*	2.0 (1.2 – 3.4)
			TKA	33.3	33.3	31.5 (12.6)	30.8 (13.8)	
			No TKA	91.7	91.7	91.2 (5.0)	89.3 (10.9)	
Moments and EMG	KAM PC1, KFM PC1, KFM PC2, LH PC1, LH PC2, MH PC2, LG PC1, VL PC2	• KAM PC1 (0.814) • MH PC2 (0.704) • LG PC1 (0.532)	*Overall*	*79.5*	*76.9*	*78.8 (4.7)*	*75.3 (7.2)*	4.1 (2.0 – 8.1)
			TKA	63.3	56.7	60.5 (9.0)	56.3 (14.1)	
			No TKA	89.6	89.6	90.2 (4.5)	87.1 (9.7)	
Covariates only	KL grade	• KL grade (1.000)	*Overall*	*67.9*	*67.9*	*70.9 (3.5)*	*67.0 (6.2)*	2.4 (1.4 – 4.0)
			TKA	76.7	76.7	54.4 (28.5)	51.7 (28.3)	
			No TKA	62.5	62.5	81.3 (17.0)	76.6 (21.6)	
Moments, EMG, and covariates	KAM PC1, KFM PC1, KFM PC2, LH PC1, LH PC2, MH PC2, LG PC1, VL PC2, KL grade	• KAM PC1 (0.635) • MH PC2 (0.548) • LG PC1 (0.507) • KL grade (0.444)	*Overall*	*80.8*	*79.5*	*81.9 (4.5)*	*77.2 (6.8)*	4.8 (2.3 – 10.1)
			TKA	63.3	63.3	65.3 (8.4)	58.5 (14.3)	
			No TKA	91.7	89.6	92.2 (4.0)	88.9 (8.1)	

EMG = electromyography, KAM = knee adduction moment, KFM = knee flexion moment, KL = Kellgren Lawrence, LG = lateral gastrocnemius, LH = lateral hamstrings, MH = medial hamstrings, OR = odds ratio, PC = principal component, TKA = total knee arthroplasty, VL = vastus lateralis

§Correct classification rate presented as mean (standard deviation) of n = 1000 bootstrap samples

4.4.3 Model Cross-Validation And Bootstrapping

For all models, the original CCR and the leave-one-out cross-validated CCR were similar, suggesting that there was minimal overtraining in the models (Table 4.4). The largest difference between the CCR and cross-validated CCR across all models was only 3% (moments and EMG model).

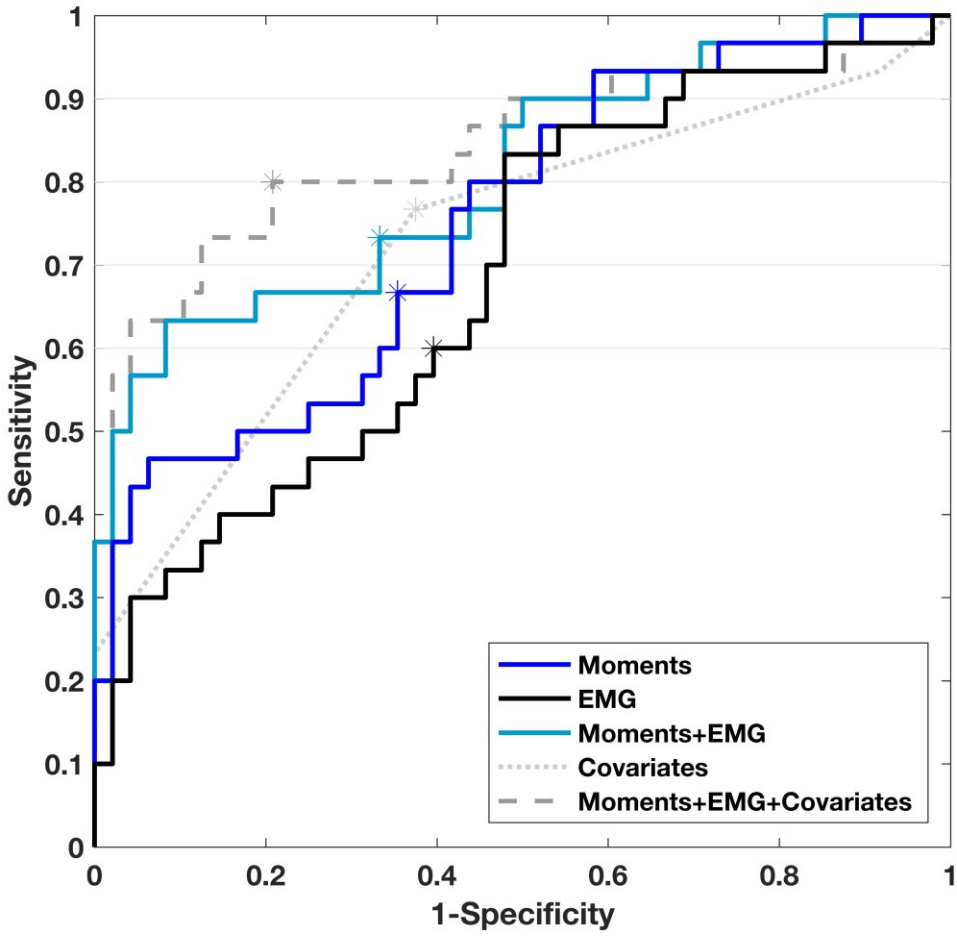

Figure 4.2 Receiver operating characteristic curves for stepwise discriminant models based on moments only, EMG only, moments and EMG, covariates only, or all three data types (moments, EMG, and covariates)

The overall CCRs from the bootstrapping train and test sets were similar to the original and cross-validated CCRs for all five models. The test and train no TKA and TKA CCRs were also similar to the original and cross-validated CCRs for all models except for the covariates only model, where the no TKA CCR was higher and TKA CCR lower in both bootstrap datasets than the corresponding original or cross-validated CCRs (Table 4.4).

Table 4.5 Sensitivity, specificity and area under the curve for each of the five discriminant models

Model	AUC (95% CI)	Maximized sensitivity & specificity		Specificity at given level of sensitivity			
		Sens.	Spec.	Sens. = 60%	Sens. = 70%	Sens.= 80%	Sens.= 90%
Moments only	0.749 (0.637 – 0.860)	66.7	64.6	66.7% spec.	58.3% spec.	56.2% spec.	41.7% spec.
EMG only	0.685 (0.564 – 0.807)	60.0	60.4	60.4% spec.	54.2% spec.	52.1% spec.	33.3% spec.
Moments and EMG	0.808 (0.705-0.911)	73.3	66.7	91.7% spec.	66.7% spec.	52.1% spec.	50.0% spec.
Covariates only	0.728 (0.608-0.849)	76.7	62.5	‡	‡	‡	‡
Moments, EMG, and Covariates	0.844 (0.745-0.942)	80.0	79.2	95.8% spec.	87.5% spec.	79.2% spec.	52.1% spec.

AUC = area under the curve, CCR = correct classification rate, CI = confidence interval, OR = odds ratio for TKA progression, ROC = receiver operating characteristic

‡The covariates only model had a low number of points on the ROC curve and thus did not have data to include in this table. The closest points to the sensitivity levels in this table for the covariates only model were: 76.7% sensitivity with 62.5% specificity and 93.3% sensitivity with 8.3% specificity.

4.5 Discussion

Discriminant models were created for a group of individuals with clinically moderate, medial compartment knee OA to discriminate between individuals who would progress clinically (TKA) at 5-10 year follow-up and those that would not using combinations of moment, EMG, and covariate data. The usefulness of a

progression model is two-fold: (1) it can help understand which variables may be important to progression to aid in developing effective treatments, and (2) it can help identify which individuals may be at greater risk for progression and in need of more immediate interventions. The goal of this study was to determine which data types or combinations of data types would best predict clinical knee OA progression and to discuss the relative usefulness of the different models.

Overall the two groups were similar in terms of covariates (Table 4.1), with the only difference being higher radiographic scores in the TKA group. Thus, KL grade was the only term in the covariates only model. The two terms that emerged in the model based on moments only were the overall KAM (KAM PC1) and the difference between the early stance KFM and late stance knee extension moment (KFM PC2), both of which were identified as discriminating factors between groups in the only other model for clinical knee OA progression in the literature (G. L. Hatfield et al. 2015b). Furthermore, increased KAM and a reduced range of KFM have both been associated with clinical OA severity (J. L. Astephen et al. 2008). The model based on EMG variables only included a single term describing prolonged medial hamstrings activity through mid-stance (MH PC2). Prolonged muscle activity has been related to both OA severity (C. L. Hubley-Kozey et al. 2009) and OA progression (C. L. Hubley-Kozey et al. 2013a, P. W. Hodges et al. 2015) with more severe individuals and individuals who later progress having more prolonged activity and co-contraction of the knee musculature, indicating prolonged loading on the joint. Furthermore, while prolonged lateral hamstring activity appears to occur across the severity spectrum in OA, prolonged medial hamstring activity appears to occur only in a more severe group (C. L. Hubley-Kozey et al. 2006, C. Hubley-Kozey et al. 2008, C. L. Hubley-Kozey et al. 2009). In the moment and EMG model, both types of variables emerged with higher overall KAM (KAM PC1), prolonged activity in the medial hamstring (MH PC2), and higher overall lateral gastrocnemius activity (LG PC1) appearing in the model. The hamstrings and gastrocnemii both act to flex the knee which may explain why KFM PC2 was not included in this model. The fifth model, in which moments, EMG variables, and covariates were entered, included the same three variables as the moment and EMG model along with the addition of KL

grade, where higher KL grade at baseline was associated with increased likelihood of progression.

Collectively, the models created in this study indicate that OA progression is multi-factorial, based on radiographic severity, joint moments, and muscle activation patterns all emerging as factors in the models. Currently, there are no treatments to decrease radiographic scores so while this variable has predictive value for clinical progression, it is not currently an effective target for intervention. Furthermore, while a high KL score makes someone more likely to progress, having a low KL score does not necessarily equate to low risk of progression, as evidenced by the low specificity (62.5 %) in the covariates only model. Last, the difference between bootstrapped CCRs and the original or cross-validated CCRs suggest that this model is not very robust and would not be generalizable to all samples from the OA population.

Both moment variables and muscle patterns, on the other hand, may be effective targets for treatments to reduce rates of clinical progression to TKA. Gait retraining programs, bracing, and shoe inserts have all been considered as potential mechanisms to reduce the KAM (N. D. Reeves and F. L. Bowling 2011). Most of these interventions aim to reduce a single peak of the KAM, without considering how the rest of the KAM waveform or the KFM are affected (M. W. Creaby 2015). Thus, while there is promise for these types of interventions to affect clinical progression, more work still needs to be done in this area with concern for both the overall KAM and overall pattern of the KFM through stance. The prolonged activation of MH suggests that interventions targeting muscle activation patterns may also be appropriate. Neuromuscular training programs or bracing may be effective at reducing prolonged muscle activity and co-contraction (D. K. Ramsey et al. 2007, R. F. Moyer et al. 2015), and may also improve cyclic loading patterns (i.e. greater unloading) in joint moments (C. L. Hubley-Kozey et al. 2018), which could further affect clinical progression rates.

The second purpose of a progression model is to be able to identify who is at risk of progression (and thus in need of treatment). While the best classification of those at risk of clinical progression to TKA within 5-10 years was made with a

model incorporating all three types of predictor variables, the models that utilized only one type of predictor variable (e.g. moment-only model) or only a single variable (covariates only or EMG variables only models) still achieved at least 60% sensitivity and specificity in discriminating between those who would and would not progress. EMG in particular requires less equipment and has a more portable set-up than collection of joint reaction moments, for which a force plate and motion capture system are required. Thus, while the models that include moments have better CCRs for TKA, a simple EMG model may be more useful as a clinical screening tool.

For these models to be implemented clinically, they would need to be validated in an independent test set. With the exception of the covariates only model, the similar CCRs between original, cross-validated, and bootstrap train and test sets, suggest that these models are fairly robust. One limitation of the current models is that they were developed using individuals who were considered clinically moderate at baseline and developed for a specified follow-up of 5-10 years. Thus, these models would not be applicable to individuals who were more or less severe clinically, such as the n = 9 individuals that were excluded who had progressed to TKA within 3 years from baseline (average 1.2 +/- 0.5 years). As stated previously, the reason for this exclusion was to focus on a group with a higher likelihood of success and enough time to implement a biomechanically or neuromuscular-driven intervention. Longitudinal studies would be needed to understand whether these types of interventions are successful in a group similar to the current study or whether similar areas for intervention could be identified for a group that may be more severe at baseline and have a higher risk for progression in a shorter time frame. The specified time frame also had effects on the high end cutoff (10 years). Of those who were included in the current study, one individual reported being on the waitlist for TKA at 10 years and received a TKA just after 10 years. This person was included in the TKA group in the current study and was correctly classified by the EMG only model as being in the TKA group but incorrectly classified as being in the no TKA group for all four other models, which may reflect the fact that this individual was right on the cutoff of follow-up time for the current

study. There were also two individuals in the no TKA group who did not have a TKA at 10-year follow-up but did both undergo TKA at approximately 13 years post-baseline. One of these individuals was classified in the no TKA group by only two models (moments only, moments and EMG) while the other was classified in the no TKA group by only one model (covariates only). Thus, there may be some overlap between groups at the limits of the follow-up time frame defined by the current models. Despite this, the shorter time to follow-up in the TKA group makes us more confident that the no TKA group would not progress to TKA in a similar time frame (i.e. it was not that they were merely not followed for long enough to progress to TKA).

While this is the first study to investigate the relative contributions of moments, EMG, and covariates to clinical OA progression, the results of the moment only model were consistent with a previous model for clinical progression based on moments only. Hatfield et al. (G. L. Hatfield et al. 2015b) examined 3D moments at the hip, knee, and ankle, and found that the overall magnitude and shape of the KAM, the difference between knee flexion and extension moments, and a variable describing ankle plantar flexion moments were able to produce a CCR of 74% for clinical progression using a TKA endpoint. The moments only model in the current study also identified the overall magnitude and shape of the KAM and the difference between KFM and knee extension moments as important variables. Compared to the study population used in Hatfield et al., the population included here is slightly younger with lower mass (but similar BMI) and has slightly lower WOMAC function scores (corresponding to better function) but similar pain and stiffness scores, a slightly lower proportion of women, similar walking speed, and similar radiographic severity. The time to TKA in the Hatfield et al. study was 4 ± 3 years compared to the 7 ± 2 years in the current study but time to follow-up in the no TKA group was similar between studies at 8 ± 2 years. This is likely a result of the current study limiting follow up to between 5-10 years and excluding anyone who had at TKA within 3 years from baseline and may indicate that the group that progressed clinically in Hatfield et al. study was either more severe at baseline or represented a

more quickly progressing group than the group that progressed clinically in the current study.

In conclusion, we were able to achieve 60-80% sensitivity and specificity for discriminating between clinical progression (using a TKA endpoint) versus no progression at 5-10 year follow-up using one to four model variables. While the best CCR and odds ratio for clinical progression were found in the model that incorporated moment, EMG, and covariate data, prolonged MH activity alone was able to achieve almost 70% correct classification, suggesting EMG data may be useful as a clinical screening tool given the minimal effort and equipment required to collect this information. Furthermore, EMG data was found to contribute unique information to the prediction of clinical progression, as evidenced by the higher correct classification rates and odds ratio in the combined moment and EMG model than with either data type alone.

Chapter 5. Differences In Using A Single Week Of Accelerometer Data Versus Averaging Multiple Weeks Over A Year In Individuals With Knee Osteoarthritis And Asymptomatic Controls

5.1 Abstract

Objective: There is growing interest in using physical activity metrics derived from accelerometer data, such as step count, light intensity physical activity, moderate to vigorous intensity physical activity, and sedentary behavior, in osteoarthritis outcomes research. While data from 3-5 consecutive days provides reliable estimates of these metrics, there are large intra-individual differences across non-consecutive monitoring periods, suggesting that a single consecutive monitoring session does not capture habitual physical activity levels. The purpose of this study was to examine whether average metrics across two or three one-week sessions during a year showed the same between-group differences as a single session using individuals with knee osteoarthritis and asymptomatic controls as a model. A secondary purpose was to examine the limits of agreement between averaged metrics and single session metrics to understand variations in physical activity metrics at the individual level.

Methods: Thirty-eight individuals with knee osteoarthritis and 47 asymptomatic individuals wore a tri-axial accelerometer for 2 or 3 one-week sessions during a one-year period. General linear models were used to examine the effects of number of *sessions* averaged (within-subjects factor) and *group* (between-subjects factor) ($\alpha = 0.05$). Bland Altman analyses examined agreement in accelerometer metrics between a single session, a two-session average, and/or a three-session average.

Results: Across all participants, while there were knee osteoarthritis versus asymptomatic *group* main effects for all variables, there was a main effect of *sessions* for wear time and sedentary behavior only. Sedentary behavior expressed as percent wear time had only borderline significance across *sessions* ($p = 0.05$). These results were nearly identical in the smaller cohort that had three sessions of data, with the one exception being a lack of difference in percent of wear time in sedentary behavior among *sessions*. The limits of agreement from the Bland-Altman analyses indicated that using a two-session average versus a single session resulted in differences of approximately ± 50 minutes for light physical activity, ± 20 minutes for moderate to vigorous physical activity, and ± 2100 steps for step count.

Conclusions: Future studies investigating step count, light or moderate to vigorous physical activity in knee osteoarthritis may be able to use a single session of accelerometer data to examine group level differences in habitual PA metrics, however, caution should be taken when using a single session to examine these metrics at the individual level. A single session of sedentary behavior data may be appropriate if wear time is taken into account.

5.2 Introduction

Physical activity (PA) data derived from accelerometers has many applications in osteoarthritis (OA) research. These include investigating the effects of PA and sedentary behavior (SED) on comorbidities (S. H. Liu et al. 2015), using PA data as a surrogate metric of joint loading frequency to understand the effects of cumulative joint load on OA progression (H. Tateuchi et al. 2016, N. M. Brisson et al. 2017, H. Tateuchi et al. 2017), and examining the effects of PA intervention programs on OA outcomes (A. L. Gilbert et al. 2017), among others. Depending on the application, an overall metric of PA like step count, intensity based metrics like light PA (LPA) and moderate to vigorous PA (MVPA), or a measure of physical inactivity (SED), might be relevant. These metrics can vary over time around a true mean, or habitual level, of PA (P. Bergman 2018), thus repeated measurements may

need to be averaged to calculate habitual PA. The ability to establish a baseline level of habitual PA is essential to understanding the effects of PA on OA outcomes.

Previous research has shown that in adults, 80% reliability can be achieved after 3 consecutive days of monitoring (of 10+ hours/day) for metrics of moderate and higher intensity PA, and 90% reliability can be achieved after 7 days for both SED/LPA and MVPA (C. E. Matthews et al. 2002). Similarly, Hart et al. found that 80% reliability can be achieved after 2 days of monitoring for MVPA, 3 days for LPA, and 5 days for SED in older adults (T. L. Hart et al. 2011). Based on these studies and other similar work, common practice is to monitor participants for one week of accelerometer wear, from which at least 3 days are used to calculate average daily values across the week of wear (C. E. Matthews et al. 2012).

In any given week, however, many factors can influence PA level. For example, PA levels may be affected by weather (J. Feinglass et al. 2011, S. M. Robbins et al. 2013b) or current pain level (S. M. Robbins et al. 2011), which can be difficult to control for or measure. Furthermore, reliance on self-report activity logs to capture data that could give an indication of whether the week was representative of a typical week (e.g. illness, irregular work hours, vacation, family emergencies, or other unusual events) can be problematic due to non-compliance and good subject bias (A. L. Nichols and J. K. Maner 2008). Thus, there are many potential sources of variability for PA during a given week that could lead to an incorrect estimation of habitual PA but these are not always easy to measure or control. Despite this, the degree to which accelerometer metrics vary over non-consecutive periods has received little attention.

There have been two studies that showed intra-individual variations over longer periods in adults. Levin et al. found variations in PA over the course of one year when measured every 26 days and suggested that six repeated accelerometer measurement sessions were needed to achieve 80% reliability in estimating their accelerometer derived PA metric of MET (metabolic equivalent of task)-minutes per day (S. Levin et al. 1999). This study only measured two days per monitoring session, however, and only a single accelerometer metric was investigated. Pedersen et al. also found variability among non-consecutive monitoring periods, in

this case when examining work and leisure time standing, sitting, and MVPA in adults when measured for 5 days at baseline, 1- and 3-months follow-up (E. S. Pedersen et al. 2016). While much of this variation in PA level over a year is typically attributed to seasonal changes (weather, day-length, etc.) (C. A. Brandon et al. 2009, M. S. Buchowski et al. 2009, D. Sumukadas et al. 2009, M. Hagstromer et al. 2014, S. E. O'Connell et al. 2014), in OA outcomes studies it may not be feasible to record or control for all sources of variance in the analysis. Thus, it is of interest to understand whether these intra-individual variations would affect the ability to identify between-group differences and the likely error in using a single session to estimate habitual physical activity.

Using individuals with medial compartment knee OA and asymptomatic controls as a model, the objectives of this study were to (1) determine whether there were interactions between group and number of sessions averaged in accelerometer-derived metrics (including SED, LPA, MVPA, and step count) in order to understand whether multiple sessions were needed to identify group level differences in habitual PA, and (2) to examine the limits of agreement between using one, two, and/or three weeks of averaged data during a year to gain insight into the possible error associated with using a single-session of data to estimate habitual PA at an individual level. We tested the null hypothesis that measurements from a single session would not differ from the average measurement across multiple sessions in any of the variables tested.

5.3 Methods

5.3.1 Study Overview And Participants

This study included 85 individuals from two previous studies in the Dynamics of Human Motion laboratory (DOHM) (G. L. Hatfield et al. 2015b, J. L. Astephen Wilson et al. 2016) who had multiple (two or three) one-week long sessions of accelerometer data collected between 2012 and 2015. All participants gave Nova Scotia Health Authority Research Ethics Board-approved informed consent before participating in these studies.

Table 5.1 Sample characteristics of OA and ASYM groups

	Full cohort (at least 2 sessions)			Sub-cohort with 3-sessions		
	OA	**ASYM**	***P* §**	**OA**	**ASYM**	***P* §**
N	38	47		18	25	
Women:Men	15:23	30:17	**0.03**	8:10	16:9	0.20
Age (years)	63.1 (7.8)	55.4 (8.1)	**<0.01**	66.1 (7.8)	53.8 (8.2)	**<0.01**
Mass (kg)	90.4 (18.9)	77.2 (16.0)	**<0.01**	95.6 (18.9)	75.1 (14.3)	**<0.01**
BMI (kg/m^2)	30.9 (6.0)	27.2 (4.6)	**<0.01**	32.8 (6.5)	26.5 (4.8)	**<0.01**
Strength (Nm/kg)†						
Knee extensors	1.30 (0.29)	1.67 (0.54)	**<0.01**	1.23 (0.20)	1.73 (0.56)	**<0.01**
Knee flexors	0.65 (0.20)	0.79 (0.21)	**<0.01**	0.53 (0.10)	0.82 (0.19)	**<0.01**
Plantar flexors	0.95 (0.29)	1.18 (0.44)	**0.01**	0.87 (0.23)	1.24 (0.47)	**<0.01**
Radiographic scores‡						
KL grade (1, 2, 3, 4)	0, 9, 18, 11	2, 39, 5, 0	**<0.01**	0, 3, 9, 6	1, 21, 3, 0	**<0.01**
Medial JSN (0, 1, 2, 3)	0, 11, 18, 9	2, 36, 8, 0	**<0.01**	0, 4, 8, 6	2, 17, 6, 0	**<0.01**
Lateral JSN (0, 1, 2, 3)	19, 14, 5, 0	29, 15, 2, 0	0.16	6, 9, 3, 0	13, 11, 1, 0	0.14
PF JSN (0, 1, 2, 3)	5, 16, 16, 1	16, 29, 1, 0	**<0.01**	2, 6, 9, 1	7, 18, 0, 0	**<0.01**
WOMAC						
Pain (/20)	3.7 (3.9)	1.1 (2.6)	**<0.01**	2.5 (3.1)	0.7 (2.5)	**<0.01**
Stiffness (/8)	1.8 (1.7)	0.6 (1.1)	**<0.01**	1.6 (1.4)	0.4 (1.0)	**<0.01**
Function (/68)	12.1 (12.2)	4.2 (8.5)	**<0.01**	8.2 (9.4)	3.1 (8.5)	**<0.01**
Time (months) between:						
Sessions 1 and 2	8.5 (2.6)	8.4 (2.5)	0.66	7.4 (1.5)	7.3 (1.1)	0.56
Sessions 1 and 3	-	-		13.8 (1.1)	13.8 (1.0)	0.95

Data presented as mean (standard deviation) at baseline except where noted. ASYM = asymptomatic group, BMI = body mass index, JSN = joint space narrowing, KL = Kellgren Lawrence, OA = osteoarthritis group, PF = patellofemoral, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

§ Between-group differences were examined with chi square tests (sex), Mann-Whitney U-tests (radiographic scores, WOMAC scores, and time between sessions), or student's t-tests (demographics and strength)

† Strength data unavailable for n = 1 ASYM and n = 2 OA individuals

‡ Radiographic scores unavailable for n = 1 ASYM individual

Of the 85 participants, 38 were diagnosed with medial compartment knee OA and 47 were asymptomatic (ASYM). OA was diagnosed by a single high-volume orthopedic surgeon according to clinical and radiographic criteria (R. Altman et al. 1986). Medial compartment knee OA was determined by the presence of medial knee pain and medial tibiofemoral joint space narrowing (JSN) (W. W. Scott, Jr. et al. 1993) that was greater than or equal to lateral JSN. Individuals who had previously undergone a total knee arthroplasty (TKA) or high tibial osteotomy (HTO) on the study leg or were on a waitlist for either TKA or HTO, were under 35 years old, or who had any cardiovascular, neuromuscular, or musculoskeletal conditions other than knee OA that would affect walking gait or the safety of the participant during data collection were excluded as per the original study criteria.

Sample characteristics, including demographic variables, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores, radiographic scores, and strength data were also collected according to standard protocols as part of the original studies (G. L. Hatfield et al. 2015b, J. L. Astephen Wilson et al. 2016). Standing anterior-posterior and lateral view radiographs were scored by a single high-volume orthopedic surgeon for Kellgren-Lawrence (KL) grade (J. H. Kellgren and J. S. Lawrence 1957) and JSN (W. W. Scott, Jr. et al. 1993). We have previously reported high intra-rater reliability for these scores for this rater (G. L. Hatfield et al. 2015b, J. L. Astephen Wilson et al. 2016). Maximum voluntary isometric contractions targeting the knee extensors, flexors, and plantar flexors were performed on a Cybex dynamometer (Lumex, NY) to collect the strength data (protocol described in detail in (C. L. Hubley-Kozey et al. 2006)). The OA group was older, with a higher mass and body mass index, higher radiographic (KL) and clinical (WOMAC) scores, and lower knee extension, knee flexion, and plantar flexion strength than the ASYM group (Table 5.1), as might be expected due to the relationships between OA and these variables. There was also a higher ratio of men to women in the OA group versus the ASYM group (Table 5.1). Due to these demographic and clinical differences, between-group differences in certain accelerometer metrics (particularly MVPA and step count) were expected based on previous research (D. D. Dunlop et al. 2011). This allowed us to investigate whether

these expected between-group differences could be detected in both average data from multiple one-week sessions of accelerometer wear during a year and data from a single session of accelerometer wear, i.e. whether there were interactions between group and number of sessions averaged. There was no difference between groups in time between sessions in either the full cohort with at least two-sessions of accelerometer data or the sub-cohort that had three sessions of accelerometer data.

5.3.2 Accelerometer Data Collection

At baseline and beginning at 6-months and 12-months after baseline, participants wore a GT3X+ accelerometer (ActiGraph™, Pensacola, FL, USA) for one-week. The accelerometers were worn approximately over the anterior superior iliac spine (P. S. Freedson et al. 2011) during all waking hours for 7 days, except during water-based activities (e.g. bathing, showering, swimming). Participants were given a demonstration on proper device placement in the laboratory at baseline and written instructions along with a diagram for all sessions. Participants also kept written logs in which they recorded the time the accelerometer was put on each morning and taken off each night as well as start and stop times for any activities done in the morning, afternoon, and evening of each day.

5.3.3 Accelerometer Data Processing

Data was collected at 30 Hz and resampled to 1-minute epochs within the ActiLife software (ActiGraph, Pensacola, FL, USA). The data was transformed within ActiLife into units of counts per minute (CPM), where CPM is a composite metric describing the frequency and intensity of accelerations. Wear time validation was performed using a non-wear criteria of at least 90 minutes of zero activity counts with a 2 minute non-zero spike tolerance (L. Choi et al. 2011), based on recommendations for individuals with OA (J. Song et al. 2010). The data for each individual from this wear time validation was also compared with written logs to ensure validity. For 2 individuals in the OA group (3 sessions total) who reported being “mostly sedentary” during the days on which they wore the accelerometer,

data was reprocessed without the Song et al. non-wear threshold to include this data as valid wear time because visual inspection of the data did confirm some activity during the reported times. This included one session for a man that had two sessions of data and two sessions for a woman that had three sessions of data. A session with at least 4 days of 10 or more hours of valid wear time per day was considered a valid session and included in the analysis (L. Choi et al. 2011). Of the 85 individuals (38 OA, 47 ASYM) who had valid data for 2 sessions, 43 of those (18 OA, 25 ASYM) also had valid data for a third session.

Each minute of valid data was then categorized into an intensity level using previously defined standard cut points (P. S. Freedson et al. 1998): sedentary behavior (SED, 0-99 CPM), light PA (LPA, 100-1951 CPM), or moderate-to-vigorous PA (MVPA, 1952+ CPM). Daily totals were averaged over the week of accelerometer wear to obtain daily average minutes in each intensity for each session. To account for possible differences in minutes of accelerometer wear between groups, sessions, or individuals, these values (SED, LPA, and MVPA) were also expressed as a percent of total wear time (E. Aadland and E. Ylvisaker 2015). Average daily step count (steps/day) was automatically calculated in ActiLife over the week of accelerometer wear for each session according to proprietary manufacturer formulas.

5.3.4 Statistical Analysis

A general linear model (GLM) was used to examine the effects of number of sessions averaged (within-subjects factor) and group (between-subjects factor) for each accelerometer-derived variable (wear time (minutes/day), SED (minutes/day), LPA (minutes/day), MVPA (minutes), SED (% wear time), LPA (% wear time), MVPA (% wear time), and step count (steps/day)). Using data from the full cohort of 85 individuals, *SESSIONS* was a two-level within-subjects factor (single session or 2-session average) and *GROUP* was a two-level between-subjects factor (OA or ASYM). Significance was set at $\alpha < 0.05$. In the smaller cohort of individuals with three complete accelerometer sessions (n = 43), *SESSIONS* was a three-level within-subjects factor (single session, 2-session average, or 3-session average) and *GROUP*

was again a two-level between-subjects factor (OA or ASYM). Post-hoc, differences among the repeated metric, *SESSIONS*, were examined where appropriate using a Bonferroni correction to α.

Bland Altman analyses (J. M. Bland and D. G. Altman 1986) were used to examine agreement for each accelerometer variable between a single session and a two-session average for both the full cohort and smaller sub-cohort with data for all three sessions, and between a two-session average and a three-session average for the smaller sub-cohort with data for all three sessions. Paired t-tests were used to examine whether the difference between the two measurements (bias) was significantly different from zero. Limits of agreement from the Bland Altman analyses gave an estimate of variation at the individual level between using a single session and a two-session average or between a two-session average and a three-session average. All statistical analyses were performed in SPSS (IBM, Armonk, USA).

5.4 Results

5.4.1 Single Session Versus Two-Session Average

In the full cohort with at least two sessions, there were a few statistically significant main effects of *SESSIONS*: both wear time and SED (minutes) had lower two-session average values than single session values ($p < 0.01$ for both). SED was still lower in the two-session average versus single session when expressed as percent of wear time ($p = 0.05$) (Table 5.2). As expected, there were main effects of *GROUP* including lower wear time, SED (minutes and % wear time), MVPA (minutes and % wear time), and step count in OA compared to ASYM, but higher LPA (minutes and % wear time) in OA compared to ASYM.

5.4.2 Single Session Versus Two- Or Three-Session Average

In the sub-cohort that had three valid sessions of data, there were main effects of *SESSIONS* for wear time (where the single session wear time was higher

than the two- or three-session average time, p = 0.05) and SED in minutes (where post-hoc tests showed a trend, p = 0.06, towards higher single session SED than two- or three-session average SED) but not in % wear time (Table 5.3). There were also main effects of *GROUP* with lower wear time, SED (minutes but not % wear time), MVPA (minutes and % wear time), and step count in OA compared to ASYM, as well as higher LPA (minutes and %) in the OA group compared to ASYM.

5.4.3 Bland Altman Analyses

For the full cohort, when comparing a two-session average to a single session value, the systematic bias was low (not significantly different from zero) for LPA (minutes), MVPA (minutes), LPA (%), MVPA (%), and step count (Table 5.4, Figure 5.1). The limits of agreement, however, indicated that using a two-session average versus a single session may result in differences of ± 53 minutes for LPA, ± 20 minutes for MVPA, ± 6% for LPA (%), ± 2.5% for MVPA (%), and ± 2100 steps for step count for an individual (Table 5.4, Figure 5.1). There was no evidence of proportional bias in these metrics with the exception of MVPA (minutes or %) where the differences between the two-session average and single session MVPA were greater for individuals with higher MVPA (Figure 5.1). Bland Altman analysis plots for all variables are presented in Appendix B.

Table 5.2 Accelerometer data for OA and ASYM groups over two data collection sessions

	SESSIONS	*GROUP*			*P*		
		OA (n = 38)	ASYM (n = 47)	*Combined*	Inter-action	Main effect: *SESS.*	Main effect: *GRP.*
Wear time (min)	1	856 (87)	898 (76)	**879 (84)**	0.24	**<0.01**	**0.04**
	Avg. of 2	845 (80)	876 (78)	**862 (80)**			
	Combined	**851 (82)**	**887 (74)**				
SED (min)	1	535 (103)	604 (90)	**573 (102)**	0.50	**<0.01**	**<0.01**
	Avg. of 2	520 (103)	583 (84)	**555 (98)**			
	Combined	**527 (100)**	**593 (86)**				
LPA (min)	1	299 (82)	252 (56)	273 (72)	0.60	0.71	**<0.01**
	Avg. of 2	300 (78)	250 (51)	272 (69)			
	Combined	**300 (79)**	**251 (51)**				
MVPA (min)	1	23 (16)	42 (25)	33 (24)	0.66	0.21	**<0.01**
	Avg. of 2	25 (18)	43 (25)	35 (24)			
	Combined	**24 (16)**	**42 (25)**				
SED (%)	1	62.3 (9.4)	67.1 (7.2)	**65.0 (8.6)**	0.64	**0.05**	**0.01**
	Avg. of 2	61.3 (9.8)	66.5 (6.4)	**64.2 (8.5)**			
	Combined	**61.8 (9.4)**	**66.8 (6.6)**				
LPA (%)	1	35.0 (9.2)	28.2 (6.0)	31.2 (8.3)	0.68	0.11	**<0.01**
	Avg. of 2	35.7 (9.3)	28.6 (6.6)	31.8 (8.2)			
	Combined	**35.4 (9.1)**	**28.4 (5.6)**				
MVPA (%)	1	2.6 (1.9)	4.7 (2.9)	3.8 (2.7)	0.74	0.06	**<0.01**
	Avg. of 2	3.0 (2.2)	4.9 (3.1)	4.1 (2.9)			
	Combined	**2.8 (1.9)**	**4.8 (2.9)**				
Step Count	1	6938 (2467)	8282 (2976)	7681 (2840)	0.48	0.92	**0.02**
	Avg. of 2	6841 (2419)	8354 (3015)	7678 (2865)			
	Combined	**6890 (2397)**	**8318 (2938)**				

Data presented as mean (standard deviation) in minutes per day (min), percent of wear time (%), or steps per day (for step count). P-values are presented from general linear models with # sessions averaged (SESS.) as a within subjects factor and group (GRP.) as a between subjects factor ($\alpha = 0.05$)
ASYM = asymptomatic group, LPA = light intensity physical activity, MVPA = moderate-vigorous physical activity, OA = osteoarthritis group, SED = sedentary behavior

Table 5.3 Accelerometer data for OA and ASYM groups over three data collection sessions

	SESSIONS	*GROUP*			*P*		
		OA (n = 19)	ASYM (n = 25)	*Combined*	Inter-action†	Main effect: *SESS.*	Main effect: *GRP.*
Wear time (min)	1	854 (84)	904 (92)	**883 (92) [A]**	0.14	**0.04**	**0.05**
	Avg. of 2	851 (72)	879 (89)	**867 (83) [B]**			
	Avg. of 3	849 (60)	882 (86)	**868 (78) [B]**			
	Combined	**851 (70)**	**889 (86)**				
SED (min)	1	542 (100)	614 (95)	**584 (103) [A]**	0.08	**0.01**	**0.05**
	Avg. of 2	541 (85)	588 (90)	**568 (91) [A]**			
	Avg. of 3	535 (80)	589 (92)	**566 (91) [A]**			
	Combined	**539 (86)**	**597 (91)**				
LPA (min)	1	294 (74)	247 (57)	267 (69)	0.94	0.73	**0.02**
	Avg. of 2	292 (63)	248 (47)	266 (59)			
	Avg. of 3	295 (68)	250 (49)	269 (62)			
	Combined	**294 (67)**	**248 (49)**				
MVPA (min)	1	18 (14)	43 (26)	33 (25)	0.88	0.86	**<0.01**
	Avg. of 2	18 (15)	43 (25)	33 (25)			
	Avg. of 3	19 (16)	43 (25)	33 (25)			
	Combined	**18 (15)**	**43 (25)**				
SED (%)	1	63.4 (8.8)	67.7 (7.0)	65.9 (8.1)	0.48	0.25	0.10
	Avg. of 2	63.5 (7.3)	66.7 (5.9)	65.4 (6.7)			
	Avg. of 3	63.0 (8.0)	66.5 (6.3)	65.1 (7.3)			
	Combined	63.3 (7.8)	67.0 (6.2)				
LPA (%)	1	34.5 (8.3)	27.4 (5.9)	30.4 (7.8)	0.44	0.27	**<0.01**
	Avg. of 2	34.4 (7.1)	28.3 (5.3)	30.9 (6.8)			
	Avg. of 3	34.8 (7.4)	28.5 (5.8)	31.1 (7.2)			
	Combined	**34.5 (7.5)**	**28.1 (5.5)**				
MVPA (%)	1	2.1 (1.7)	4.9 (3.0)	3.7 (2.9)	0.93	0.71	**<0.01**
	Avg. of 2	2.1 (1.8)	5.0 (3.1)	3.8 (3.0)			
	Avg. of 3	2.2 (2.0)	5.0 (3.0)	3.8 (2.9)			
	Combined	**2.1 (1.7)**	**4.9 (3.0)**				

	SESSIONS	*GROUP*			*P*		
		OA (n = 19)	ASYM (n = 25)	*Combined*	Inter-action†	Main effect: *SESS.*	Main effect: *GRP.*
Step count	1	6266 (1960)	8419 (3063)	7517 (2862)	0.63	0.76	**0.01**
	Avg. of 2	6091 (1968)	8456 (2973)	7466 (2850)			
	Avg. of 3	6169 (2164)	8560 (2951)	7559 (2901)			
	Combined	**6175 (1984)**	**8478 (2930)**				

Data presented as mean (standard deviation) in minutes per day (min), percent of wear time (%), or steps per day (for daily step count). P-values are presented from general linear models with # sessions averaged (SESS.) as a within subjects factor and group (GRP.) as a between subjects factor (α = 0.05). ASYM = asymptomatic group, LPA = light intensity physical activity, MVPA = moderate-vigorous physical activity, OA = osteoarthritis group, SED = sedentary behavior

†Bonferroni post-hoc comparisons for significant status by sex interactions are indicated by capital letters next to each group. Groups that do not share a letter were significantly different from each other.

In the sub-cohort that had three valid sessions, when comparing a single session to a two-session average, the systematic bias for LPA (minutes), MVPA (minutes), SED (%), LPA (%), MVPA (%), and step count was not different from zero and the limits of agreement were similar to those seen in the full cohort (Table 5.4). Again, there was evidence of proportional bias in MVPA, with a greater difference between the two-session average and single session MVPA for individuals that had higher MVPA. There was also evidence of proportional bias in LPA (minutes and %), with those that had higher LPA also having a higher value for the single session compared to the two-session average and those with lower LPA often having a lower value for the single session compared to the two-session average. A similar trend was seen in SED (%), although it was mainly driven by two OA individuals with low SED (%) values. Bland Altman plots are available in Appendix B.

In the sub-cohort with three sessions, when comparing a two-session average to a three-session average, the systematic bias was low for all variables, including SED (minutes), and the limits of agreement showed that using a three-session average versus a two-session average may result in differences of ± 45

minutes for SED, ± 37 minutes for LPA, ± 10 minutes for MVPA, ± 4% for SED (%), ± 4% for LPA (%), ± 1% for MVPA (%), and ± 1250 steps for step count (Table 5.4, Appendix B). There was no evidence of proportional bias in the three-session versus two-session average for any variable.

Table 5.4 Bland Altman Analyses

	Full cohort			**Sub-cohort with three sessions**					
	Single Session vs. Two Session Average			**Single Session vs. Two Session Average**			**Two Session vs. Three Session Average**		
	Bias	**95% CI Lower limit**	**95% CI Upper Limit**	**Bias**	**95% CI Lower limit**	**95% CI Upper Limit**	**Bias**	**95% CI Lower limit**	**95% CI Upper Limit**
SED (min)	-18†	-95	60	-15†	-89	58	-2	-48	44
LPA (min)	-1	-54	52	0	-56	55	3	-34	39
MVPA (min)	1	-19	21	0	-21	20	0	-9	10
SED (%)	-0.8†	-7.8	6.3	-0.6	-7.4	6.2	-0.3	-4.5	3.9
LPA (%)	0.5	-5.4	6.4	0.5	-5.3	6.3	0.3	-3.9	4.4
MVPA (%)	0.3	-2.2	2.7	0.1	-2.3	2.4	0.0	-1.1	1.2
Step count	-3	-2136	2130	-52	-2246	2142	93	-1160	1346

† Bias was significantly different from zero at $\alpha = 0.05$.

Data presented in minutes per day or % total wear time except for daily step count, which is presented as steps per day.

CI = confidence interval, LPA = light intensity physical activity, MVPA = moderate-vigorous physical activity, SED = sedentary behavior

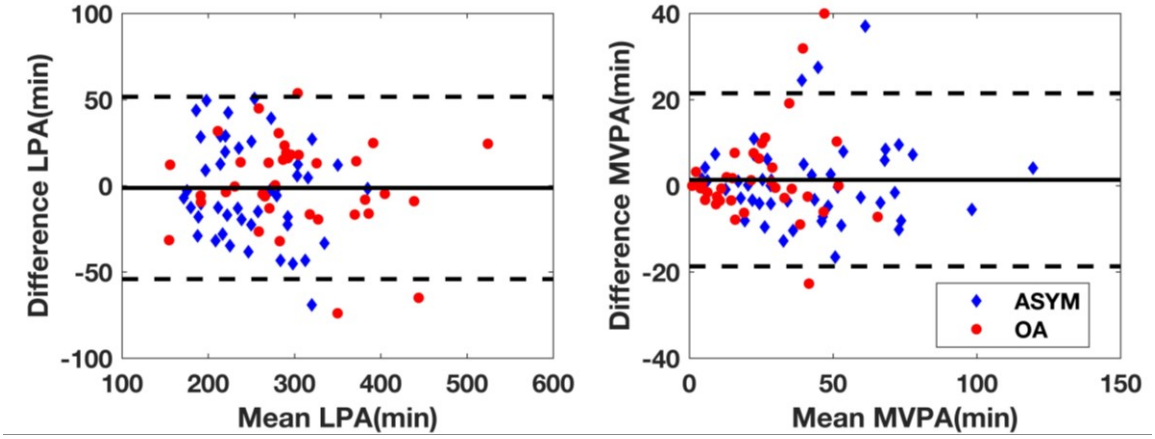

Figure 5.1 Example Bland Altman analysis plots comparing a two-session average to a single-session in the full cohort for LPA (minutes/day) and MVPA (minutes/day) where there is evidence of proportional bias in MVPA but not LPA

5.5 Discussion

With the growing use of accelerometer data in OA outcomes research, it is important to understand the degree to which variations in PA levels over time affect our ability to capture between-group differences in "habitual" PA levels at baseline. Using OA and ASYM groups as a model, this was the first study to show that the number of sessions averaged (1, 2, or 3) did not affect the ability to detect between group differences in SED, LPA, MVPA, or step count, and that the number of sessions averaged only affected estimates of SED across both groups. Despite this, the results also showed that differences in metrics derived from a single session versus an average of two- or three-sessions is quite high at an individual level.

One of the main findings of this study was the lack of significant interactions or main effects of *SESSIONS* for LPA and MVPA (whether expressed as absolute values in minutes or as a percent of wear time), and for step count. The lack of interactions means that the differences between-groups did not depend on the number of sessions averaged while the lack of main effects of *SESSIONS* means that there were not differences in the values of LPA, MVPA, and step count depending on the number of sessions averaged. This lends credibility to the results of previous studies of PA and OA outcomes that used a single week of data to derive these

accelerometer metrics (S. H. Liu et al. 2015, H. Tateuchi et al. 2016, N. M. Brisson et al. 2017, A. L. Gilbert et al. 2017, H. Tateuchi et al. 2017). At the individual level, however, the Bland Altman analyses showed differences of 53 minutes in LPA, 20 minutes in MVPA, and 2133 steps when using a single session value versus an average value from two sessions, amounting to approximately 19%, 63%, and 29% respectively, of the recorded LPA, MVPA, and step count in this study sample. Thus, if the between-group differences of interest are smaller than these values, averaging multiple sessions could provide more accurate estimates of habitual LPA, MVPA, and step count for the purposes of comparing between groups.

The differences in SED between the single session and the two- or three-session averages could have implications for study designs aimed at examining the effects of baseline SED on OA outcomes. While the differences were small between using a single session versus a two-session average (maximum of 18 minutes or <1% across sessions in the full cohort), these results support previous research showing that reliable metrics of SED require more days of monitoring than other PA metrics derived from accelerometer data (C. E. Matthews et al. 2002, T. L. Hart et al. 2011, E. Aadland and E. Ylvisaker 2015). This is especially of concern when trying to estimate habitual SED in an OA population, where less stringent criteria are already recommended for identifying non-wear time due to difficulties in distinguishing SED from accelerometer non-wear in this population (J. Song et al. 2010). In the current study, even when using these less stringent criteria, SED wear time was misclassified as non-wear time for 2 participants (total of 3 sessions). Despite this, the difference in SED among *SESSIONS* when expressed as a percent of wear time was only borderline significant ($p = 0.05$) in the full cohort and was not significant in the sub-cohort with three sessions, thus it may be acceptable to use a single week of data to determine SED if expressed as a percent of wear time or if the analysis corrects for wear time, as has been recommended previously (E. Aadland and E. Ylvisaker 2015).

The longer wear time seen in the single session compared to the two- or three-session averages may be a result of "good subject bias" (wanting to be diligent about wearing the accelerometer to look good for the researchers) (A. L. Nichols and

J. K. Maner 2008) or similarly, the effect of in-person interaction with the researchers at baseline compared to only telephone and mail contact at the other two time points. While this may be relevant to compliance in accelerometer wear, the investigation of wear time in this study was primarily undertaken to demonstrate the potential need for SED, LPA, and MVPA to be expressed as percentages of wear time instead of in absolute values (minutes). The maximum difference between the single session and the two- or three-session average wear times was only 26 minutes, or approximately 3% of total wear time, however, and wear time differences only appeared to affect SED in this sample.

The results of the Bland Altman analyses indicate fairly large differences at the individual level between using a single-session versus two- or three-sessions to calculate accelerometer metrics, which, in addition to affecting measurements of habitual PA, could be relevant to understanding the effects of PA interventions on individual patients. For example, the limits of agreement between a single session and two-session average for MVPA were approximately ± 20, which is the same as the difference between the OA and ASYM groups. Thus, if an individual with OA was working on increasing their MVPA levels and only a single session was recorded to determine their level of improvement, they might appear to have improved to the average level of the ASYM group if a particularly active week was recorded while a two-session average might show that they are actually still close to the average of the OA group. This finding is also supported by research from Bergman, who found that greater than 7 days of monitoring is needed to capture PA to within 20% of habitual levels in adults (P. Bergman 2018). Slightly higher limits of agreement were found in a study of three consecutive weeks of monitoring in adults (± 58 minutes for LPA and ± 44 minutes for MVPA) (E. Aadland and E. Ylvisaker 2015), which may reflect lower levels of PA in the OA population in the current study, but also supports the current finding of high variability at the individual level. At the very least, the results of the current study indicate that care should be taken to control or adjust for factors that could affect physical activity levels (e.g. weather or symptoms) when monitoring changes in PA levels in an individual patient.

The proportional bias in MVPA (in minutes and as a percent of total PA) may be due to the fact that participants who had very low MVPA in one session typically had consistently low MVPA across all sessions (i.e. they were generally not engaging in MVPA thus had little variance in that measure compared to individuals who did regularly engage in MVPA). The proportional bias in LPA in the sub-cohort for the single session compared to the two-session average could indicate an effect of good subject bias in those with low PA levels (where they may have increased LPA for the first but not subsequent accelerometer sessions), but may simply be due to the smaller sample size in the sub-cohort, as there was no proportional bias seen in LPA between the single session and two-session average in full cohort.

The higher limits of agreement for LPA versus MVPA suggest that interventions to increase LPA in this population could be more successful than interventions to increase MVPA, as this indicates that the individuals in the current study do engage in higher LPA but just do not do so consistently throughout a year. Further research is needed, however, to understand the distribution of PA among intensity categories in the OA population and caution should be taken in interpreting between group differences in the accelerometer metrics reported in this study in light of the stated differences in group characteristics (Table 5.1). As stated earlier, these groups were used as a model because of the expected differences in PA metrics and the goal was not to investigate between group differences but rather the ability to detect these differences using a single session of accelerometer data compared to an average of multiple sessions over a year.

In conclusion, future studies investigating accelerometer-based PA measures, including LPA, MVPA, and step count, for use in OA outcomes research may be able to use a single one-week session of accelerometer wear to examine the effects of habitual baseline PA on outcomes at the group level. Caution should be taken, however, in using a single session to calculate SED, as it may need to be expressed as a percent of wear time, or to examine differences at the individual level, as the natural variability of PA metrics within an individual can be quite high during the course of a given year.

Chapter 6. Physical Activity Is Accumulated In Different Intensities In Women And Men With Symptomatic Versus Asymptomatic Knee Osteoarthritis

6.1 Abstract

Objective: Physical activity has been shown to reduce pain and improve function in individuals with knee osteoarthritis, but physical activity in individuals with osteoarthritis, particularly in women, is often below recommended levels. The aim of this study was to compare step count and physical activity accumulated in different intensities between symptomatic and asymptomatic women and men with radiographic signs of osteoarthritis to investigate the effects of clinical symptoms and sex on physical activity levels.

Methods: Forty-two symptomatic individuals (14 women, 28 men) and 56 asymptomatic individuals (36 women, 20 men) wore a tri-axial accelerometer for one week. Step count, physical activity in light and moderate-to-vigorous intensity, and sedentary behavior were compared among the four groups using two-way analysis of variance for clinical status and sex.

Results: Light intensity physical activity was higher in symptomatic versus asymptomatic individuals. In women this was due to lower moderate-to-vigorous physical activity in the symptomatic group, while in men it was due to lower sedentary behavior in the symptomatic group. Symptomatic men and women differed only in step count. Step count was affected by both sex and clinical status.

Conclusions: The distribution of physical activity in different intensities may be affected by both the presence of osteoarthritis symptoms and sex. Light intensity physical activity was engaged in more often by symptomatic individuals, suggesting that light, rather than moderate-to-vigorous, intensity physical activity may be more achievable in this population, but it may also represent disparities in clinical advice

on physical activity and pain control strategies between the sexes. Future studies on physical activity should take both clinical status and sex into account.

6.2 Introduction

Physical activity (PA) is of interest in knee osteoarthritis (OA) as a potential treatment avenue. It has been shown to reduce pain and improve function (M. Fransen et al. 2015) and is currently recommended in many OA treatment guidelines (M. C. Hochberg et al. 2012, L. Fernandes et al. 2013, T. E. McAlindon et al. 2014). While individuals with OA do express interest in PA programs (A. M. Davis et al. 2016) and view the potential symptom benefits of PA as a facilitator to engaging in PA (U. Petursdottir et al. 2010, F. Dobson et al. 2016), PA in the OA population is low (C. C. Winter et al. 2010, A. Holsgaard-Larsen and E. M. Roos 2012) with many individuals not meeting PA guidelines (J. A. Wallis et al. 2013). In order to determine how PA levels could be improved in individuals with OA, a better understanding of how individuals with OA accumulate PA, and the factors that influence this, is needed.

Despite viewing potential symptom benefits as a facilitator of PA, individuals with OA report current pain levels and fear of negative consequences (e.g. worse symptoms) as deterrents to engaging in PA (U. Petursdottir et al. 2010, F. Dobson et al. 2016). OA symptoms have also been implicated in low PA levels using a more objective (accelerometer) measurement of PA. Song et al. (J. Song et al. 2018) found that higher levels of pain (categorized using the Intermittent and Constant Osteoarthritis Pain (ICOAP) instrument (G. A. Hawker et al. 2008)) were associated with lower levels of moderate to vigorous intensity PA (MVPA), but not light intensity PA (LPA). These results suggest that clinical symptoms of OA influence PA levels, particularly higher intensity PA, but in this study there was no indication whether these results differed between women and men.

Sex-based differences in PA levels have been identified in both the general population (R. P. Troiano et al. 2008, J. M. Tucker et al. 2011) and in those with knee OA (J. N. Farr et al. 2008, D. D. Dunlop et al. 2011), where women typically engage in

less MVPA than men and are less likely to meet PA guidelines based on MVPA (U.S. Department of Health and Human Services 2008). Interestingly, higher daily MVPA and higher daily step count have been associated with higher daily pain in older adult women but not men (A. Ho et al. 2016), which suggests that in OA, clinical symptoms such as pain may affect PA differently in women versus men. Given the higher rates and greater severity of radiographic and symptomatic OA (V. K. Srikanth et al. 2005) and higher rates of total knee arthroplasty (TKA) in women compared to men (S. N. Williams et al. 2015), understanding interactions between clinical status (symptomatic versus asymptomatic) and sex (women versus men) may not only provide insight into how PA is accumulated in different sub-populations in OA but could also provide insight into these different rates of OA and OA progression in women versus men.

Achieving 150 minutes per week of MVPA in bouts of 10 minutes or longer has been a target in PA guidelines (U.S. Department of Health and Human Services 2008). Newer guidelines highlight that PA of any intensity has health benefits when replacing sedentary behavior (SED) (U.S. Department of Health and Human Services 2018), thus it is of interest to quantify the amounts of SED, LPA, and MVPA in relation to sex and clinical status to understand where improvements in PA participation can be made across the OA population. Achieving 10,000 steps per day is a popular PA target in the media (C. Tudor-Locke and D. R. Bassett, Jr. 2004) and step count is also of interest as it has been used as a surrogate metric of joint loading frequency to explore how joint loading is related to OA outcomes (e.g. (N. M. Brisson et al. 2017)). Thus, exploring differences in step count related to sex and clinical status could help inform future study design by identifying whether sex or clinical status should be included as factors in these studies.

The objective of the current study was to determine whether clinical status (symptomatic or asymptomatic), sex (women or men), or their interaction affect step count, SED, LPA, or MVPA in individuals with radiographic knee OA. We hypothesized that women would have lower overall PA compared to men and that there would be a greater difference between symptomatic and asymptomatic women than between symptomatic and asymptomatic men.

6.3 Methods

6.3.1 Participants

As a sub-objective of two longitudinal studies of gait and medial tibiofemoral compartment knee OA progression (G. L. Hatfield et al. 2015b, J. L. Astephen Wilson et al. 2016), objective physical activity data was collected from 134 individuals. The original study exclusion criteria were age under 35 years, primarily lateral knee pain, any health conditions other than knee OA that would affect participant safety or walking gait, and high tibial osteotomy (HTO), TKA, or being on a waitlist for TKA or HTO. Sixty-seven of the 134 participants (symptomatic group) had been diagnosed with medial tibiofemoral compartment knee OA by a high-volume orthopedic surgeon according to clinical and radiographic criteria (R. Altman et al. 1986). The remaining 67 individuals (asymptomatic group) had responded to a study recruitment call for individuals without knee OA or pain, and self-reported no prior clinical diagnosis of knee OA. All participants had the study protocol explained to them and signed Nova Scotia Health Authority Research Ethics Board-approved informed consent forms before participating.

All participants underwent standard, standing anterior-posterior and lateral view radiographs if they had not had radiographs taken within the preceding year as part of their clinical care. These radiographs were scored for Kellgren-Lawrence (KL) grade (J. H. Kellgren and J. S. Lawrence 1957) and joint space narrowing (JSN) (W. W. Scott, Jr. et al. 1993) by a single orthopedic surgeon who was blinded to clinical status (symptomatic or asymptomatic). Radiographic scores were unavailable for 3 symptomatic men and 6 asymptomatic individuals (4 women, 2 men), who were subsequently excluded from further analysis. To better match the symptomatic and asymptomatic groups in terms of radiographic severity only individuals with KL scores of 2 or 3 were included in the final analysis.

6.3.2 Data Collection

Participants wore a GT3X tri-axial accelerometer (ActiGraph, Pensacola, FL, USA) attached approximately over the anterior-superior iliac spine on the side of the test leg (more symptomatic leg for the symptomatic group and randomly chosen leg for the asymptomatic group, modified for this population from (P. S. Freedson et al. 2011)) for one week. This study length has previously been found to sufficiently capture habitual PA differences between groups (**Chapter 5**). Participants were instructed to wear the device during all waking hours except during water-based activities (e.g. bathing, showering, swimming). Proper device placement was explained and demonstrated in the laboratory and participants were given written instructions and a diagram to take home. Participants were also asked to keep written logs in which they recorded the time the accelerometer was put on in the morning and taken off at night, as well as start and stop times for any activities done in the morning, afternoon, and evening of each day.

6.3.3 Data Processing

One individual (symptomatic man) did not return the device and was excluded. The data from the remaining participants, recorded initially at 30 Hz, was resampled to one-minute epochs within the ActiLife software (ActiGraph, Pensacola, FL, USA) where the recorded three-dimensional accelerations were transformed into units of counts per minute (CPM).

Wear time validation was performed using Choi et al. (L. Choi et al. 2011) non-wear criteria of 90 minutes of zero activity counts (with a 2 minute non-zero spike tolerance), in accordance with recommendations for individuals with knee OA (J. Song et al. 2010). Additionally, the wear time validation analysis from ActiLife was compared with written activity logs to ensure validity. Each individual was required to have at least 4 days with 10 or more hours per day of valid wear time to be included in the analysis (L. Choi et al. 2011). Three symptomatic women and one asymptomatic man did not meet these minimum wear time requirements and were excluded from further analysis. This left a final sample size of 98: 42 symptomatic

individuals (14 women, 29 men) and 56 asymptomatic individuals (36 women, 20 men).

Each minute was then categorized into an intensity level using Freedson et al. cut points (P. S. Freedson et al. 1998): sedentary behavior (SED, 0-99 CPM), light PA (LPA, 100-1951 CPM), and moderate-to-vigorous PA (MVPA, 1952+ CPM), and daily totals were averaged over the week of accelerometer wear to obtain daily average minutes in each intensity for the week. These values were also calculated as percent of wear time to account for potential differences in accelerometer wear time among individuals (E. Aadland and E. Ylvisaker 2015). Average daily step count (steps/day) for the week was automatically calculated in ActiLife according to proprietary manufacturer formulas.

6.3.4 Statistical Analysis

Continuous data were checked for normality and equal variance using Shapiro-Wilk and Levene's tests, respectively. Logarithmic or Johnson (N. L. Johnson 1949) transformations were used to transform data in cases of non-normal distributions. Two-way analysis of variance (ANOVA) tested for main effects of group and sex and their interaction on physical activity metrics ($\alpha = 0.05$). When significant interactions were found, post-hoc Tukey tests were performed. To account for the possible confounding effects of covariates, two sensitivity analyses were performed by including KL grade only, and including KL grade, age, and body mass index (BMI) as covariates in the two-way ANOVA.

6.4 Results

All individuals included in the final sample (both symptomatic and asymptomatic) had radiographic signs of OA with KL grades of 2 or 3. The excluded group consisted of n = 15 individuals with incomplete data (9 radiographic, 5 accelerometer, 1 radiographic and accelerometer), 4 asymptomatic individuals (2 women, 2 men) with KL grades of 1, and 17 symptomatic individuals (7 women, 10 men) with KL grades of 4. The included group had a higher percentage of women

and higher radiographic scores than the excluded group but a similar percentage of symptomatic individuals and similar age, mass, and BMI as the excluded group (Table 6.1). There was also a trend towards higher Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores in the excluded group. Within those that were included in the final analysis, consistent with their clinical OA status, symptomatic women and men had higher WOMAC scores than asymptomatic women and men (Table 6.2). Despite only including individuals with KL = 2 or 3, radiographic severity was also significantly higher in the symptomatic group (Table 6.2).

Table 6.1 Group characteristics for included and excluded individuals

	Excluded (n = 36)	Included (n = 98)	*P*†
Women:Men (%Women)	16:20 (44%)	50:48 (51%)	**0.01**
Symptomatic:Asymptomatic (%SYM)	23:13 (64%)	42:56 (43%)	0.50
Age (years)	60.3 (9.0)	57.8 (8.1)	0.16
Mass (kg)	84.5 (20.3)	83.0 (16.7)	0.74
BMI (kg/m^2)	29.8 (6.1)	28.9 (4.9)	0.60
Radiographic scores*			
KL grade (1, 2, 3, 4)	4, 4, 1, 17	0, 61, 37, 0	**<0.01**
Medial JSN (0, 1, 2, 3)	2, 6, 3, 15	3, 56, 39, 0	**<0.01**
Lateral JSN (0, 1, 2, 3)	8, 11, 5, 2	56, 36, 6, 0	**<0.01**
PF JSN (0, 1, 2, 3)	6, 7, 11, 2	23, 66, 7, 2	**0.01**
WOMAC			
Pain (/20)	3.2 (3.7)	2.0 (3.3)	0.06
Stiffness (/8)	1.7 (1.8)	1.0 (1.3)	0.06
Function (/68)	10.8 (12.7)	6.9 (9.8)	0.07

BMI = body mass index, JSN = joint space narrowing, KL = Kellgren Lawrence, PF = patellofemoral, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

†Chi square tests used for sex and clinical status, Mann-Whitney U-tests for all others

*Radiographic scores missing for n = 10 excluded individuals

The accelerometers were worn for an average of 6.3 ± 0.9 days for 14.6 ± 1.3 hours per day. There was no interaction between clinical status and sex for the

amount of time the accelerometers were worn, however, asymptomatic individuals wore them for longer than symptomatic individuals and men wore them for longer than women (Table 6.3). When including KL grade as a covariate, the clinical status difference in wear time was no longer significant, and when including KL grade, age, and BMI as covariates there were no significant main effects of status or sex on wear time.

There were significant clinical status by sex interactions for SED and MVPA, both when expressed in minutes or as a percent of total time worn (Table 6.3). Asymptomatic men had greater minutes in SED compared to both asymptomatic women ($p = 0.02$) and symptomatic men ($p < 0.01$), with a trend towards greater minutes in SED compared to symptomatic women as well ($p = 0.08$). Post-hoc analysis of the interaction in SED (%) identified a difference between asymptomatic and symptomatic men only ($p = 0.01$). Asymptomatic women had greater minutes and percent of time worn spent in MVPA compared to all three other groups (Table 6.3). There was a main effect of clinical status for both minutes and percent of time worn spent in LPA, where symptomatic individuals engaged in a greater amount of LPA than asymptomatic individuals (Table 6.3). Last, there was a significant interaction for step count with post-hoc analysis identifying that symptomatic women had lower step count than asymptomatic women ($p < 0.01$). Symptomatic women also had lower step count than symptomatic men ($p = 0.01$) and asymptomatic women had greater step count than asymptomatic men ($p = 0.05$). There was no difference between asymptomatic and symptomatic men ($p = 0.45$). Adjusting for KL grade or KL grade, age, and BMI did not change which results were significant with the exception of LPA (minutes), where the main effect of group became non-significant, although still had a low p-value ($p = 0.07$), when including KL grade, age, and BMI as covariates. The main effect of group on LPA (%), however, remained even after adjusting for covariates.

Table 6.2 Group characteristics by sex (women versus men) and clinical status (symptomatic versus asymptomatic)

Sex	Women		Men		*P*		
Clinical Status	Symptomatic (n = 14)	Asymptomatic (n = 36)	Symptomatic (n = 28)	Asymptomatic (n = 20)	Status by Sex†	Status	Sex
Age (years)	61.1 (8.6)	54.3 (7.4)	61.1 (5.7)	57.1 (9.4)	0.39	**<0.01**	0.40
Mass (kg)	81.7 (15.8)	72.0 (13.7)	94.2 (13.9)	87.8 (14.2)	0.60	**0.01**	**<0.01**
BMI (kg/m^2)	31.1 (6.3)	27.1 (4.6)	30.3 (4.1)	28.3 (4.7)	0.40	**<0.01**	0.68
Radiographic severity							
KL grade (1, 2, 3, 4)	0, 4, 10, 0	0, 31, 5, 0	0, 7, 21, 0	0, 19, 1, 0	0.44	**<0.01**	0.74
Medial JSN (0, 1, 2, 3)	0, 5, 9, 0	0, 29, 7, 0	1, 7, 20, 0	2, 15, 3, 0	0.39	**<0.01**	0.60
Lateral JSN (0, 1, 2, 3)	9, 4, 1, 0 ^{A}	18, 15, 3, 0 ^{A}	13, 13, 2, 0 ^{A}	16, 4, 0, 0 ^{A}	**0.03**	0.33	0.43
PF JSN (0, 1, 2, 3)	4, 9, 0, 1 ^{AB}	10, 25, 1, 0 ^{A}	1, 20, 6, 1 ^{B}	8, 12, 0, 0 ^{A}	**0.03**	**<0.01**	0.32
WOMAC							
Pain (/20)	3.9 (4.0)	0.8 (2.2)	3.0 (3.6)	1.5 (2.9)	0.26	**<0.01**	0.92
Stiffness (/8)	1.6 (1.4)	0.6 (1.1)	1.5 (1.5)	0.7 (1.2)	0.56	**<0.01**	0.95
Function (/68)	13.5 (11.8)	3.1 (7.1)	9.9 (10.0)	4.7 (8.8)	0.19	**<0.01**	0.60

Data presented as mean (standard deviation) except where noted. BMI = body mass index, JSN = joint space narrowing, KL = Kellgren Lawrence, PF = patellofemoral, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

† Tukey post-hoc comparisons for significant clinical status by sex interactions are indicated by capital letters next to each group. Groups that do not share a letter were significantly different from each other.

Table 6.3 Physical activity outcomes by clinical status and sex

		Clinical status			*P*		
	Sex	Symptomatic	Asymptomatic	*Combined*	Status by Sex†	Status	Sex
Wear time	Men	869 (81)	925 (82)	**891 (85)**	0.20	**0.04**	**0.03**
(min)	Women	853 (67)	867 (68)	**863 (68)**			
	Combined	**864 (77)**	**888 (78)**				
SED	Men	**535 (99)^{B}**	**644 (99)^{A}**	580 (112)	**0.01**	0.01	0.23
(min)	Women	**565 (84)^{AB}**	**565 (88)^{B}**	565 (86)			
	Combined	545 (94)	593 (99)				
LPA	Men	304 (90)	250 (63)	282 (83)	0.34	**0.02**	0.51
(min)	Women	273 (66)	253 (53)	258 (57)			
	Combined	**294 (83)**	**252 (56)**				
MVPA	Men	**31 (19)^{B}**	**30 (22)^{B}**	31 (20)	**<0.01**	<0.01	0.75
(min)	Women	**15 (7)^{B}**	**49 (29)^{A}**	40 (29)			
	Combined	26 (18)	42 (28)				
SED	Men	**62 (10)^{B}**	**70 (8)^{A}**	65 (10)	**0.01**	0.07	0.99
(%)	Women	**66 (8)^{AB}**	**65 (8)^{AB}**	65 (8)			
	Combined	63 (10)	67 (8)				
LPA	Men	35 (10)	27 (7)	32 (9)	0.16	**<0.01**	0.93
(%)	Women	32 (8)	29 (7)	30 (7)			
	Combined	**34 (9)**	**29 (7)**				

		Clinical status			*P*		
	Sex	Symptomatic	Asymptomatic	*Combined*	Status by Sex†	Status	Sex
MVPA	Men	**4 (2)^{B}**	**3 (2)^{B}**	3 (2)	**<0.01**	0.01	0.66
(%)	Women	**2 (1)^{B}**	**6 (3)^{A}**	5 (3)			
	Combined	3 (2)	5 (3)				
Step count	Men	**8037 (2626)^{AB}**	**6879 (2428)^{BC}**	7554 (2584)	**<0.01**	0.04	0.54
	Women	**5471 (1800)^{C}**	**9160 (3494)^{A}**	8127 (3518)			
	Combined	7182 (2659)	8345 (3320)				

Data presented as daily mean (standard deviation) in minutes per day (min), percent of wear time (%), or steps per day (for step count). LPA = light intensity physical activity, MVPA = moderate to vigorous intensity physical activity, SED = sedentary behavior.

† Tukey post-hoc comparisons for significant clinical status by sex interactions are indicated by capital letters next to each group. Groups that do not share a letter were significantly different from each other.

6.5 Discussion

This is the first study to examine the effects of clinical OA status, sex, and their interaction on PA in a group of individuals that all had radiographic signs of OA. Our hypothesis that women would have lower overall PA levels than men was only partially supported. Step count (but not LPA or MVPA) was lower in symptomatic women compared to symptomatic men, but asymptomatic women had higher step count and MVPA than asymptomatic men (with no difference in LPA). We also hypothesized that there would be greater differences between asymptomatic and symptomatic women than between asymptomatic and symptomatic men. Instead we found that symptomatic women engaged in PA for a similar percent of time as asymptomatic women, albeit in LPA rather than MVPA while symptomatic men engaged in PA (versus SED) for a greater percent of time than asymptomatic men, with the extra PA done in LPA.

The recently released update to the 2008 Physical Activity Guidelines for Americans (U.S. Department of Health and Human Services 2018) reports that newer evidence suggests MVPA done in bouts of any duration (rather than the previously recommended 10 minutes or longer) provide health benefits and count towards the total recommended volume of PA. In the current study, although there was a range of MVPA levels within each group, on average all groups except for symptomatic women would meet the recommended PA guideline of 150 min/week of MVPA. Furthermore, the updated guidelines (U.S. Department of Health and Human Services 2018) emphasize that replacement of SED with PA of any intensity contributes towards overall health. Both symptomatic women and men achieved higher levels of LPA compared to asymptomatic individuals, despite a lower level of MVPA in symptomatic compared to asymptomatic women, which suggests that symptomatic individuals are engaging in PA that will help them achieve health benefits. LPA has also been suggested to be beneficial for reduced risk of disability in OA (D. D. Dunlop et al. 2014, J. Lee et al. 2015, D. K. White et al. 2017). Thus while there appears to be a deficit in MVPA in symptomatic women compared to current

guidelines, symptomatic women and men are engaging in lower intensity PA that will provide health benefits and could help manage their OA symptoms.

The reason for higher LPA and lower SED in symptomatic compared to asymptomatic men is unclear but may be in response to advice from a healthcare team to engage in PA for OA symptom management. The lower MVPA and higher LPA in symptomatic women compared to asymptomatic women may be an attempt to reduce load on the joint and could represent concern that PA could cause further harm to the joint. Many individuals with OA express concern regarding negative consequences related to PA participation (U. Petursdottir et al. 2010, F. Dobson et al. 2016) and it has been reported that only 25% of individuals with OA who could benefit from advice on PA from a health professional actually receive it (L. C. Li et al. 2011). Thus, these differences may highlight a need for better education in women with OA regarding the effects of PA on OA.

Part of this education could be related to pain management and PA. Although WOMAC pain scores were similar between asymptomatic women and men and between symptomatic women and men in the current study (below a minimal clinically important difference (F. Angst et al. 2001)), women are more likely to report musculoskeletal pain than men (R. B. Fillingim et al. 2009) and women report greater pain at similar levels of radiographic severity, suggesting greater central sensitization in women than men (N. Glass et al. 2014, E. J. Bartley et al. 2016). As men may be less likely to report OA symptoms, it is possible that some of the "asymptomatic" men in the current study have experienced OA symptoms but have not yet received a clinical OA diagnosis due to lack of reporting. This could account for the surprising findings of greater PA in symptomatic compared to asymptomatic men and higher MVPA and step count in asymptomatic women compared to asymptomatic men.

Understanding the effects of sex and clinical status on PA may also be relevant to OA outcomes. Within the last decade, a few groups have explored using step count as a surrogate metric of joint loading frequency to approximate the total loading exposure, or cumulative load on the joint (M. R. Maly 2008, S. M. Robbins et al. 2009, S. M. Robbins et al. 2011, M. R. Maly et al. 2013, H. Tateuchi et al. 2016, N.

M. Brisson et al. 2017, H. Tateuchi et al. 2017). Due to the improvements in pain and function that have been reported with PA (M. Fransen et al. 2015) and the fact that PA is recommended in many treatment guidelines for OA (M. C. Hochberg et al. 2012, L. Fernandes et al. 2013, T. E. McAlindon et al. 2014), it is of interest to understand the relationships between joint loading due to PA and OA progression outcomes. Understanding these relationships could identify appropriate PA levels for individuals with OA that could prevent further structural damage and symptom progression. In the current study, step count was different between asymptomatic men and women, between symptomatic men and women, and between asymptomatic and symptomatic women. Thus, future studies exploring the relationships between joint loading frequency or cumulative load and OA progression should consider including sex and clinical status as factors in their analyses.

In the current study, symptomatic individuals had clinically meaningful higher WOMAC pain and function scores, and marginally higher WOMAC stiffness scores than asymptomatic individuals, in accordance with the asymptomatic group self-reporting no knee pain or diagnosis of knee OA. While there were also small group differences in KL grade, age, and BMI between symptomatic and asymptomatic groups, the results of the sensitivity analyses suggest that these covariates only had a slight influence on the group effect seen in LPA (in minutes), which was no longer significant, although still a small p-value ($p = 0.07$), after adjusting for these three covariates. The fact that including the covariates did not change the significant effects seen in LPA measured as a percent of wear time may highlight the importance of normalizing to wear time when investigating between-group differences (E. Aadland and E. Ylvisaker 2015).

The current study used data measured over a single week of accelerometer wear to estimate habitual PA levels. Due to large intra-individual variations in PA reported during a given year (S. Levin et al. 1999, E. S. Pedersen et al. 2016), particularly in SED (min) (**Chapter 5**), caution should be taken in interpreting the result that asymptomatic men engaged in greater minutes of SED than symptomatic men. Despite this, the large difference (109 minutes) between asymptomatic and

symptomatic men is greater than the variations that could be expected when using a single session versus an average of two sessions during a year (**Chapter 5**) and thus likely is an accurate representation of habitual SED differences between these two groups.

In conclusion, the effects of interactions between sex and clinical status on PA variables seen in this study provide insight for improving future research on PA in OA and potential opportunities for OA management. First, this study clearly demonstrates differences in how PA is accumulated between symptomatic and asymptomatic individuals with radiographic OA, supporting previous research showing OA symptoms are a deterrent to PA participation (M. Hendry et al. 2006, N. C. Gyurcsik et al. 2009, U. Petursdottir et al. 2010, F. Dobson et al. 2016), particularly for women. Future research should focus on homogenous populations, either clinically diagnosed OA only or asymptomatic radiographic OA only. Second, the results of this study suggest that lower PA reported in women versus men with OA is related to differences in the experience of OA symptoms in women versus men because only step count was different in symptomatic individuals between women and men, while asymptomatic women had greater MVPA than asymptomatic men. The higher LPA in both symptomatic groups (women and men) compared to the two asymptomatic groups suggests that increases in light rather than moderate-to-vigorous PA in individuals with symptomatic, clinical OA may be more achievable in this population and a way to achieve the health benefits of OA, however, the differences in this study may also represent disparities between women and men in advice received regarding using PA as a symptom management strategy in OA.

Chapter 7. Relationships Between Physical Activity, Gait, And Clinical Knee Osteoarthritis Progression

7.1 Abstract

Objective: Physical activity data collected with accelerometers can provide information about joint loading that is not captured by gait analysis, specifically a surrogate metric of joint loading frequency (step count) and the intensity in which that frequency is accumulated during daily life. This data may provide further insight into the relationships between joint loading and clinical osteoarthritis progression. The objectives of this study were 1) to determine whether joint loading magnitude/duration from gait data and joint loading frequency or physical activity intensity from accelerometer data were correlated, and 2) to explore differences in joint loading magnitude/duration, joint loading frequency and physical activity intensity between individuals who progress clinically (total knee arthroplasty endpoint) and those that do not at 3.5-year follow-up.

Methods: Fifty-seven individuals with knee osteoarthritis underwent baseline gait analysis and wore a tri-axial accelerometer for one week following gait analysis. Principal component analysis extracted major patterns of variation from gait waveforms. Spearman correlation coefficients were calculated between gait metrics that have been associated with osteoarthritis progression and accelerometer-derived metrics. Jonckheere-Terpstra tests for ordered alternatives examined gait patterns across quartiles of step count. Mann Whitney U-tests examined baseline differences in gait and accelerometer-derived metrics between individuals who progressed to total knee arthroplasty at 3.5-year follow-up and those that did not.

Results: Significant correlations were found between gait variables related to osteoarthritis progression and both step count and moderate to vigorous intensity physical activity. Inspection of gait variables across quartiles of step count revealed that individuals in the lowest step count quartile (averaging approximately 4000 steps/day) exhibited gait patterns that have been related to osteoarthritis

progression. The group that progressed clinically at 3.5 year follow-up had a higher overall knee adduction moment and prolonged vastus medialis activation through mid-stance at baseline compared to those who did not progress but there were no differences in step count or intensity-based physical activity metrics.

Conclusions: These results suggest that below a certain level of step count, joint loading frequency dictates joint loading magnitude or vice versa. Thus, information about joint loading frequency might only improve prediction of osteoarthritis progression outcomes in individuals above a certain threshold of step count. While the results of the longitudinal analysis support prior work showing baseline gait differences related to progression, a longer follow-up period may be needed to determine whether joint loading frequency or physical activity intensity metrics are also different between those who progress clinically and those who do not.

7.2 Introduction

Knee osteoarthritis (OA) is a highly prevalent and growing health burden (R. C. Lawrence et al. 2008, T. Vos et al. 2012, A. G. B. D. Obesity Collaborators: Afshin et al. 2017), for which there is no cure. Current treatment consists of symptom management followed by end-stage surgical interventions when appropriate (W. Zhang et al. 2008), however, this model of care does not address the underlying condition. A better understanding of the factors involved in OA progression could help identify targets for interventions to slow or stop progression.

Mechanical loading has been identified as a major factor in OA disease processes (K. D. Brandt et al. 2008, F. Guilak 2011). In humans, much attention has been paid to the knee adduction moment (KAM), considered a surrogate metric of medial to lateral tibiofemoral compartment joint loading ratio (D. E. Hurwitz et al. 1998). Higher KAM magnitude features have been linked to both structural (T. Miyazaki et al. 2002, A. Chang et al. 2007, K. L. Bennell et al. 2011, J. D. Woollard et al. 2011, E. F. Chehab et al. 2014, A. H. Chang et al. 2015, N. M. Brisson et al. 2017) and clinical OA progression, using total knee arthroplasty (TKA) as an endpoint (G. L. Hatfield et al. 2015b, G. L. Hatfield et al. 2015a). The knee flexion moment (KFM)

has also been examined given that can contribute to compressive loads on the joint, although evidence tying it to OA progression has been mixed. While a small longitudinal study found higher peak KFM was associated with a loss of cartilage thickness at 5-year follow-up (E. F. Chehab et al. 2014), this was not replicated in a large cohort study with a 2-year follow-up (A. H. Chang et al. 2015). The pattern of the KFM, however, and more specifically a smaller difference between early stance KFM and late stance knee extension moment, was associated with clinical progression (TKA endpoint) at 8-year follow-up (G. L. Hatfield et al. 2015b). Thus, the magnitude and/or patterns of joint moments during gait have been associated with both structural and clinical OA progression and may be suitable targets for interventions to slow OA progression.

Gait variables, however, only describe the magnitude and/or duration of load during as single step and thus do not describe the overall loading environment. Understanding whether joint loading frequency plays a role in OA progression could reveal further opportunities to intervene in the OA process. The influence of joint loading frequency on OA disease processes in humans has only recently been explored (N. M. Brisson et al. 2017, H. Tateuchi et al. 2017) using measures derived from accelerometers, specifically step count, as a surrogate metric of joint loading frequency (M. R. Maly 2008). While physical activity (PA), including walking, has been shown to improve symptoms in OA (M. Fransen et al. 2015) and thus is recommended in many OA guidelines (e.g. (T. E. McAlindon et al. 2014), higher OA pain has been found in individuals with higher step count (S. M. Robbins et al. 2011), suggesting there may be a complex relationship between joint loading frequency (step count) and OA disease processes. Despite this, only two studies have examined both joint loading magnitude/duration from gait data and joint loading frequency from accelerometer data in OA progression, with one investigating structural hip OA progression (H. Tateuchi et al. 2017) and the other investigating structural knee OA progression (N. M. Brisson et al. 2017). In the knee, Brisson et al. found that a model containing baseline KAM impulse and step count did not explain more variance in cartilage volume change over a 2.5-year period than a model without step count (N. M. Brisson et al. 2017), which could mean that joint loading frequency and joint

loading magnitude are related. This study also found, however, that a model with only step count and demographics (no KAM) did not improve prediction of structural progression over a model with demographics only. Thus further exploration of the correlations between joint loading frequency and joint loading magnitude/duration variables is warranted to help understand these results and determine if joint loading frequency provides additional information about the overall joint loading environment or if it is dictated by joint loading magnitude/duration (or vice versa). Furthermore, given the associations between walking and OA symptoms (S. M. Robbins et al. 2011, M. Fransen et al. 2015), it is also of interest to explore the relationships between baseline joint loading frequency and clinical OA progression (defined by a TKA outcome), where both structural joint damage and clinical symptoms are factors in progression, as these may differ from the relationships between baseline joint loading frequency and structural OA progression.

To understand whether or not joint loading frequency may be an important factor in clinical OA progression, the objectives of this study were: (1) to explore whether gait metrics that have previously been associated with either structural or clinical knee OA progression are correlated with an objective surrogate measure of joint loading frequency (step count) or PA intensity metrics derived from accelerometer data, and (2) to examine differences in baseline gait and accelerometer metrics between individuals who progressed clinically (to a TKA endpoint) versus those who did not at 3.5-year follow-up. This study tested the null hypotheses that (1) there would be no significant correlations between gait variables linked to OA progression and accelerometer variables, and (2) there would be no differences in accelerometer-derived variables at baseline between individuals who do and do not progress clinically.

7.3 Methods

7.3.1 Study Overview And Participants

As part of two longitudinal studies of gait and knee OA progression (C. L. Hubley-Kozey et al. 2006, J. L. Astephen Wilson et al. 2016), 57 participants with medial compartment knee OA participated in a gait data collection session between 2012 and 2015, and wore an accelerometer for one week following their gait data collection. All participants were diagnosed with knee OA by a single high-volume orthopedic surgeon (WDS) using clinical and radiographic criteria (R. Altman et al. 1986). At study entry, all participants were diagnosed with medial compartment involvement based on the presence of medial knee pain and medial tibiofemoral joint space narrowing (mJSN) greater than or equal to lateral joint space narrowing (W. W. Scott, Jr. et al. 1993). Exclusion criteria included any cardiovascular, neuromuscular, or musculoskeletal conditions other than knee OA that would affect gait or participant safety during testing, age under 35 years, and having undergone TKA or high tibial osteotomy (HTO) or being on a waitlist for TKA or HTO. All participants signed Nova Scotia Health Authority Research Ethics Board-approved informed consent forms prior to participation.

7.3.2 Kinematics, Kinetics, And EMG

Standardized protocols were employed to capture three-dimensional (3D) limb motion and ground reaction force data (S. C. Landry et al. 2007) and electromyography (C. L. Hubley-Kozey et al. 2006) during self-selected speed over-ground walking for the more symptomatic leg. Briefly, 3D motion data were collected at 100 Hz using two Optotrack 3020 cameras (Northern Digital Inc., Waterloo, Canada), in synchrony with 3D ground reaction forces from a force platform embedded in the floor (model BP400600, Advanced Medical Technology Inc., Watertown, USA), and electromyography (EMG) from seven muscle sites surrounding the knee joint (AMT-8 EMG, Bortec™ Inc., Calgary, Canada), with the ground reaction forces and EMG digitized at 2000 Hz. Muscle sites included lateral (LG) and medial (MG) heads of the gastrocnemius, vastus lateralis (VL), vastus

medialis (VM), rectus femoris (RF), biceps femoris (lateral hamstrings, LH) and semimembranosus (medial hamstrings, MH). Four to seven trials where the participant's test foot landed cleanly on the force platform were saved for analysis.

Kinematics and kinetics were calculated using custom-written MATLAB programs (Mathworks Inc., Natick, USA) (S. C. Landry et al. 2007). In brief, 3D joint angles were calculated from 3D diode positions using a least squares optimization routine (J. H. Challis 1995) and expressed in the joint coordinate system (E. S. Grood and W. J. Suntay 1983). 3D net external joint moments were calculated using inverse dynamics, time-normalized to the stance phase of the gait cycle, and amplitude normalized to body mass (C. L. Vaughan et al. 1982, P. A. Costigan et al. 1992, K. J. DeLuzio et al. 1993, J. Li et al. 1993).

EMG data were processed in MATLAB according to standardized protocols (C. L. Hubley-Kozey et al. 2006), where raw signals were corrected for bias, converted to μV, full-wave rectified, low pass filtered at 6 Hz using a Butterworth filter, and then time-normalized to the gait cycle.

7.3.3 Muscle Strength Testing And EMG Amplitude Normalization

Following gait data collection, eight maximum voluntary isometric contractions (MVICs) were performed using standardized protocols (C. L. Hubley-Kozey et al. 2006, D. J. Rutherford et al. 2011) for the purposes of EMG amplitude normalization and strength assessment. In brief, the eight exercises were: (1) plantar flexion in long sitting, (2) single leg standing heel raise with manual resistance applied to the shoulders, (3) knee extension in sitting (with knee at 45° flexion), (4) same as 3 with simultaneous hip flexion (with hip at approximately 90° flexion), (5) knee extension in supine (with knee at 15° flexion), (6) knee flexion in sitting (with knee at 55° flexion), (7) knee flexion in supine (with knee at 15° flexion), and (8) knee flexion in prone (with knee at 55° flexion). Following a practice trial, two trials were performed of each exercise with each trial held for three seconds and rest periods of at least 60 seconds given between each trial. Standardized verbal encouragement was also provided during each trial, consistent

with recommended protocols (M. D. Lewek et al. 2004). EMG data collected during the MVICs was used to amplitude-normalize EMG waveforms during gait. Waveforms for each muscle were amplitude normalized to the highest activation amplitude (based on a 0.1-second moving window) of the same muscle during the MVICs, regardless of which exercise it came from (C. L. Hubley-Kozey et al. 2006).

A Cybex dynamometer (Lumex, New York City, USA) was used to record torque data simultaneously with EMG data for exercises 1, 3, 5, 6, 7, and 8. For each muscle group, the highest amplitude steady state 0.5-second window was identified (C. L. Hubley-Kozey et al. 2006), regardless of which exercise it came from (D. J. Rutherford et al. 2011), and normalized to body mass to calculate a relative strength measure for each muscle group (Nm/kg).

7.3.4 Waveform Feature Extraction

Principal component analysis (PCA), a data reduction technique, extracted main patterns of variation from moment and EMG waveforms (C. L. Hubley-Kozey et al. 2006, K. J. Deluzio and J. L. Astephen 2007) from a larger set of knee OA and asymptomatic individuals from the Dynamics of Human Motion laboratory database (n = 428 (207 women, 221 men) with mean age: 55.2 ± 9.4 years, mass: 84.3 ± 18.3 kg, body mass index (BMI): 28.8 ± 5.3 kg/m^2, speed: 1.29 ± 0.20, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total: 17.5 ± 18.8, mJSN (0:1:2:3): 16:139:107:50, Kellgren-Lawrence (KL) grade (1:2:3:4): 25:138:101:46). Principal component (PC) scores were calculated for each waveform for all participants in the current study by multiplying the individual waveform by each PC. PC scores represent coefficients describing how closely the participant's original waveforms matched the extracted patterns. We used PCs extracted from a larger dataset because this method allows extraction of more robust and generalizable PCs (J. W. Osborne and A. B. Costello 2004). In the larger dataset, 2-4 PCs per variable were retained to cumulatively explain 90% of the variability among waveforms. In the current study, this list was then narrowed to only those features that have been related to either structural or clinical OA progression: overall KAM magnitude

(PC1), the difference between early and mid-stance KAM (PC2), early stance KFM magnitude (PC1) and the difference between early stance KFM and late stance knee extension moment (KEM) (PC2) (G. L. Hatfield et al. 2015b), the difference between early stance internal and late stance external KRM (PC1) (E. Davis et al. 2018), the internal KRM magnitude through mid-stance PC2 (**Chapter 3**), higher overall activation of gastrocnemii, quadriceps and hamstrings (PC1), and prolonged quadriceps and hamstrings activation (PC2) (C. L. Hubley-Kozey et al. 2013a). The included moment features have intraclass correlation coefficients (ICCs) ranging from 0.70 to 0.94 (S. M. Robbins et al. 2013a), and EMG features have ICCs ranging from 0.73 to 0.98 (C. L. Hubley-Kozey et al. 2013b).

7.3.5 Accelerometer Data Collection And Analysis

For 7 days following gait data collection, participants wore an ActiGraph GT3X+ tri-axial accelerometer (ActiGraph, Pensacola, FL, USA) on a waist belt, approximately over the anterior superior iliac spine of the same leg that was tested in the gait laboratory (P. S. Freedson et al. 2011). Participants were instructed to wear the accelerometer during all waking hours except when bathing or engaging in other water-based activities and kept written logs to record all activities done in the morning, afternoon, and evening of each day and the times that the device was put on and taken off each day. A demonstration of appropriate accelerometer placement was given to participants at the time of gait testing along with a diagram and written instructions to take home.

Once the accelerometers were returned, the data was downloaded into ActiLife software (ActiGraph, Pensacola, FL, USA), resampled from the original 30 Hz to one-minute epochs, and transformed into units of counts per minute (CPM), a composite metric describing the frequency and intensity of accelerations. Within ActiLife, wear time validation was performed by identifying periods of non-wear (90 minutes of zero activity with a 2-minute non-zero spike tolerance (L. Choi et al. 2011)) using criteria recommended for individuals with knee OA (J. Song et al. 2010). This analysis was compared to written activity logs to ensure validity. Data

for two participants (one woman, one man) who reported wearing the accelerometer but engaging in mostly sedentary behavior was reprocessed without the minimum wear time criteria to include this data as valid wear time, because visual inspection of the data did confirm some activity during the reported times. All participants in the current study wore the accelerometer for at least four days with at least ten hours per day of valid wear time (L. Choi et al. 2011).

Within the ActiLife software, step count (steps/day) was automatically calculated through proprietary manufacturer formulas. Each minute of valid data was also categorized by intensity level (P. S. Freedson et al. 1998) into sedentary behavior (SED, 0-99 CPM), light PA (LPA, 100-1951 CPM), and moderate-to-vigorous PA (MVPA, 1952+ CPM). SED, LPA, and MVPA were calculated as average daily totals over the week of accelerometer wear and expressed in minutes. SED, LPA, and MVPA were also expressed as a percent of wear time to account for possible differences in wear time among participants (E. Aadland and E. Ylvisaker 2015).

7.3.6 Follow-Up Regarding Surgical Status

Follow-up regarding current surgical status took place between 2015 and 2017. Of the 57 participants in the current study, 54 were at least 2.5 years past their gait and accelerometer testing sessions at the time of follow-up. Those 54 individuals were contacted by phone or email and asked about their current surgical status, specifically, whether they had undergone any surgeries to their lower extremities since their previous testing sessions or whether they were scheduled for surgery. Of these, 2 did not respond to contact attempts, 2 had contact information that was no longer valid, 1 was deceased, and the remaining 49 provided follow-up data. Two participants that had undergone contralateral TKA and one that had undergone ipsilateral total hip arthroplasty (THA) were excluded. Ten participants had undergone or were on a waitlist for TKA of the study knee and 36 had not had any surgeries to the lower extremities.

7.3.7 Statistical Analysis

7.3.7.1 Part 1. Cross-Sectional Analysis

To gain insight into the relationships between joint loading frequency, joint loading magnitude/duration, and clinical OA progression, a cross-sectional analysis was performed on all individuals (n = 57) who had both accelerometer data and gait data at baseline (regardless of whether or not they had follow-up data). Spearman correlation coefficients were calculated between PA variables (step count, SED, LPA, and MVPA) and gait variables that have previously been linked to OA progression (described above). To visualize the relationships between PA and gait, the sample was divided into four quartiles by step count with average gait waveforms plotted for each quartile. Jonckheere-Terpstra tests for ordered alternatives were used to compare demographics, clinical data, gait, and PA among the quartiles. All statistical analyses were performed in SPSS (IBM, Armonk, USA) with a priori significance level set at $\alpha < 0.05$. Post-hoc tests were adjusted with Bonferroni corrections.

7.3.7.2 Part 2. Longitudinal Analysis

To investigate baseline differences between progression and no progression groups, data from the sub-sample of individuals with gait and accelerometer data at baseline and follow-up surgical status data at least 2.5 years later (with no surgeries to other joints) were used with one exception. Further inspection of individuals meeting the above criteria revealed that those who had undergone or were on a waitlist for TKA all had baseline KL grades greater than 2 while those who had not had surgery included n = 10 with KL grades of 2, n = 3 without radiographic data available, and n = 23 with KL grades greater than 2. To reduced potential confounding effects of baseline radiographic differences between groups, the no progression (no TKA) group was limited to individuals with KL > 2, resulting in a final sample size of 33 participants (n = 10 TKA, n = 23 no TKA) for this analysis. Chi square tests and Mann-Whitney U-tests were used to examine between-group differences in sex and ordinal radiographic scores, respectively. Due to the small

sample sizes in this analysis and skewed distributions of some variables due to bounding at zero combined with low activity in that intensity (e.g. MVPA), non-parametric Mann-Whitney U-tests examined between-group differences in group characteristics, gait, and PA variables. All statistical analyses were performed in SPSS (IBM, Armonk, USA) with a significance level of $\alpha = 0.05$.

7.4 Results

7.4.1 Part 1. Cross-Sectional Analysis

7.4.1.1 Descriptive Characteristics Of Study Sample

The full cohort consisted of 20 women and 37 men with a KL grade ≥ 2 (Table 7.1). JSN scores ranged from 0 – 3 for all compartments (Table 7.1), although all participants were defined as primarily medial compartment OA by the presence of medial knee pain and medial JSN ≥ lateral JSN. Age ranged from late forties to eighty years old with BMI ranging from healthy weight to class 3 obese (Table 7.1). There was a wide range of PA levels within the study sample, with average step count ranging from just over 2,000 to just under 13,000 steps per day (Table 7.1). The group, on average, spent 64% of their time in SED, 33% in LPA, and 3% in MVPA, although the distribution varied within the group (Table 7.1).

7.4.1.2 Correlations Between PA Variables And Gait PCs

Step count, MVPA (min), and MVPA (%) were positively correlated ($p < 0.05$) with greater mid-stance unloading in the KAM (KAM PC2), higher overall KFM amplitude in early stance (KFM PC1), a greater difference between early stance flexion and late stance extension moments (KFM PC2), and a greater difference between external and internal KRM (KRM PC1) (Table 7.2). There were also significant negative correlations between these three PA variables and EMG PCs, particularly for both higher amplitude and prolonged activation of the quadriceps and hamstrings, although the exact variables with significant correlations differed for each PA variable, as many had significance values close to $p = 0.05$ (Table 7.2).

When there were significant correlations they were in the direction of higher step count, MVPA (min), or MVPA (%) being associated with lower overall amplitude and lack of prolonged activation through mid-stance. There were no significant correlations between SED or LPA (in minutes or percent of wear time) and gait variables (all $p > 0.05$) (Table 7.2). Example scatterplots showing the relationships between step count and gait PCs are presented in Appendix C.

7.4.1.3 Step Count Quartiles

The sample (n = 57) was divided into quartiles of 14 or 15 individuals per quartile based on daily step count (Table 7.3). There were trends towards increasing LPA and MVPA (minutes or %) across quartiles and decreasing SED (minutes or %) across quartiles, although not all of the differences between consecutive quartiles were significant (Table 7.3). There were also some differences among quartiles in severity and strength, with a trend towards a higher percentage of women in the lower versus the higher step count quartiles (Table 7.4).

A number of gait variables showed significant differences among quartiles (Table 7.5). Qualitatively, in many of the waveforms, the quartile with the lowest step count (Q1) appeared to have a different magnitude or pattern than the other 3 quartiles (Figure 7.1, Figure 7.2). Post-hoc testing showed differences in Q1 compared to other quartiles (Table 7.5), including a smaller early stance KFM magnitude (KFM PC1) (Figure 7.1), a smaller difference between early stance flexion and late stance extension moments (KFM PC2) (Figure 7.1), a smaller difference between external and internal rotation moments (KRM PC1) (Figure 7.1), and prolonged activation of VM and LH through mid-stance (PC2) (Figure 7.2).

Table 7.1 Group characteristics and physical activity data for the full cohort in the cross-sectional analysis

		Range
N	57	
Women:Men (%Women)	20:37 (35%)	
Age (years)	62.1 (6.9)	48 - 80
Mass (kg)	89.9 (17.1)	55.5 - 134.3
BMI (kg/m^2)	31.0 (5.5)	23.0 – 48.7
Gait speed (m/s)	1.26 (0.20)	0.89 – 1.81
Radiographic Scores†		
Kellgren-Lawrence grade (1, 2, 3, 4)	0, 10, 28, 16	2 - 4
Medial JSN (0, 1, 2, 3)	1, 11, 28, 14	0 - 3
Lateral JSN (0, 1, 2, 3)	23, 22, 7, 2	0 - 3
Patellofemoral JSN (0, 1, 2, 3)	4, 30, 16, 4	0 - 3
WOMAC scores		
Pain (/20)	3.7 (3.7)	0 – 12
Stiffness (/8)	1.8 (1.6)	0 – 5
Function (/68)	12.3 (11.4)	0 – 47
Strength§		
Knee Extensor (Nm/kg)	1.29 (0.37)	0.60 – 2.45
Knee Flexor (Nm/kg)	0.69 (0.22)	0.30 – 1.28
Plantar Flexor (Nm/kg)	0.96 (0.33)	0.31 – 1.69
Physical activity data		
Total wear time (min)	854 (79)	602 – 998
SED (min)	547 (98)	325 – 777
LPA (min)	283 (78)	150 – 512
MVPA (min)	24 (16)	1 – 79
SED (%)	64.0 (9.3)	38.3 – 82.8
LPA (%)	33.2 (8.9)	16.0 – 60.3
MVPA (%)	2.8 (1.8)	0.1 – 8.7
Step count (steps/day)	6697 (2367)	2173 – 12653

Data presented as mean (standard deviation) except where noted. BMI = body mass index, JSN = joint space narrowing, LPA = light intensity PA, MVPA = moderate to vigorous intensity PA, SED = sedentary behavior, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

† Current radiographic scores were unavailable for n = 3 individuals

§ Strength data was unavailable for n = 5 individuals

Table 7.2 Spearman correlations (ρ) between physical activity and gait variables

PCs		Interpretation	Step Count	SED (min)	LPA (min)	MVPA (min)	SED (%)	LPA (%)	MVPA (%)
Moments (n = 57):									
KAM	1	Overall shape and magnitude	0.01	0.14	-0.09	0.10	0.14	-0.15	0.10
	2	Early-, mid-stance difference	**0.31***	0.11	0.17	**0.38***	-0.09	0.04	**0.33***
KFM	1	Early stance flexion moment magnitude	**0.27***	0.18	0.12	**0.32***	0.02	-0.06	**0.28***
	2	Early stance flexion, late stance extension difference	**0.42***	-0.14	0.15	**0.42***	-0.22	0.14	**0.42***
KRM	1	External, internal rotation moment difference	**0.33***	0.10	0.04	**0.37***	0.01	-0.05	**0.36***
	2	Mid-stance internal rotation moment magnitude	-0.02	0.05	-0.12	0.03	0.08	-0.10	0.03
EMG (n = 52):									
LG	1	Overall shape and magnitude	-0.06	0.12	0.00	0.02	0.13	-0.13	-0.01
MG	1	Overall shape and magnitude	0.02	-0.07	0.00	-0.09	0.00	0.03	-0.10
VL	1	Overall shape and magnitude	-0.19	-0.14	0.00	-0.13	-0.07	0.11	-0.13
VM	1	Overall shape and magnitude	-0.21	-0.24	0.05	**-0.28***	-0.08	0.15	-0.25
RF	1	Overall shape and magnitude	-0.23	-0.26	0.11	-0.25	-0.15	0.23	-0.23
LH	1	Overall shape and magnitude	-0.19	-0.01	-0.13	-0.12	0.08	-0.04	-0.11
MH	1	Overall shape and magnitude	**-0.30***	-0.01	-0.12	**-0.36***	0.10	-0.01	**-0.36***
VL	2	Prolonged mid-stance activation	**-0.33***	-0.08	-0.02	**-0.28***	0.05	0.05	-0.25
VM	2	Prolonged mid-stance activation	**-0.35***	0.02	-0.02	-0.21	0.07	0.00	-0.20
RF	2	Prolonged mid-stance activation	**-0.36***	0.10	-0.02	-0.26	0.13	-0.06	-0.26
LH	2	Prolonged mid-stance activation	**-0.42***	0.07	-0.27	**-0.31***	0.25	-0.17	**-0.28***
MH	2	Prolonged mid-stance activation	-0.22	0.03	-0.11	-0.21	0.12	-0.06	-0.19

* Significant at $p < 0.05$. EMG = electromyography, LG = lateral gastrocnemius, LH = lateral hamstring, LPA = light physical activity, KAM = knee adduction moment, KFM = knee flexion moment, KRM = knee rotation moment, MG = medial gastrocnemius, MH = medial hamstring, MVPA = moderate to vigorous physical activity, PCs = principal components, RF = rectus femoris, SED = sedentary behavior, VL = vastus lateralis, VM = vastus medialis

Table 7.3 Physical activity data across quartiles of step count (Q1 = lowest to Q4 = highest)

Quartile:	Q1 (n = 15)	Q2 (n = 14)	Q3 (n = 14)	Q4 (n = 14)	*P*†
Step Count	*3915 (668) A*	*5641 (641) B*	*7646 (383) C*	*9784 (1316) D*	***<0.01****
SED (min)	606 (106) A	560 (77) A	546 (92) AB	473 (70) B	**<0.01***
LPA (min)	221 (49) A	254 (55) A	324 (52) B	337 (86) B	**<0.01***
MVPA (min)	9 (6) A	21 (7) B	25 (11) B	41 (16) C	**<0.01***
SED (%)	72.1 (6.5) A	67.0 (5.7) AB	60.7 (6.9) BC	55.7 (8.5) C	**<0.01***
LPA (%)	27.9 (6.5) A	33.0 (5.7) AB	39.3 (6.9) BC	44.3 (8.5) C	**<0.01***
MVPA (%)	1.1 (0.7) A	2.6 (0.9) B	2.7 (1.2) B	4.8 (1.9) C	**<0.01***

Data presented as mean (standard deviation) except where noted. LPA = light physical activity, MVPA = moderate to vigorous physical activity, SED = sedentary behavior

* Significant at $p < 0.05$

† Jonckheere-Terpstra test for ordered alternatives. Post-hoc Bonferroni corrections were used to adjust for multiple comparisons. Quartiles that do not share a letter were significantly different from each other.

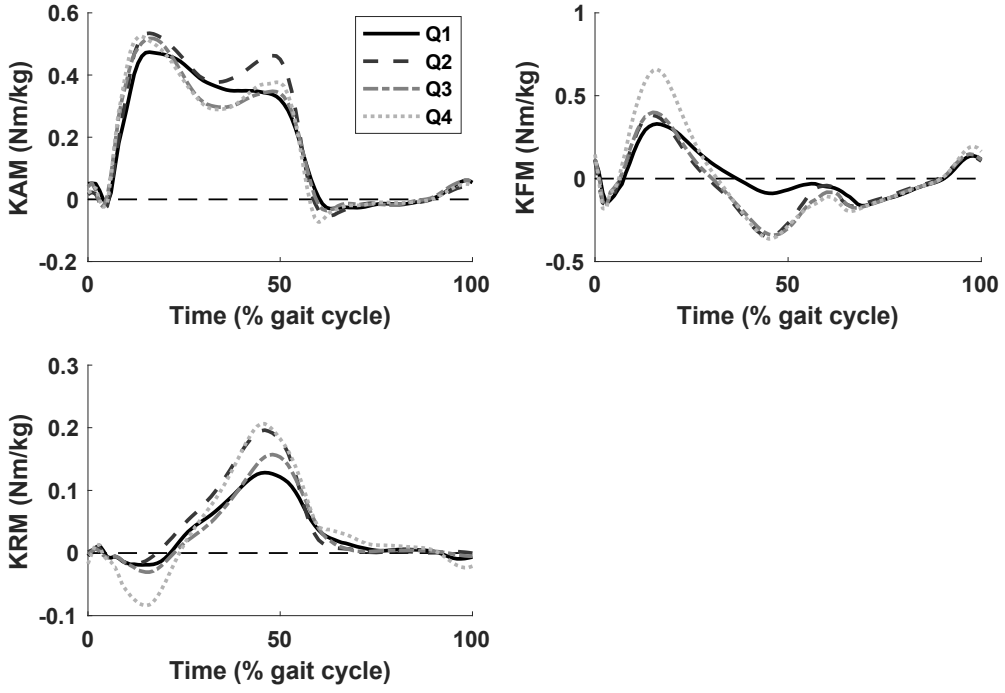

Figure 7.1 Moment waveforms across quartiles of step count (Q1 = lowest to Q4 = highest)

Table 7.4 Group characteristics across quartiles of step count (Q1 = lowest to Q4 = highest)

	Q1 (n = 15)	Q2 (n = 14)	Q3 (n = 14)	Q4 (n = 14)	*P*†
Women:Men (%W)	8:7 (53%)	7:8 (50%)	3:11 (21%)	2:12 (14%)	0.06
Age (years)	66.5 (8.0)	58.1 (4.9)	60.5 (6.6)	63.1 (4.7)	0.64
Mass (kg)	96.3 (19.7)	81.2 (18.9)	91.0 (12.8)	90.8 (13.8)	0.81
BMI (kg/m^2)	34.8 (7.0)	28.0 (4.3)	30.9 (4.2)	30.3 (3.6)	0.35
Gait speed (m/s)	1.18 (0.15)	1.29 (0.24)	1.22 (0.19)	1.35 (0.17)	0.07
Radiographic Scores §					
KL grade (1, 2, 3, 4)	0, 0, 8, 6 ^{A}	0, 3, 4, 6 ^{AB}	0, 3, 8, 3 ^{AB}	0, 4, 8, 1 ^{A}	**0.01***
mJSN (0, 1, 2, 3)	0, 1, 8, 5 ^{A}	1, 2, 4, 6 ^{A}	0, 4, 8, 2 ^{A}	0, 4, 8, 1 ^{A}	**0.03***
latJSN (0, 1, 2, 3)	3, 8, 3, 0	8, 3, 0, 2	5, 7, 2, 0	7, 4, 2, 0	0.27
PF JSN (0, 1, 2, 3)	0, 8, 5, 1	3, 5, 3, 2	0, 8, 6, 0	1, 9, 2, 1	0.41
WOMAC scores					
Pain (/20)	4.3 (3.6) ^{A}	4.8 (4.4) ^{A}	4.3 (3.8) ^{A}	1.5 (1.7) ^{A}	**0.05***
Stiffness (/8)	1.7 (1.4)	2.3 (1.9)	1.8 (1.6)	1.4 (1.3)	0.39
Function (/68)	13.1 (9.6)	15.2 (16.4)	13.1 (11.2)	7.6 (5.6)	0.24
Strength (Nm/kg) §§					
Knee Extensor	0.99 (0.29) ^{A}	1.35 (0.28) ^{B}	1.38 (0.33) ^{B}	1.44 (0.41) ^{B}	**<0.01***
Knee Flexor	0.55 (0.17)	0.78 (0.17)	0.65 (0.21)	0.78 (0.24)	0.08
Plantar Flexor	0.73 (0.28)	1.10 (0.32)	1.02 (0.33)	0.97 (0.31)	0.12

Data presented as mean (standard deviation) except where noted. BMI = body mass index, KL = Kellgren Lawrence, latJSN = lateral joint space narrowing, mJSN = medial joint space narrowing, PF JSN = patellofemoral joint space narrowing, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

§ Current radiographic scores were unavailable for n = 1 in Q1, n = 1 in Q2, and n = 1 in Q4.

§§ Strength data was unavailable for n = 2 in Q1, n = 2 in Q3, and n = 1 in Q4.

* Significant at $p < 0.05$

† Jonckheere-Terpstra test for ordered alternatives, except for sex where a chi-square test was used. Post-hoc Bonferroni corrections were used to adjust for multiple comparisons. Quartiles that do not share a letter were significantly different from each other.

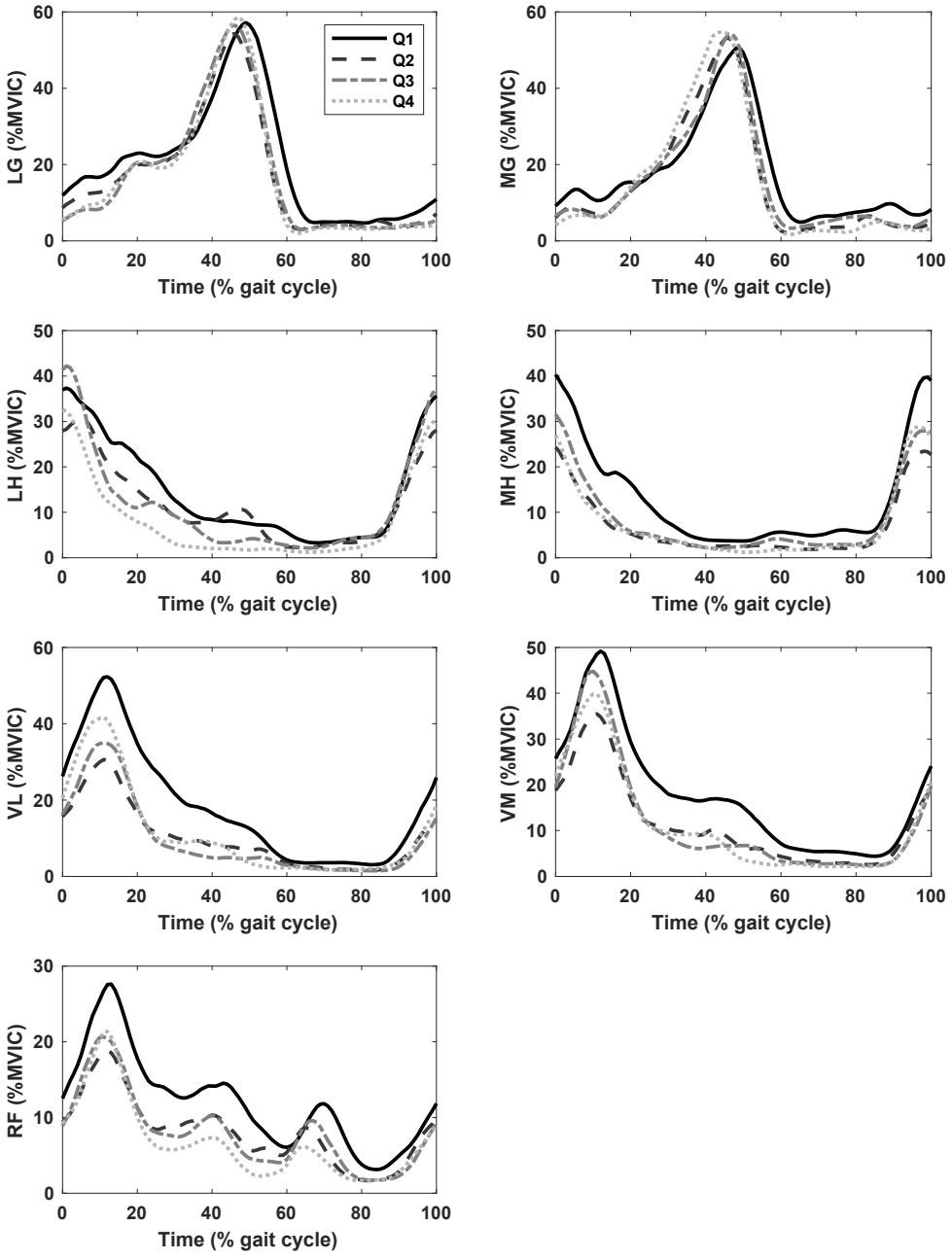

Figure 7.2 EMG waveforms across quartiles of step count (Q1 = lowest to Q4 = highest)

Table 7.5 Gait data across quartiles of step count (Q1 = lowest to Q4 = highest)

PCs		Q1 (n = 15)	Q2 (n = 14)	Q3 (n = 14)	Q4 (n = 14)	*P*†
Moments:						
KAM	1	0.20 (0.91)	0.73 (1.22)	0.23 (1.12)	0.29 (1.14)	0.86
	2	-0.19 (0.50) ^{A}	-0.30 (0.52) ^{A}	0.09 (0.62) ^{A}	0.09 (0.49) ^{A}	**0.04***
KFM	1	-0.01 (0.79) ^{A}	-0.09 (1.63) ^{AB}	0.07 (1.45) ^{AB}	1.10 (1.45) ^{B}	**0.04***
	2	-1.19 (1.00) ^{A}	0.07 (1.11) ^{B}	0.08 (0.96) ^{B}	0.22 (1.10) ^{B}	**<0.01***
KRM	1	-0.13 (0.40) ^{A}	0.02 (0.39) ^{AB}	-0.01 (0.39) ^{AB}	0.29 (0.42) ^{B}	**0.01***
	2	-0.16 (0.38)	0.13 (0.35)	-0.13 (0.29)	-0.05 (0.33)	0.84
EMG: §						
LG	1	244.1 (99.6)	225.0 (82.5)	235.9 (125.1)	232.4 (86.0)	0.93
MG	1	212.3 (66.2)	213.5 (142.5)	211.1 (71.3)	223.7 (84.8)	0.65
VL	1	232.9 (151.8)	128.8 (45.7)	137.0 (55.3)	162.0 (100.6)	0.14
VM	1	216.6 (126.2)	147.3 (60.3)	166.6 (86.0)	157.9 (83.4)	0.27
RF	1	131.4 (73.8)	90.1 (34.4)	92.9 (53.2)	84.5 (53.1)	0.07
LH	1	180.6 (92.8)	144.1 (80.8)	158.4 (81.7)	119.0 (62.5)	0.10
MH	1	171.8 (122.6)	93.6 (27.1)	116.2 (48.0)	104.1 (71.5)	0.14
VL	2	9.8 (46.5) ^{A}	-1.8 (36.0) ^{A}	-22.7 (27.0) ^{A}	-28.2 (42.9) ^{A}	**0.02***
VM	2	15.0 (38.8) ^{A}	-7.2 (41.3) ^{AB}	-28.9 (31.4) ^{B}	-23.4 (27.6) ^{B}	**0.01***
RF	2	32.6 (39.0) ^{A}	19.6 (25.8) ^{A}	13.2 (34.9) ^{A}	1.7 (21.9) ^{A}	**0.01***
LH	2	21.0 (56.3) ^{A}	16.3 (60.7) ^{AB}	-14.3 (44.2) ^{AB}	-23.5 (23.3) ^{B}	**<0.01***
MH	2	-17.7 (65.9)	-23.3 (28.6)	-28.1 (21.4)	-34.5 (24.5)	0.05

§ EMG data was unavailable for n = 2 in Q1, n = 2 in Q3, and n = 1 in Q4. EMG = electromyography, LG = lateral gastrocnemius, LH = lateral hamstring, LPA = light physical activity, KAM = knee adduction moment, KFM = knee flexion moment, KRM = knee rotation moment, MG = medial gastrocnemius, MH = medial hamstring, MVPA = moderate to vigorous physical activity, NSD = no significant differences after Bonferroni correction, PCs = principal components, RF = rectus femoris, SED = sedentary behavior, VL = vastus lateralis, VM = vastus medialis

* Significant at $p < 0.05$

† Jonckheere-Terpstra test for ordered alternatives. Post-hoc Bonferroni corrections were used to adjust for multiple comparisons. Quartiles that do not share a letter were significantly different from each other.

7.4.2 Part 2. Longitudinal Analysis

7.4.2.1 Descriptive Characteristics Of Study Sample

Consistent with the large proportion of individuals with KL scores of 2 that were excluded from the longitudinal analysis in order to better match radiographic

scores in the TKA and no TKA groups, the excluded individuals represented a less severe group than those included in the final analysis, with lower radiographic scores, WOMAC sores, higher knee flexor strength, lower BMI, and higher gait speed, along with a trend towards higher plantar flexor strength (Table 7.6).

Table 7.6 Group characteristics for individuals included in the longitudinal analysis versus those that were excluded

	Excluded (n = 24)	Included (n = 33)	*P*†
Women:Men (%W)	6:18 (25%)	14:19 (42%)	0.17
Age (years)	61.9 (7.8)	62.3 (6.3)	0.46
Mass (kg)	86.5 (14.0)	92.4 (18.9)	0.19
BMI (kg/m^2)	29.3 (3.5)	32.3 (6.3)	0.08
Gait speed (m/s)	1.31 (0.20)	1.22 (0.19)	0.08
Radiographic scores*			
Kellgren-Lawrence grade (1, 2, 3, 4)	0, 10, 9, 2	0, 0, 19, 14	**<0.01**
Medial JSN (0, 1, 2, 3)	1, 10, 9, 1	0, 1, 19, 13	**<0.01**
Lateral JSN (0, 1, 2, 3)	12, 7, 1, 1	11, 15, 6, 1	0.09
Patellofemoral JSN (0, 1, 2, 3)	3, 13, 4, 1	1, 17, 12, 3	0.06
WOMAC			
Pain (/20)	2.3 (2.9)	4.8 (3.8)	**0.01**
Stiffness (/8)	1.0 (1.3)	2.4 (1.5)	**<0.01**
Function (/68)	7.2 (6.4)	15.9 (12.9)	**0.02**
Strength**			
Knee Extensor (Nm/kg)	1.36 (0.38)	1.24 (0.36)	0.23
Knee Flexor (Nm/kg)	0.78 (0.24)	0.64 (0.19)	**0.03**
Plantar Flexor (Nm/kg)	1.08 (0.38)	0.88 (0.28)	0.06

BMI = body mass index, JSN = joint space narrowing, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

†Mann-Whitney U-tests between included and excluded groups, Chi square for sex

*Radiographic scores missing for n = 3 excluded individuals

**Strength scores missing for n = 4 excluded individuals and n = 1 included individual

7.4.2.2 Group Differences In Gait And PA Variables

At baseline, the TKA and No TKA groups had a similar distribution of women and men, similar age, mass, BMI, radiographic scores, and muscle strength but the

TKA group had higher WOMAC pain, stiffness, and function scores at baseline (Table 7.7). Qualitatively, there appeared to be differences in both moment and EMG waveforms between the two groups (Figure 7.3, Figure 7.4), but only a few of these reached statistical significance. The TKA group had a higher overall KAM (PC1) (Figure 7.3), prolonged activation of VM through mid-stance (Figure 7.4), and a trend towards prolonged activation of RF through mid-stance (p = 0.08) (Figure 7.4) compared to the no TKA group (Table 7.8). There were no statistically significant differences in PA variables between TKA and no TKA groups (Table 7.9).

Table 7.7 Group characteristics for clinical progression (TKA) and no progression (no TKA) groups in the longitudinal analysis

	TKA (n = 10)	No TKA (n = 23)	*P*†
Women:Men (%W)	4:6 (40%)	10:13 (43%)	0.85
Age (years)	61.7 (5.5)	62.6 (6.6)	0.71
Mass (kg)	86.9 (20.0)	94.8 (18.3)	0.31
BMI (kg/m^2)	31.9 (7.2)	32.5 (6.0)	0.77
Gait speed (m/s)	1.18 (0.21)	1.24 (0.18)	0.55
Radiographic scores			
Kellgren-Lawrence grade (1, 2, 3, 4)	0, 0, 4, 6	0, 0, 15, 8	0.27
Medial JSN (0, 1, 2, 3)	0, 0, 4, 6	0, 1, 15, 7	0.17
Lateral JSN (0, 1, 2, 3)	5, 4, 1, 0	6, 11, 5, 1	0.18
Patellofemoral JSN (0, 1, 2, 3)	0, 4, 6, 0	1, 13, 6, 3	0.52
WOMAC			
Pain (/20)	7.9 (3.0)	3.5 (3.4)	**<0.01**
Stiffness (/8)	4.0 (0.7)	1.7 (1.3)	**<0.01**
Function (/68)	24.8 (13.0)	12.1 (11.0)	**0.01**
Strength*			
Knee Extensor (Nm/kg)	1.22 (0.26)	1.26 (0.40)	0.89
Knee Flexor (Nm/kg)	0.65 (0.19)	0.63 (0.19)	0.37
Plantar Flexor (Nm/kg)	0.92 (0.32)	0.86 (0.27)	0.56
Time to follow-up (years)	3.5 (1.1)	3.6 (0.9)	0.92

BMI = body mass index, JSN = joint space narrowing, TKA = total knee arthroplasty, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

†Mann-Whitney U-test between TKA and No TKA groups, Chi square for sex

*Strength data was unavailable for n = 1 individuals in the No TKA group

Table 7.8 Baseline joint moment and EMG differences between clinical progression (TKA) and no progression (no TKA) groups in the longitudinal analysis

PCs		Interpretation	TKA (n = 10)	No TKA (n = 23)	Mean difference	95% CI	*P*†
Moments:							
KAM	1	Overall shape and magnitude	1.05 (1.11)	0.13 (1.19)	-0.92	-1.82, -0.02	**0.05**
	2	Early-, mid-stance difference	-0.22 (0.44)	-0.08 (0.56)	0.14	-0.26, 0.55	0.36
KFM	1	Early stance flexion moment magnitude	-0.23 (1.42)	0.34 (1.32)	0.57	-0.48, 1.61	0.36
	2	Early stance flexion, late stance extension difference	-0.86 (0.80)	-0.37 (1.12)	0.49	-0.31, 1.29	0.24
KRM	1	External, internal rotation moment difference	-0.04 (0.33)	-0.14 (0.33)	-0.10	-0.36, 0.15	0.45
	2	Mid-stance internal rotation moment magnitude	-0.08 (0.19)	-0.13 (0.35)	-0.05	-0.29, 0.19	0.80
EMG:							
LG	1	Overall shape and magnitude	232 (106)	256 (89)	24	-50, 98	0.48
MG	1	Overall shape and magnitude	181 (84)	203 (81)	22	-42, 86	0.39
VL	1	Overall shape and magnitude	178 (76)	167 (61)	-11	-62, 40	0.83
VM	1	Overall shape and magnitude	166 (95)	180 (79)	14	-52, 79	0.65
RF	1	Overall shape and magnitude	113 (39)	105 (57)	-8	-49, 33	0.43
LH	1	Overall shape and magnitude	170 (74)	170 (85)	0	-64, 63	0.95
MH	1	Overall shape and magnitude	109 (67)	126 (96)	17	-52, 86	0.56
VL	2	Mid-stance activation	19 (46)	-11 (36)	-30	-60, 1	0.12
VM	2	Mid-stance activation	22 (37)	-10 (37)	-32	-61, -3	**0.04**
RF	2	Mid-stance activation	37 (31)	19 (30)	-18	-41, 6	0.08
LH	2	Mid-stance activation	39 (71)	-9 (48)	-49	-92, -5	0.27
MH	2	Mid-stance activation	-21 (45)	-24 (44)	-3	-37, 31	0.20

Data presented as mean (standard deviation) except where noted. CI = confidence interval, EMG = electromyography, LG = lateral gastrocnemius, LH = lateral hamstring, KAM = knee adduction moment, KFM = knee flexion moment, KRM = knee rotation moment, MG = medial gastrocnemius, MH = medial hamstring, PCs = principal components, RF = rectus femoris, TKA = total knee arthroplasty, VL = vastus lateralis, VM = vastus medialis

†Mann-Whitney U-test between TKA and no TKA groups

Table 7.9 Baseline PA differences between clinical progression (TKA) and no progression (no TKA) groups in the longitudinal analysis

PA metric	TKA (n = 10)	No TKA (n = 23)	Mean difference	95% CI	*P*†
Minutes in each intensity					
Total time worn (min)	819 (83)	864 (84)	45	-19, 110	0.11
SED (min)	513 (92)	563 (115)	50	-35, 134	0.16
LPA (min)	279 (80)	279 (90)	0	-68, 67	0.95
MVPA (min)	26 (20)	22 (15)	-4	-17, 9	0.66
Percent of total time worn in each intensity					
SED (%)	62.7 (9.5)	65.0 (10.9)	2.3	-5.8, 10.5	0.50
LPA (%)	34.2 (9.4)	32.5 (10.5)	-1.7	-9.6, 6.1	0.60
MVPA (%)	3.2 (2.2)	2.5 (1.7)	-0.6	-2.0, 0.8	0.48
Step count (steps/day)	6551 (2573)	6324 (2414)	-227	-2128, 1675	0.95

Data presented as mean (standard deviation) except where noted. CI = confidence interval, LPA = light intensity physical activity, MVPA = moderate to vigorous intensity physical activity, SED = sedentary behavior, TKA = total knee arthroplasty

†Mann-Whitney U-test between TKA and no TKA groups

7.5 Discussion

This study had two objectives aimed at furthering our understanding of how both joint loading magnitude/duration and joint loading frequency contribute to clinical OA progression outcomes. In contrast to our hypothesis for the first objective, significant correlations were present between gait features linked to OA progression and both step count and MVPA, which appeared to be due to the presence of these gait patterns in individuals in the lowest quartile of step count. Consistent with the null hypothesis for the second objective, there were no differences in step count, SED, LPA, or MVPA at baseline between individuals who did or did not progress clinically (TKA endpoint) at 3.5-year follow-up.

7.5.1 Part 1. Cross-Sectional Analysis

There were a number of significant correlations between gait variables and both step count and MVPA with the highest correlations between LH PC2 (prolonged activation of LH through mid-stance) and step count (ρ = - 0.42) and

between KFM PC2 (the difference between early stance knee flexion and late stance extension moment) and both step count and MVPA (ρ = 0.42) (Table 7.2). Thus, a lower step count was associated with prolonged LH activation and a less dynamic KFM, two features have been linked to future clinical progression (C. L. Hubley-Kozey et al. 2013a, G. L. Hatfield et al. 2015b).

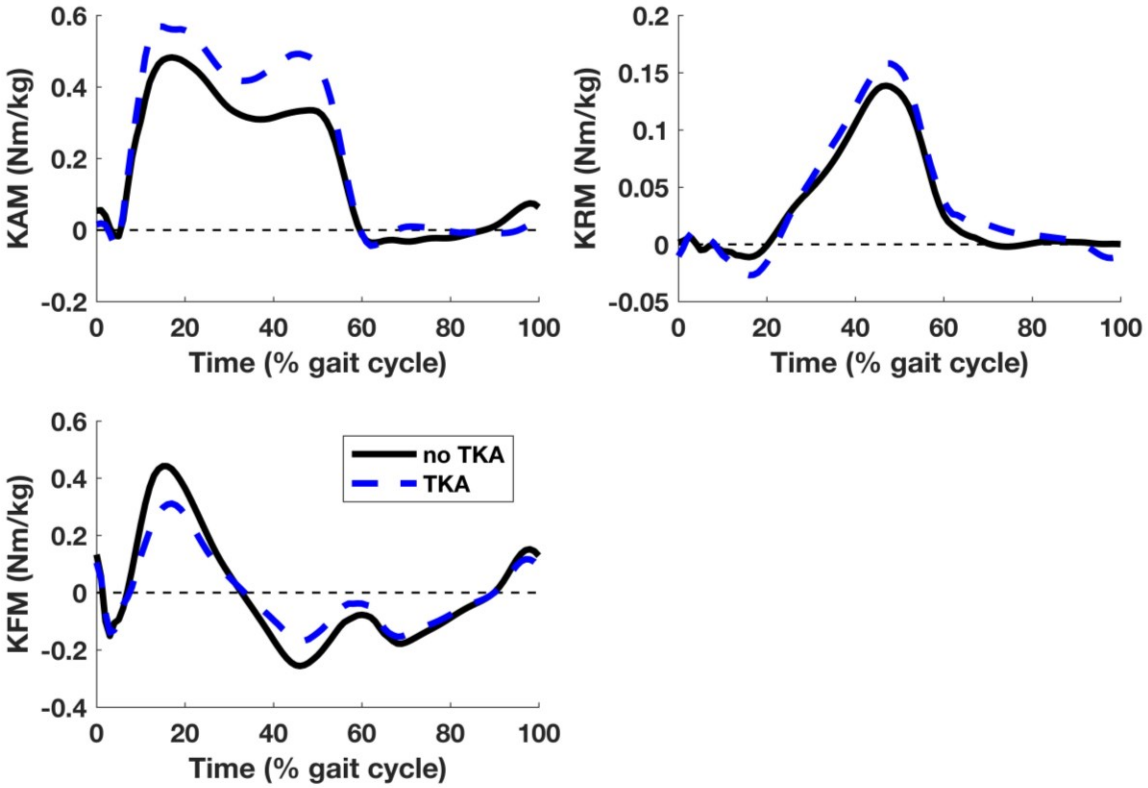

Figure 7.3 Baseline knee moment waveforms for clinical progression (TKA) and no progression (no TKA) groups in the longitudinal analysis

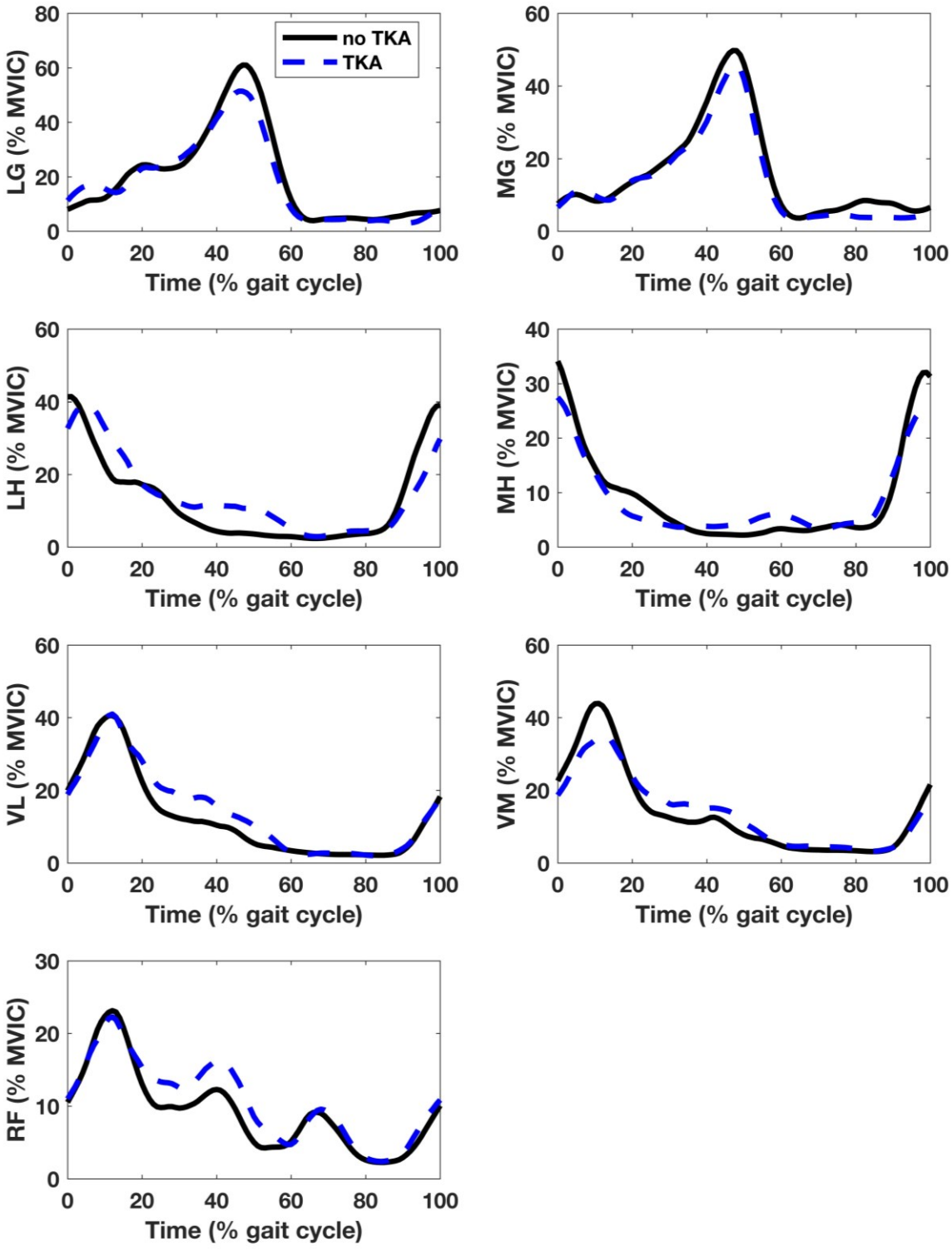

Figure 7.4 Baseline EMG waveforms for clinical progression (TKA) and no progression (no TKA) groups in the longitudinal analysis

Interestingly, visual examination of gait variables across quartiles of step count appeared to show that the group with the lowest average step count exhibited gait patterns similar to those associated with clinical knee OA progression, including increased and prolonged muscle activation (Figure 7.2) and lack of dynamic moment patterns (Figure 7.1), while the other three quartiles did not (Table 7.5). Post-hoc testing supported this finding, with significant differences indicating that the lowest quartile had higher overall EMG magnitude variables, higher prolonged muscle activity, and less dynamic loading patterns (smaller difference between early and late stance values) in the KFM and KRM, but that there were no differences in gait variables among the highest three quartiles (Table 7.5, Figure 7.1, Figure 7.2). These differences could be related to the more severe KL grades in the lowest quartile compared to the highest, or lower knee extensor strength in the lowest quartile compared to all other quartiles, but there were no other significant demographic or clinical differences between groups, despite trends towards higher proportions of women in the lower two compared to the higher two quartiles and lower WOMAC pain in the highest quartile compared to all others (Table 7.4).

Previous research has found that a step count below 5800-6000 steps/day is related to future incidence of physical disability in knee OA (D. K. White et al. 2014). In the current study, all individuals in the lowest quartile had fewer than 6000 steps/day while all individuals in the highest two quartiles were above this threshold and the second lowest quartile was split above and below the threshold. Patient symptoms, including functional disability, typically factor into TKA decisions (L. Gossec et al. 2011b), and thus the fact that all individuals in the lowest quartile are below the threshold reported by White et al. for risk of future functional disability further supports the link found in the current study between low step count and gait patterns that are predictive of future clinical progression. It is not clear from the current data if these less dynamic gait patterns lead to low levels of step count or vice versa, but the lack of differences among the highest three quartiles implies that joint loading frequency may only contribute unique

information to understanding OA progression (beyond that of gait data) if step count is above a certain threshold.

While the majority of this analysis focused on step count because it can be considered a surrogate metric of joint loading frequency, the correlations between gait variables and SED, LPA, and MVPA were also explored. With a few exceptions, MVPA had similar correlations with gait variables as those that were seen between step count and gait variables, both when expressed as an absolute value in minutes and as a percent of wear time (Table 7.2). SED and LPA (in absolute values or percent wear) were not correlated with any gait variables. These results may mean that higher intensity of physical activity (i.e. MVPA) might be more challenging to perform for those who walk with less dynamic moments and prolonged muscle activation patterns, but this gait pattern may have less of an effect on levels of LPA. Alternatively, this could indicate higher risk of clinical progression in individuals who do not engage in MVPA, although longitudinal analysis is needed to explore this fully.

7.5.2 Part 2. Longitudinal Analysis

Supporting previous research ((C. L. Hubley-Kozey et al. 2013a, G. L. Hatfield et al. 2015b) and **Chapter 4**), higher overall KAM magnitude and prolonged quadriceps activation (Table 7.8) were seen at baseline in those who progressed clinically at follow-up (TKA endpoint). The small sample size and short follow-up (average of 3.5 years) in this analysis may have led to the lack of significant differences (despite visual and statistical trends) in other gait metrics that have previously been related to clinical OA progression at 7-8 year follow-up. For example, the higher and more prolonged hamstrings activation seen in **Chapter 4** and by Hubley-Kozey et al. (C. L. Hubley-Kozey et al. 2013a) were not seen in the current study. While the differences in comparison to previous studies likely are a result of sample size, they could also represent differences in the features associated with clinical progression within a short (3.5-year) versus long (8-year) time frame.

It also should be noted that the group that went on to progress (TKA group) was more severe at baseline in terms of WOMAC scores (Table 7.7), and while there were not statistically significant differences in radiographic scores, the median KL and medial tibiofemoral JSN scores were also higher in the group that progressed, suggesting this group may have represented a more severe group at baseline. The qualitative trends and significant statistical differences in prolonged muscle activation patterns, higher KAM and flattening of the KFM seen in the TKA group in the current study have previously been associated with OA severity (J. L. Astephen et al. 2008, Janie L. Astephen et al. 2008), as well as with clinical OA progression (C. L. Hubley-Kozey et al. 2013a, G. L. Hatfield et al. 2015b). Additionally, there were 10 individuals with KL grades of 2 that were excluded from this analysis to better match radiographic severity between TKA and no TKA groups, however, all of these individuals did not progress (no TKA) at follow-up, again suggesting that radiographic severity may play a role in clinical OA progression. Further study with matched groups or in larger samples that could control for baseline severity would help clarify whether these gait features were indeed related to progression at short-term (3.5-year) follow-up or merely due to baseline differences in severity between groups.

There were no differences in baseline accelerometer-derived variables (step count, SED, LPA, or MVPA) between individuals who did and did not progress clinically at 3.5-year follow-up, supporting the null hypothesis (Table 7.9). While it appeared there was a trend towards greater SED (in minutes) in the no TKA group compared to the TKA group ($p = 0.16$) (Table 7.9), it seems this was due to a difference in wear time, as there was no difference between-groups in SED as a percent of wear time ($p = 0.50$). The lack of significant differences in PA variables may mean that joint loading frequency is less important than joint loading magnitude/duration features in relation to progression over a shorter time frame, such as the 3.5 year follow-up in the current study. A difference in joint loading frequency between two groups would lead to greater differences in overall loading exposure between groups if they were followed over a longer period. This hypothesis could be explored in a larger study with a longer follow-up.

Furthermore, while the average step counts for both TKA and no TKA groups in this longitudinal analysis were marginally above the 6000 steps/day threshold reported by White et al. (D. K. White et al. 2014), based on the results of the cross-sectional analysis, the overall low step count in this population may be another reason why there were no differences in step count between those who progressed and those who did not.

One limitation of the current study is that men and women were analyzed together. Both gait (K. A. McKean et al. 2007, J. L. Astephen Wilson et al. 2015) and PA (**Chapter 6**) in OA are affected by sex. The distribution of women to men in the current sample is not representative of the higher prevalence of OA seen in women versus men (V. K. Srikanth et al. 2005) and the proportion of women in the lowest two quartiles of step count was higher, although not statistically different, than the highest two quartiles of step count. Thus, comparisons among quartiles may be confounded by sex differences. The percent of women in the TKA and no TKA groups in the longitudinal analysis, however, was similar.

Another limitation is the use of accelerometer-derived step count as a surrogate metric of joint loading frequency. In using step count as a surrogate metric of joint loading frequency along with metrics from gait analysis that describe joint loading magnitude/duration during a single step, the assumption is made that all steps taken during the course of a day are producing the same loading magnitude/duration as the steps that were captured in the gait laboratory. Thus, the overall loading exposure on the joint may be over or underestimated depending on whether the laboratory measured data is reflective of gait in daily life. Furthermore, the calculation of step count is done within ActiLife software according to proprietary formulas and thus it is not clear whether the accelerometer-derived step count metric is strictly measuring the number of steps taken each day or more likely, based on the correlations between gait variables and both step count and MVPA but not LPA, taking into account the intensity of PA in calculating step count. Despite this, it still represents a feasible and relevant surrogate for joint loading frequency as long as these assumptions are kept in mind.

Together, the two analyses performed in the current study provide novel information to aid in our understanding of the relationships between joint loading magnitude/duration, joint loading frequency, and clinical OA progression. While joint loading magnitude/duration metrics related to clinical OA progression were also related to step count and MVPA in the cross-sectional analysis, we were unable to show baseline differences in step count or MVPA between individuals who did or did not progress clinically at 3.5 year follow-up, which may indicate longer follow-up periods are needed to see the effects of joint loading frequency on clinical progression. Alternatively, joint loading frequency may only have an effect on clinical progression if it falls above a certain threshold. Future research should investigate whether increasing step count in individuals falling below this threshold could improve gait patterns and/or whether improving gait patterns would lead to increased step count in this population. In conclusion, these findings provide evidence that joint loading frequency (step count) may contribute unique information regarding the overall loading environment for individuals falling above a certain threshold of step count, but a longer follow-up period may be needed to see the effects of differences in step count on clinical OA progression.

Chapter 8. Conclusion

8.1 Key Findings

This thesis aimed ***to better understand how features of the knee joint loading environment are related to clinical progression of medial tibiofemoral knee OA***. While the KAM peak and impulse have been studied frequently in relation to structural OA progression, clinical progression may better represent the burden of OA on individual patients and the healthcare system. Thus, studying the relationships between features of the overall knee joint loading environment and clinical OA progression may identify targets for interventions that are more effective at slowing rates of clinical OA progression (defined in this thesis as reaching a TKA endpoint).

Chapter 3 addressed the first objective of this thesis, which was *to determine differences in baseline three-dimensional knee joint moment and EMG waveform features between progression and no progression groups using both a structural and a clinical progression definition within the same cohort*. By examining baseline gait characteristics related to progression in individuals with medial tibiofemoral knee OA when using a structural progression definition (medial JSN) and in the same group when using a clinical progression definition (TKA outcome), this chapter showed that a biomechanical magnitude feature (higher KRM through mid-stance) was associated with progression using the structural progression definition, while prolonged muscle activation through mid-stance (in the RF and LH) was associated with progression when using the clinical progression definition. Increased overall LH activation was seen in the progression group using either definition.

Chapter 4 addressed the second objective of this thesis: *to compare the ability of baseline knee joint moments, EMG waveform features, and demographic and clinical covariates, both alone and in combination, to discriminate between individuals who do or do not progress clinically at follow-up*. This study found that the odds ratio for clinical progression almost doubled when using both biomechanical and muscle

activation features together versus either data type individually and that the addition of covariates improved this combined model marginally. Supporting the results of **Chapter 3**, this study again highlighted the contribution of muscle activation patterns to clinical OA progression. Furthermore, a model with KL grade as the only factor was not found to be very robust using bootstrapping.

Chapters 5-7 addressed the third objective of this thesis: *to understand whether joint loading frequency alters the relationships between gait metrics and clinical OA progression*.

Chapter 5 addressed the sub-objective *to determine whether between-group differences in joint loading frequency that were identified when averaged data from two or three weeks throughout a year was used could also be identified using a single, one-week session of data*. By comparing joint loading frequency from a single week of accelerometer wear to the average of two or three weeks of accelerometer wear during a year in individuals with medial tibiofemoral knee OA and asymptomatic controls, this study found that a single one-week session could identify between-group differences in step count that were seen when averaging multiple sessions, despite large variations at the individual level between a single one-week session and an average of two or three one-week sessions (± 2100 steps/day).

The second sub-objective was addressed in **Chapter 6**: *to determine whether clinical status (symptomatic or asymptomatic) or sex (women or men) affect joint loading frequency in individuals with structural signs of knee OA*. By comparing women and men with symptomatic medial tibiofemoral knee OA (clinical OA diagnosis) versus asymptomatic individuals with similar radiographic severity (radiographic OA only), this study found that step count was affected by both clinical status (symptomatic or asymptomatic) and sex. There were differences in step count between asymptomatic women and men (women higher), between symptomatic women and men (men higher), and between asymptomatic and symptomatic women (asymptomatic higher), but not between asymptomatic and symptomatic men.

Chapter 7 addressed the third sub-objective *to explore correlations between joint loading frequency and joint loading magnitude/duration variables that have*

been associated with OA progression and differences in joint loading frequency between individuals who later do or do not progress clinically. This study found correlations between step count and gait variables that have been linked to OA progression, including a less dynamic KFM pattern and prolonged LH activation through mid-stance and lower step count. Interestingly, the quartile of participants with the lowest PA level (approximately 4000 steps/day) exhibited gait patterns that had less dynamic moment waveforms and prolonged muscle activation patterns compared to the other three quartiles, which were more similar in gait patterns. No difference was found in baseline step count between those who did or did not progress clinically at 3.5-year follow-up.

In summary, prolonged muscle activation plays a unique role in clinical OA progression that is different from structural progression. There also are relationships between gait patterns associated with OA progression (less dynamic moment patterns and prolonged muscle activation) and step count that are most prominent in those with the lowest levels of step count, but step count was not different between individuals who did or did not progress clinically at 3.5-year follow-up.

8.2 Impact And Clinical Significance

The main motivation for this thesis was the fact that our current model of care for OA, consisting of palliative symptom management until end-stage surgical interventions (R. Speerin et al. 2014), is both not sustainable for the growing population of individuals with OA and does not slow, stop, or reverse OA progression. By investigating how the overall joint loading environment affects clinical progression in knee OA, this thesis identified joint loading features that could be targets for the future development of conservative management strategies and clinical screening tools. While much research in recent years has gone into the development of gait interventions aimed at changing peak KAM (N. D. Reeves and F. L. Bowling 2011), the results of this thesis suggest that addressing prolonged muscle activation patterns is an important target for interventions aimed to slow clinical OA

progression. Furthermore, an important finding of this thesis resulting from the use of PCA rather than discrete metrics is that the dynamic loading patterns and not just loading magnitudes are important to clinical knee OA progression. Thus, merely changing peak loading on the joint may be less effective at slowing clinical OA progression than addressing the dynamic patterns of loading.

It is still unknown whether joint loading frequency would contribute to clinical OA progression over a long-term period, but this thesis was able to explore how joint loading frequency is accumulated in OA and the relationships between joint loading frequency and clinical status, sex, gait features, and OA outcomes over a short-term follow-up. There appear to be individuals with low step count and gait patterns that have been associated with OA progression who may be most in need of intervention as they may be at risk for clinical OA progression due to the joint loading magnitude/duration features of their gait and may be at risk of other health issues due to low step count and low PA. This work also highlighted the importance of utilizing homogenous samples or accounting for clinical status differences in the analysis of studies on joint loading frequency and PA, which is especially important when using some of the publically available large datasets like the Multi Center Osteoarthritis Study or the Osteoarthritis Initiative that collected cohorts with or at risk for knee OA (i.e. including asymptomatic and symptomatic individuals). Similarly sex was important to joint loading frequency and PA and the differences between sexes may highlight differences in access to education about PA in OA. Furthermore, when we do reach a point where we are prescribing and monitoring specific levels of joint loading frequency or PA for individuals, we may need to take an average measure of PA from multiple weeks during a year, or strictly control for confounding variables such as weather, to assess whether an individual patient has made a clinically meaningful change in PA level.

Thus, at present, addressing prolonged muscle activation patterns is an important target for interventions to slow clinical OA progression (to change joint loading magnitude/duration) but more work is needed to understand whether PA-based interventions (to change joint loading frequency) will help further slow clinical OA progression over a longer follow-up period.

While more work needs to be done, the potential benefits and opportunities for either neuromuscular or PA based interventions in knee OA are:

1. They are **less invasive and have fewer side effects** than the current model of care – we may be able to send patients to a physiotherapist or exercise specialist rather than a pharmacist or surgeon
2. We would be directly treating the factors we want to change (joint loading features) and thus can have **more immediate monitoring of their effectiveness**, and
3. **Most importantly, they have the potential to actually slow or stop OA processes** in contrast to the current model of care

The strengths of this thesis are the focus on clinical OA and clinical OA progression and addressing multiple aspects of joint loading (3D loading, dynamic loading patterns, muscle contributions, joint loading frequency). There is growing support for identifying factors related to the clinical illness of OA rather than merely the radiographic disease (V. B. Kraus et al. 2015, The Osteoarthritis Research Society International 2016, Y. Zhang and J. Niu 2016) due to discordance between the two and the need for clinically relevant interventions. As technology develops further, we may be able to better link structural damage in the joint to OA symptoms, whether through MRI features, chemical biomarkers, or other metrics that are more sensitive to change than plain radiographs, however, until that point, this thesis provides an important contribution to the literature by examining the clinical, rather than structural, burden of OA. The idea of defining the overall loading environment of the knee (M. R. Maly 2008) is also gaining support. This thesis took that a few steps further by investigating 3D moments, the contribution of muscle activation to loading, dynamic patterns rather than magnitude features of loading only, and investigating intensity-based PA variables as well as step count. While more work still needs to be done, this research adds to the current literature by providing a more complete picture of the overall loading environment of the knee joint and how the components of this loading environment relate to clinical OA progression.

8.3 Limitations And Other Considerations In Interpretation

Progression definitions

One point of consideration in interpreting the results of this thesis are the differing definitions of progression metrics that could be used to define structural and clinical OA progression and limitations in the methods used in this thesis. As was discussed in the introduction and background literature (**Chapters 1-2**), radiographic progression is the currently accepted metric of structural change in clinical trials for OA (D. J. Hunter et al. 2015). This is likely to change with the recently accepted classification of OA as a serious condition by the U.S. Food and Drug administration (The Osteoarthritis Research Society International 2016), which will allow for the use of intermediate endpoints, such as metrics derived from MRI. This may provide improvements over the currently used radiographic methods of measuring structural progression due to the ability to visual individual tissues and obtain 3D rather than 2D images, and will reduce errors due to positioning within the beam, etc., but consensus on which standardized metrics will be accepted is still forthcoming.

The clinical progression endpoint chosen for this thesis, TKA, was chosen due to its relevance to healthcare costs, patient burden, and its representation as an end-stage salvage procedure when other conservative treatments for OA have failed. TKA decisions can be affected by clinician bias, the patient's current health status and willingness to undergo surgery, healthcare coverage (as it is considered an elective surgery in some countries outside of Canada), and other factors. As an alternative, clinical progression could have been defined by symptom changes, whether self-reported pain and functional changes, or more objective but less specific tests of function such as a timed up and go test. These instruments, however, while validated to monitor symptom changes for research purposes, do not directly factor into decisions to recommend specific OA treatments or management strategies, leading to the decision to use a TKA outcome to represent clinical OA progression in this thesis.

Thus consideration should be taken for these specific metrics when interpreting the results of this thesis and comparing it to other literature. What is interesting, however, is that despite potential error in these metrics, we still see a strong signal over that noise and were able to identify different features associated with structural versus clinical progression.

Pain and Gait

Pain has the ability to influence gait and thus influence joint loading. Induced knee pain has been shown to cause gait adaptations similar to those seen in individuals with knee OA, including reduced peak KAM in early and late stance, reduced peak KFM in early stance, and reduced KEM in late stance (M. Henriksen et al. 2010). Similarly, treating pain in individuals with OA can also influence gait, with increases in peak KAM shown following treatment with nonsteroidal anti-inflammatory drugs (T. J. Schnitzer et al. 1993) or intra-articular injection of an analgesic (M. W. Shrader et al. 2004). Thus, pharmaceutical use or other pain treatments, such as cognitive-behavioral therapy or physical activity (which also has been shown to reduce pain in OA (M. Fransen et al. 2015)), could affect baseline joint loading and have even been proposed to be detrimental biomechanically to the long-term health of the joint (K. A. Boyer 2018)

In this thesis, pain treatment or other concurrent treatments were not accounted for in the analyses,. While pain treatment can affect joint loading, the focus of this thesis was on the relationships between joint loading and long-term outcomes. Thus, while including individuals who are actively treating their pain may introduce variability in baseline gait/joint loading, it also accurately reflects the experiences of the participants in their normal day-to-day life and allows us to relate baseline joint loading across a range of loading experienced by participants with OA to long-term outcomes.

Generalizability of results

This thesis focused on a group of individuals with “clinically moderate” knee OA (who were high functioning at baseline) and identified differences in certain

variables between individuals in this group who progress clinically and those who do not. These variables represent potential areas of focus for the development of conservative management strategies for this group, however, these results may not extend to individuals with very early signs of knee OA or more severe, late-stage knee OA. The decision to focus on this group was a pragmatic choice because we felt there may be a greater chance for successful interventions with a group that was still mobile and interested in understanding how gait, physical activity, and OA might be linked (as evidenced by their willingness to participate in our research studies). The other group that was not included in this thesis was individuals who went on to HTO, which could also be considered clinical progression as it is a major surgery. The sample of individuals who went on to HTO was small, and visual comparison between gait waveforms of individuals who went on to HTO versus individuals who went on to TKA, had structural progression without clinical progression, or did not progress suggested that the HTO group was distinct from all others (data not shown). Future study is warranted in this group as the treatment needs and/or prescription of appropriate joint loading frequency dose may differ from the individuals included in this thesis. Last, the sample of individuals in this thesis also did not include individuals who progressed clinically (to TKA) without structural progression. It would be interesting to study this group to see if they would exhibit the prolonged muscle activation patterns seen in the clinical progression group from **Appendix A** without the biomechanical differences that were seen in both the structural and clinical progression groups in **Appendix A**.

Motivation for physical activity

Related to the generalizability of the results of this thesis, there may be selective participation bias in the individuals who participated in these studies. One of the findings from **Chapter 7** was that individuals who had gait patterns that have been linked to OA progression (including less dynamic knee moment waveforms and prolonged muscle activation patterns) also had the lowest PA levels. While **Chapter 6** briefly covered barriers and facilitators to PA in OA, it is possible that individuals with OA did not volunteer to participate in what were advertised as

"walking studies for knee OA" due to these factors related to their motivation for PA. The individuals in **Chapter 7** that exhibited these gait patterns and low PA levels may be at higher risk for clinical OA progression and comorbidities related to low PA and thus future work should further investigate the correlations between these gait patterns and low PA.

Mechanical and biological differences between women and men

Given the higher rates and greater severity of radiographic and symptomatic OA (V. K. Srikanth et al. 2005) and higher rates of TKA (S. N. Williams et al. 2015), in women versus men, it is of interest to understand factors related to these sex differences in OA. Gait features (joint loading magnitude/duration) (K. R. Kaufman et al. 2001, K. A. McKean et al. 2007) as well as physical activity (D. D. Dunlop et al. 2011) and step count (joint loading frequency) (**Chapter 6**) have been reported to differ between women and men and thus differences in joint loading between the sexes could be relevant to these different rates of OA and clinical OA progression. While this thesis was focused on the mechanical factors related to OA and OA progression, OA is not a purely mechanical disease and biological or biochemical factors, such as hormonal or anatomical differences between women and men (K. M. Huffman and W. E. Kraus 2012), may also contribute to the different rates of OA and OA progression between the sexes. For example, lower levels of estrogen metabolites (2-hydroxyestrone and 16α-hydroxyestrone), which can affect collagen synthesis, were associated with higher incidence of knee OA development (M. R. Sowers et al. 2006) in a study of pre- and peri-menopausal women. Another study examining biochemistry in knee OA showed that leptin levels were associated with OA prevalence in women whereas a metric of insulin-resistance was associated with OA prevalence in men (C. A. Karvonen-Gutierrez et al. 2012), suggesting sex based differences in hormones can also affect rates of knee OA. The focus of this thesis on mechanical factors rather than biological factors was related to the goal of identifying potential targets for non-invasive interventions, however, it is important to keep in mind that biological factors could also contribute to OA disease processes

and may need to be considered to understand the differing rates of OA and OA progression between the sexes.

Loading on actual joint tissues

The metrics used to define joint loading in this thesis – net joint reaction moments, electromyography waveforms, and physical activity variables – all represent surrogate metrics of joint loading features rather than actual loads experienced by the joint tissues. *In vivo* load estimation is not possible in humans, except in the case of instrumented total joint replacements (e.g. (A. Arami et al. 2011, A. L. Kinney et al. 2013)), which is less relevant to investigating why people progress clinically to the point of needing a TKA. An alternative to this approach is modeling the contact loads on tissues within the joint, however, this can also involve many assumptions (L. Blankevoort et al. 1991, D. R. Carter and M. Wong 2003, D. G. Lloyd and T. F. Besier 2003). Future work investigating the relationships between load and tissue changes may need to utilize alternate measures of load, but for the purposes of this thesis, the surrogate metrics of load used here were more relevant to understanding clinical OA progression as they gave a more global description of the general loading environment of the knee to relate to our more global measurement of clinical change (TKA).

Contribution of the patellofemoral compartment and other joints

This thesis chose to focus on medial tibiofemoral compartment knee OA with all participants having lateral JSN (W. W. Scott, Jr. et al. 1993) scores less than or equal to medial JSN. Although patellofemoral compartment JSN scores were presented in this thesis, patellofemoral compartment involvement was not specifically studied or accounted for in the analyses. Patellofemoral compartment involvement can affect gait patterns (S. Farrokhi et al. 2015) and OA symptoms (R. S. Hinman and K. M. Crossley 2007), thus future research should consider this in examining relationships between joint loading and OA progression, particularly when using a clinical progression metric.

Similarly, this thesis only utilized unilateral gait and radiographic data for the more symptomatic leg although a portion of participants did report bilateral knee OA or bilateral knee pain. A change in loading at one knee can affect the contralateral knee, as well as ipsilateral joints, and a few participants (such as those included in the cross-sectional analysis but excluded from the longitudinal analysis of **Chapter 7**) reported clinical progression (TJA) of other joints. While it was beyond the scope of this thesis, future studies investigating loading across all joints of the lower limb in relation to clinical OA progression of all of these joints could help provide further understanding of how overall loading and compensatory movement strategies affect other joints.

8.4 Concluding Remarks

This thesis examined features of joint loading magnitude/duration and frequency, and the role of the overall loading environment described by these features in clinical knee OA progression. The results of this thesis indicate that gait features related to clinical progression differ from those related to structural progression only, with muscle activation patterns playing a unique role in clinical progression. Accumulation of joint loading frequency in knee OA is modulated by sex where women with clinical knee OA engage in a greater proportion of LPA and lower proportion of MVPA compared to asymptomatic women while men with knee OA have less SED and greater LPA but no difference in MVPA compared to asymptomatic men. Similarly, step count is affected by both sex and clinical status. At the individual level, PA levels and joint loading frequency vary throughout a year but at the group level, between-group differences are apparent using a single one-week time point for all but absolute metrics of SED. In a study of clinical progression over approximately 3 years, joint loading magnitude/duration, along with baseline severity appeared to be more influential in clinical progression than joint loading frequency or PA metrics, but cross-sectional analysis identified a group of individuals with low overall PA and joint loading frequency levels who also exhibited gait patterns that have been linked to clinical progression at 8-year follow-

up. Further study is needed to fully understand the contributions of joint loading frequency to clinical OA progression but these results may indicate that it is more relevant when examining individuals over longer follow-up periods and more relevant in individuals who are above a minimum PA threshold.

Clinically, these results have implications on conservative management strategies for knee OA. They indicate that management strategies that address prolonged muscle activation patterns may improve success of reducing clinical OA progression and rates of TKA. At present, these results do not lend support for or against increasing PA levels in OA as a management strategy but do indicate that women with symptomatic OA may have different challenges or strategies in achieving PA than men and that there may be a group of individuals with low PA and "at risk" gait patterns that should be examined in more detail. Intervention strategies developed with these results in mind may be able to improve the current model of care to ease the clinical burden of medial tibiofemoral knee OA on both individual patients and the healthcare system.

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Appendix A. Comparison Of Baseline Gait In Individuals Who Exhibit No Progression, Structural Progression Only, Or Clinical Progression At 7-Year Follow-Up

Table A.1 Baseline group characteristics for groups defined by status at follow-up: no structural or clinical progression (NP), structural progression without clinical progression (STRU), and structural progression with clinical progression (CLIN)

	NP (n = 17)	**STRU (n = 19)**	**CLIN (n = 13)**	***P***	**Tukey post-hoc**		
					NP v STRU	NP v CLIN	STRU v CLIN
Sex, women:men (%women)	3:14 (18%)	8:11 (42%)	4:9 (31%)	0.28			
Age (years)	55.9 (8.0)	57.9 (6.9)	58.1 (11.5)	0.73			
Mass (kg)	94.2 (16.9)	97.8 (18.9)	94.4 (12.1)	0.84			
Body mass index (kg/m^2)	30.5 (5.6)	33.6 (6.2)	30.7 (3.0)	0.21			
KL grade (1:2:3:4)	1:7:9:0	4:6:9:0	1:4:8:0	0.59			
Medial JSN (0:1:2:3)	0:5:12:0	3:8:8:0	0:6:7:0	0.14			
Lateral JSN (0:1:2:3)	13:4:0:0	16:3:0:0	8:4:1:0	0.30			
Patellofemoral JSN (0:1:2:3)	1:7:7:0	5:10:2:0	1:8:4:0	**0.04**	**0.03**	0.50	0.13
WOMAC							
Pain (/20)	7.3 (4.5)	5.4 (3.7)	8.5 (3.2)	**0.02**	0.31	0.66	0.07
Stiffness (/8)	3.6 (1.7)	3.2 (1.5)	4.4 (1.0)	0.10			
Function (/68)	20.8 (15.0)	18.7 (12.4)	26.0 (8.3)	0.27			
Strength†							
Knee Extensor (Nm/kg)	1.32 (0.48)	1.29 (0.39)	1.19 (0.42)	0.69			
Knee Flexor (Nm/kg)	0.69 (0.17)	0.66 (0.20)	0.61 (0.31)	0.65			
Plantar Flexor (Nm/kg)	1.08 (0.50)	0.98 (0.31)	0.95 (0.37)	0.70			
Speed (m/s)	1.2 (0.2)	1.3 (0.2)	1.2 (0.2)	0.23			
Time to follow-up radiograph (years)	7.1 (2.3)	7.4 (1.7)	5.9 (2.6)	0.11			

All data are presented as mean (standard deviation), except where noted. KL = Kellgren-Lawrence, JSN = joint space narrowing, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

† Strength data were unavailable for n = 1 participant in the STRU group.

Table A.2 Baseline knee joint moment waveform principal components (PCs) for three groups defined by progression status at follow-up: no structural or clinical progression (NP), structural progression without clinical progression (STRU), and structural progression with clinical progression (CLIN)

PCs		Interpretation	NP (n = 17)	STRU (n = 19)	CLIN (n = 13)	*P*	Tukey post hoc		
							NP v STRU	NP v CLIN	STRU v CLIN
KAM	1	Overall magnitude	-0.51 (1.25)	-0.05 (0.72)	0.14 (1.01)	0.36§			
	2	Early-, mid-stance difference	0.23 (0.65)	0.17 (0.43)	-0.11 (0.36)	0.17			
KFM	1	Overall magnitude	0.47 (1.33)	-0.10 (1.26)	-0.53 (1.39)	0.13			
	2	Flexion, extension moment difference	-0.10 (1.59)	0.39 (1.17)	-0.27 (0.89)	0.31			
KRM	1	External, internal rotation moment difference	0.20 (0.55)	-0.05 (0.44)	-0.09 (0.38)	0.17			
	2	Mid-stance moment	-0.21 (0.37)	0.09 (0.34)	0.07 (0.35)	0.03	0.04	0.09	0.99

All data are presented as mean (standard deviation), except where noted.

KAM = knee adduction moment, KFM = knee flexion moment, KRM = knee rotation moment, PCs = principal components

§Welch's F test performed due to a significant Levene's test result, with Games-Howell post-hoc testing when appropriate

Table A.3 Baseline electromyography waveform principal components (PCs) for three groups defined by progression status at follow-up: no structural or clinical progression (NP), structural progression without clinical progression (STRU), and structural progression with clinical progression (CLIN)

PCs		**Interpretation**	**NP (n = 17)**	**STRU (n = 19)**	**CLIN (n = 13)**	***P***	**Tukey post hoc**		
							NP v STRU	NP v CLIN	STRU v CLIN
LG	1	Overall magnitude	174.9 (89.6)	220.4 (78.0)	194.3 (74.6)	0.15			
MG	1	Overall magnitude	170.9 (53.7)	213.4 (58.5)	206.2 (94.1)	0.16			
VL	1	Overall magnitude	167.8 (96.2)	152.8 (119.3)	163.2 (83.1)	0.80			
	2	Prolonged stance activation	-16.0 (40.5)	-26.6 (27.0)	0.1 (20.9)	0.11			
VM	1	Overall magnitude	166.6 (109.0)	168.7 (89.3)	154.8 (80.9)	0.92			
	2	Prolonged stance activation	-19.7 (34.5)	-23.8 (45.1)	-2.4 (30.9)	0.35			
RF	1	Overall magnitude	92.7 (45.2)	103.2 (48.5)	114.2 (49.6)	0.48			
	2	Prolonged stance activation	7.8 (24.0)	3.3 (18.7)	28.9 (34.2)	**0.03**	0.90	0.07	**0.03**
LH	1	Overall magnitude	123.7 (51.8)	145.6 (63.3)	190.5 (79.5)	**0.03**	0.57	**0.02**	0.14
	2	Prolonged stance activation	-22.7 (29.7)	-19.2 (56.0)	16.7 (47.8)	**0.03**	>0.99	**0.05**	**0.04**
MH	1	Overall magnitude	99.2 (37.7)	123.0 (46.0)	104.3 (46.9)	0.24			
	2	Prolonged stance activation	-22.5 (28.2)	-36.5 (38.6)	-17.1 (18.0)	0.18§			

All data are presented as mean (standard deviation), except where noted.

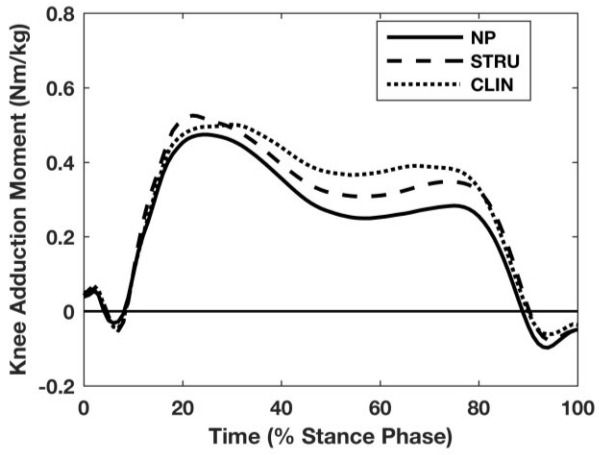
LG = lateral gastrocnemius, LH = lateral hamstrings, MG = medial gastrocnemius, MH = medial hamstrings, RF = rectus femoris, VL = vastus lateralis, VM = vastus medialis, PCs = principal components

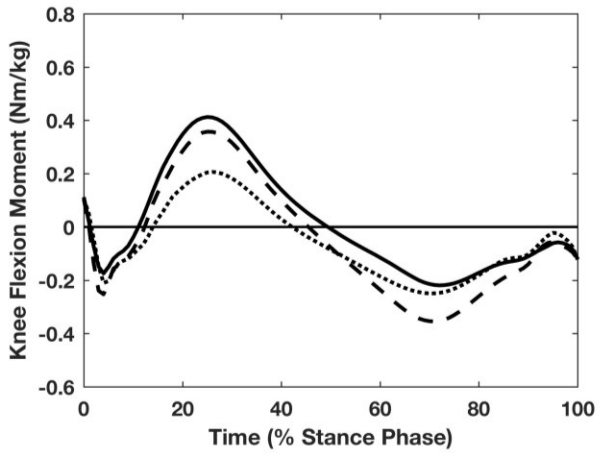
§Welch's F test performed due to a significant Levene's test result, with Games-Howell post-hoc testing when appropriate

Table A.4 Baseline knee joint moment discrete metrics for three groups defined by progression status at follow-up: no structural or clinical progression (NP), structural progression without clinical progression (STRU), and structural progression with clinical progression (CLIN)

Discrete variable	**NP (n = 17)**	**STRU (n = 19)**	**CLIN (n = 13)**	***P***	**Tukey post hoc**		
					NP v STRU	NP v CLIN	STRU v CLIN
KAM impulse (Nm*s)	0.17 (0.08)	0.19 (0.04)	0.22 (0.07)	0.16			
KAM first peak (Nm/kg)	0.51 (0.21)	0.55 (0.12)	0.54 (0.14)	0.68			
KAM mid-stance minimum (Nm/kg)	0.23 (0.13)	0.28 (0.10)	0.33 (0.10)	**0.04**	0.29	**0.03**	0.43
Peak KFM (Nm/kg)	0.48 (0.30)	0.39 (0.24)	0.29 (0.17)	0.14			
KFM Range (Nm/kg)	0.71 (0.47)	0.75 (0.33)	0.57 (0.24)	0.35			

All data are presented as mean (standard deviation). KAM = knee adduction moment, KFM = knee flexion moment.





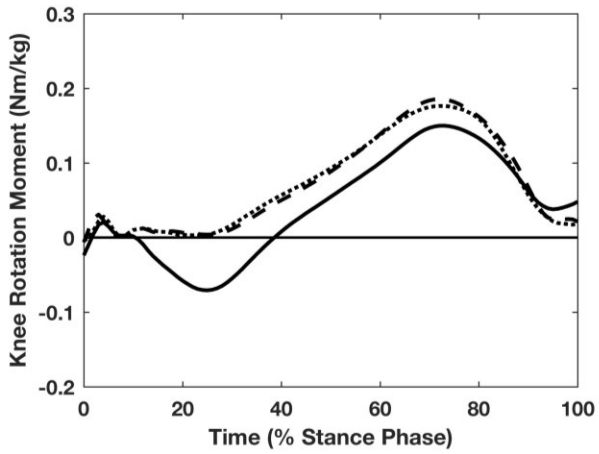


Figure A.1 Baseline knee joint moment waveforms for three groups defined by progression status at follow-up: no structural or clinical progression (NP), structural progression without clinical progression (STRU), and structural progression with clinical progression (CLIN)

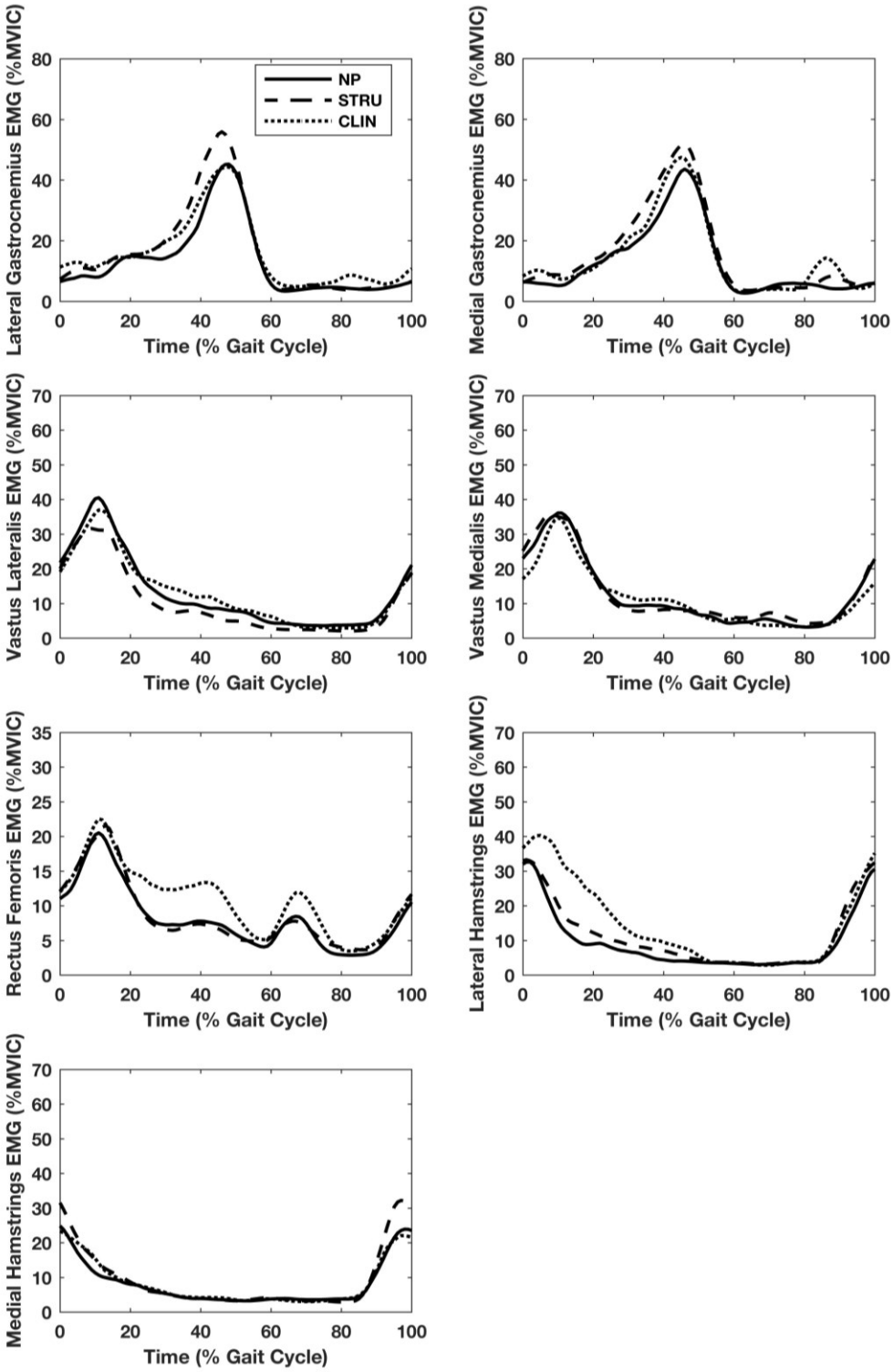


Figure A.2 Baseline electromyography waveforms for three groups defined by progression status at follow-up: no structural or clinical progression (NP), structural progression without clinical progression (STRU), and structural progression with clinical progression (CLIN)

Appendix B. Bland-Altman Analysis Plots Comparing Accelerometer Data From A Single Week And An Average Of Two Or Three Weeks During A Year

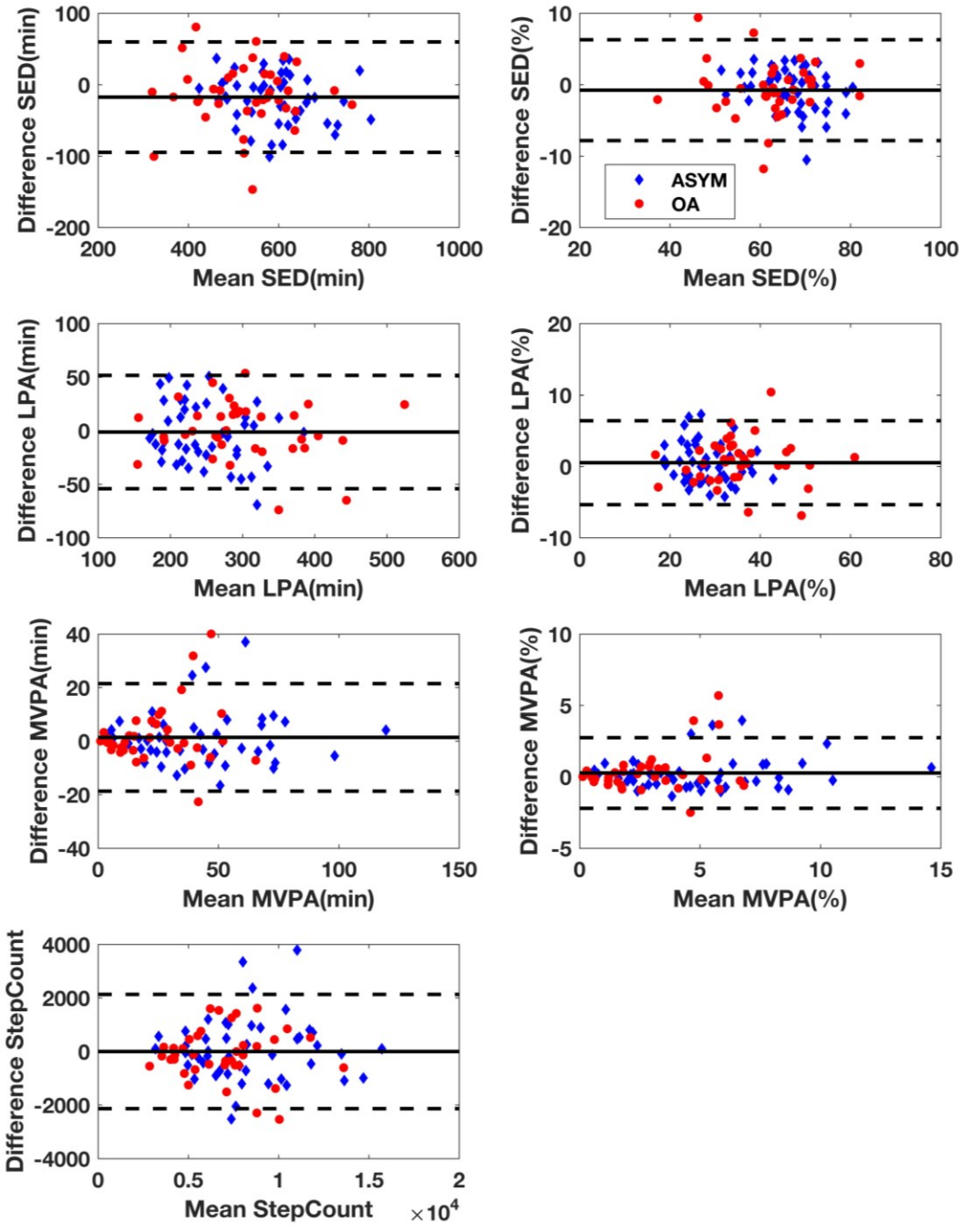


Figure B.1 Bland Altman plots comparing a two-session average to a single session of accelerometer data in individuals with at least two sessions of data

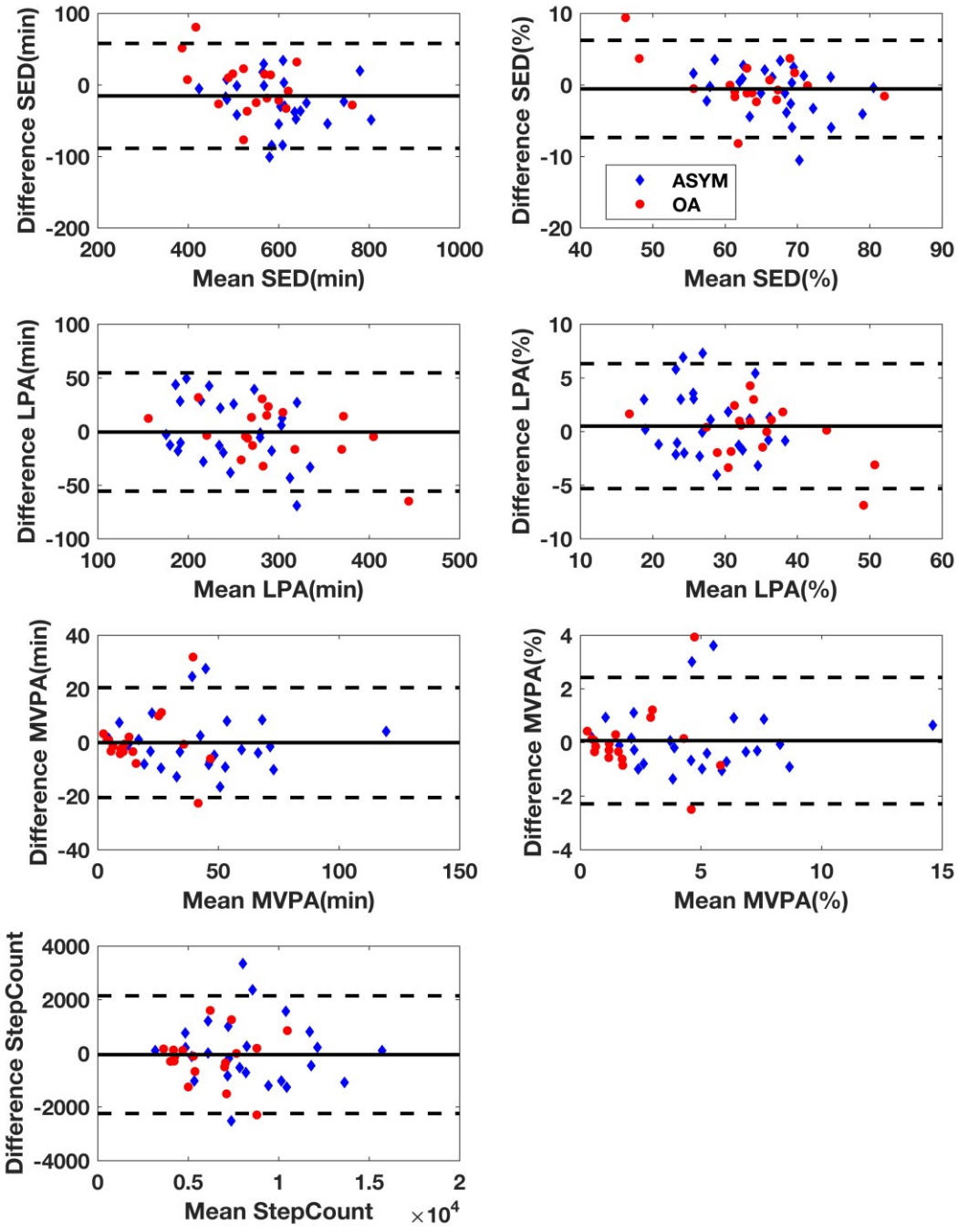


Figure B.2 Bland Altman plots comparing a two-session average to a single session of accelerometer data in individuals with three sessions of data

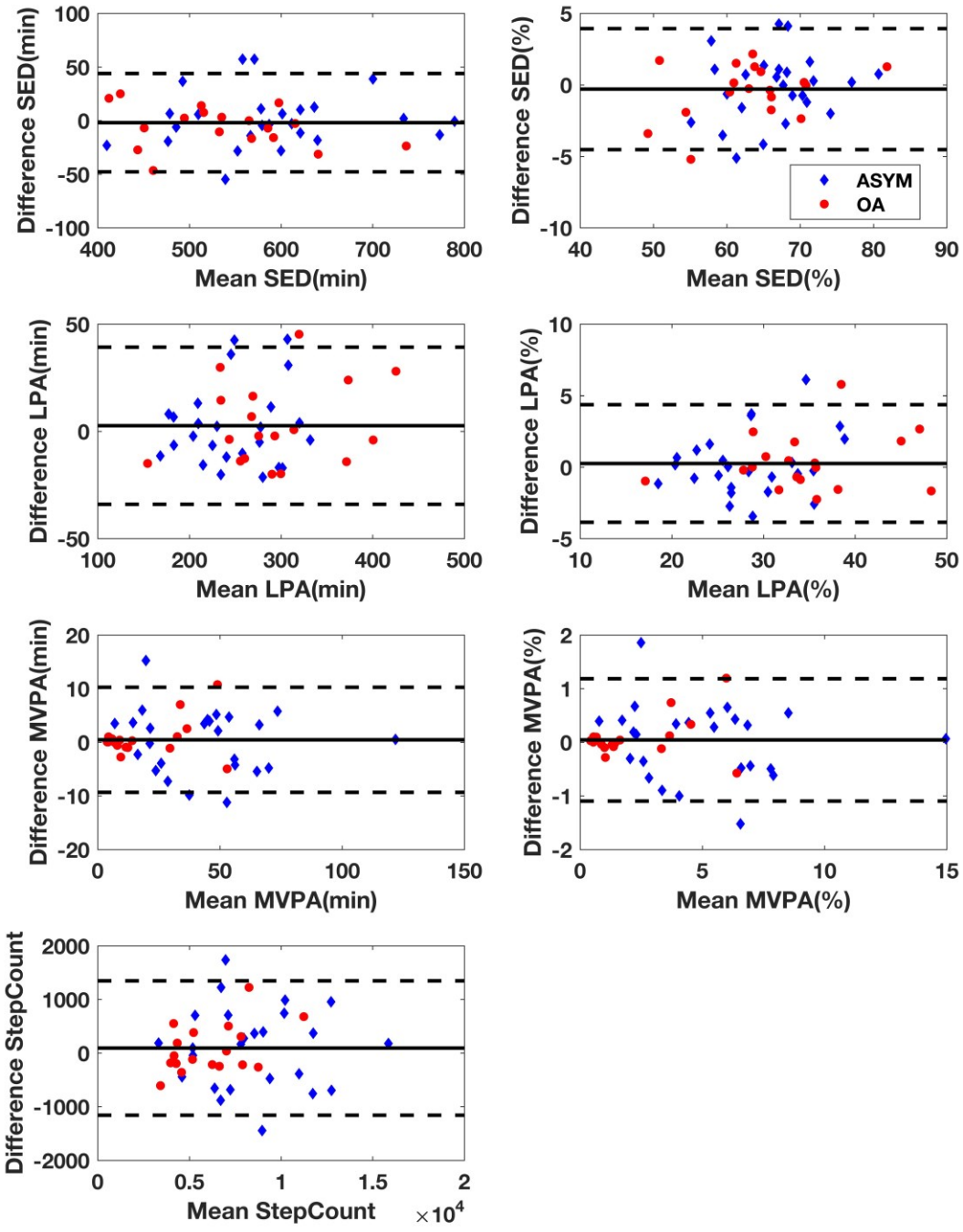


Figure B.3 Bland Altman plots comparing a three-session average to a two-session average of accelerometer data in individuals with three sessions of data

Appendix C. Correlations Between Step Count And Gait PCs

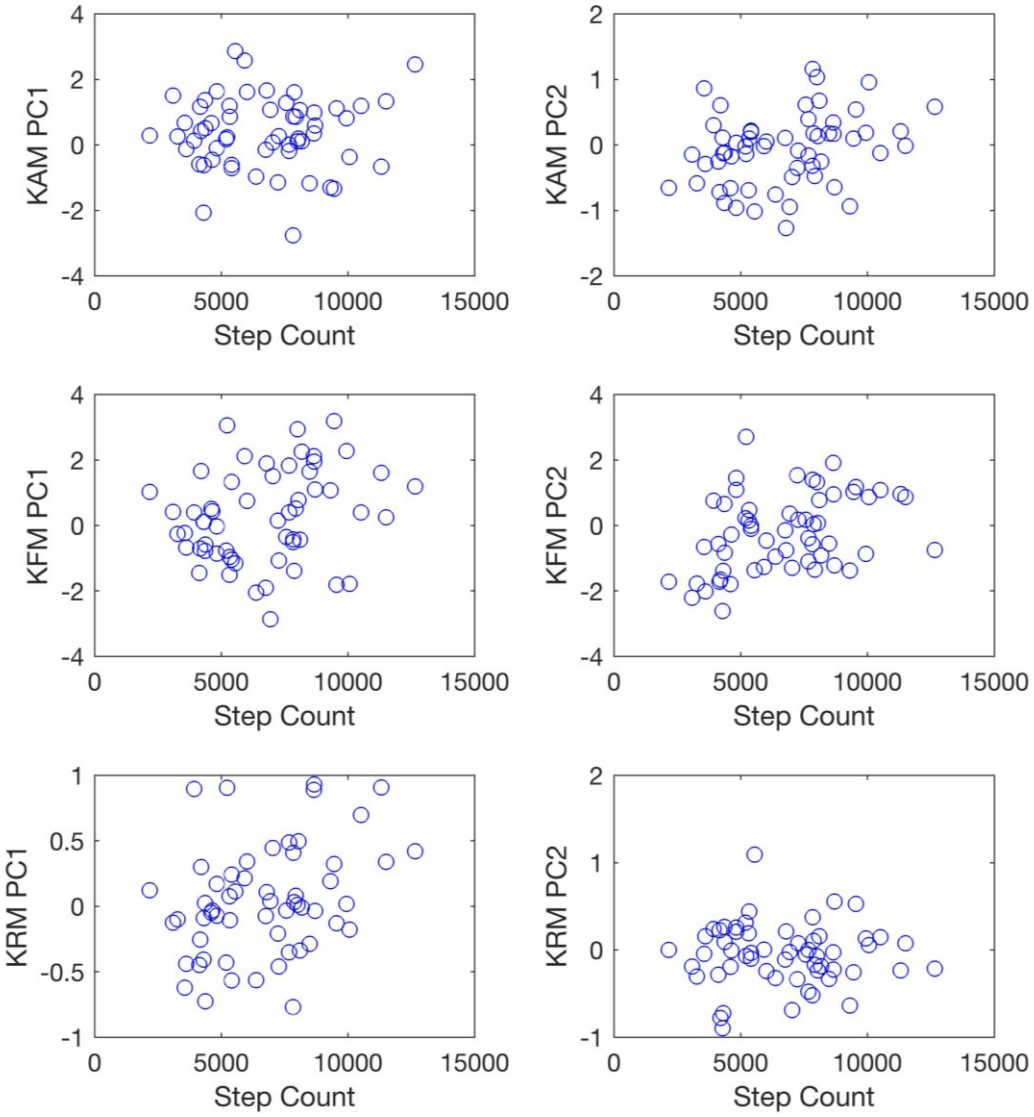


Figure C.1 Scatterplots showing relationships between step count and knee joint moment principal component features (PCs) in knee OA

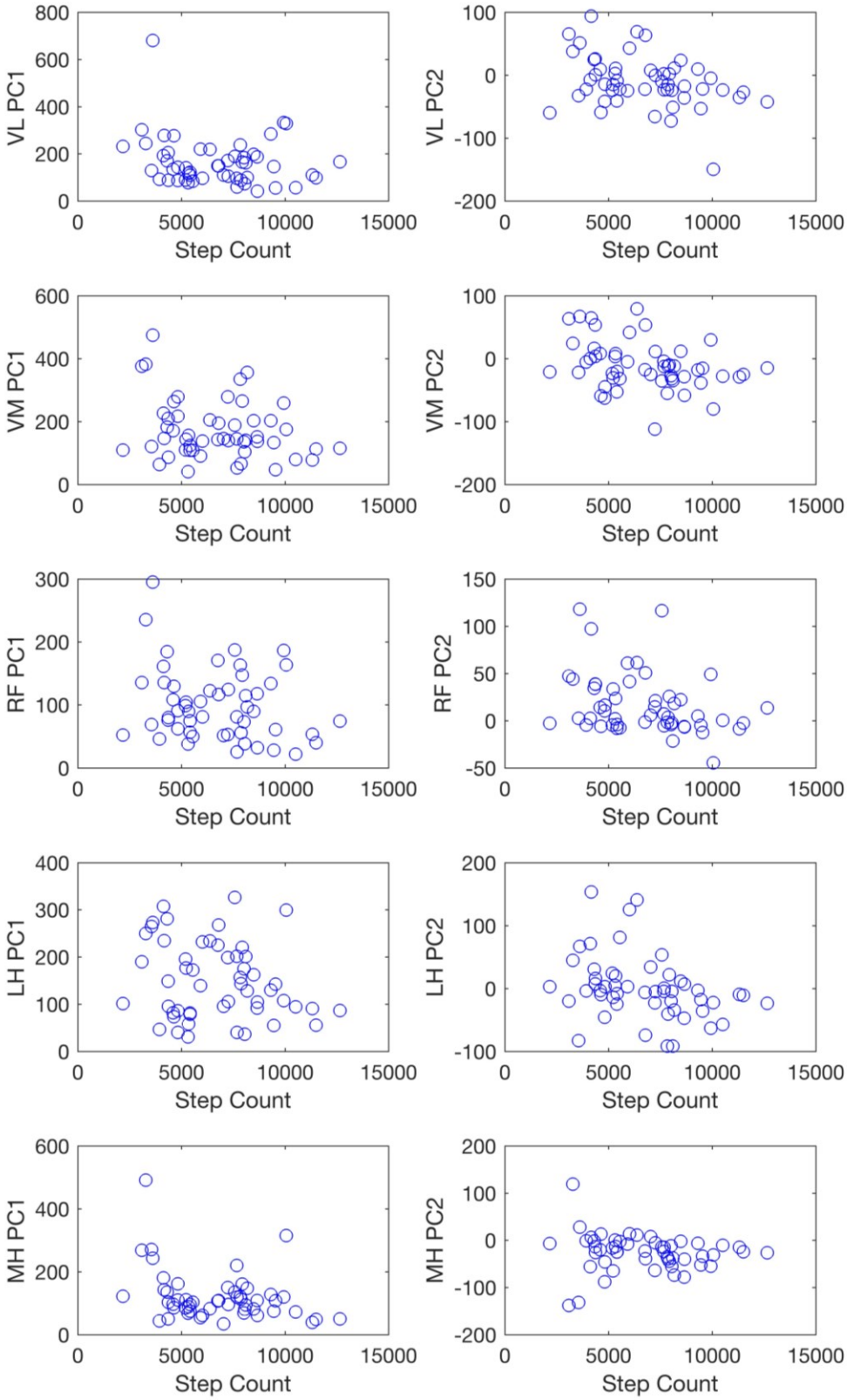


Figure C.2 Scatterplots showing relationships between step count and electromyography principal component features (PCs) in knee OA