Modeling the Patient Variability and Hierarchy in Joint-Level Kinematic and Kinetic Function Before and After Primary Total Knee Arthroplasty Surgery

by

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Dedicated to my sister,

Sarah Outerleys.

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ABSTRACT

Despite reported success with TKA surgery, it is unclear based on current tools and clinical monitoring postoperatively, if function at the knee joint-level is being optimized, specifically on a person-specific level. Or where along the functional spectrum of knee OA do individuals in terms of their biomechanics reside post-TKA. The drive to understand the variability in individual response at the knee joint-level is paramount to increasing success with TKA, and for developing objective assessment and evaluation tools for clinic, research, and industry.

The purpose of this study was to comprehensively capture the variability of improvement in knee joint-level biomechanics during walking gait of participants immediately before to one year after TKA, measured objectively using 3D gait analysis. This included examining how the pre-TKA status of knee joint-level biomechanics influences the amount of improvement after TKA, and investigating on an individual level whether joint-level biomechanics, both pre- and post-TKA, are more similar in level of function to healthy controls or those with moderate knee OA. Through calculating the change in biomechanics from pre-to post-TKA for a comprehensive list of biomechanical variables, significant and negative associations were shown between pre-TKA values and the change in values pre-to post-TKA. This suggests that pre-TKA functional status influences functional improvement, with lower function pre-TKA being associated with larger improvements post-TKA. Through investigating the number of individuals with biomechanics within asymptomatic and moderate OA ranges, it was shown both univariately and when multiple biomechanical variables were combined using a multivariate distance approach, that the majority of individuals post-TKA reach levels of knee joint function most similar to those with moderate levels of OA.

This study also examined the hierarchy of knee joint-level biomechanics in TKA to best summarize the functional variables that are most targeted by current standard of care TKA, and those that remain deficient post-TKA. Three discriminant models, with a stepwise procedure for variable selection, were developed using an optimal set of biomechanics to separate knee joint-level function during walking gait of individuals pre- and post-TKA, and from healthy controls. It was shown that current TKA management predominately alters variables of the frontal plane, resulting in relatively large deficits in sagittal plane knee joint function between TKA recipients and healthy controls. The discriminant models allowed for the development of a single functional score, able to quantify the functional gap in knee joint level biomechanics throughout triage with TKA.

The results of this study provide a comprehensive look at the variability in knee joint level improvement with TKA on a person-specific level and contribute to a framework for optimizing outcome from TKA based on objective person-specific data.

LIST OF ABBREVIATIONS AND SYMBOLS USED

2D	Two-dimensional
3D	Three-dimensional
ADL	Activities of daily living
ANOVA	Analysis of variance
B	Between-group sum of squares and cross-products matrix
BMI	Body mass index
CIHR	Canadian Institutes of Health Research
CJRR	Canadian Joint Replacement Registry
CR	Cruciate retaining
D^2	Mahalanobis distance
f	Discriminant function
HTO	High tibial osteotomy
Hz	Hertz
ICC	Intraclass correlation coefficients
IRED	Infrared light emitting diode
KAM	Knee adduction moment
λ	Eigenvalue
Λ	Wilk's Lamda statistic
LDA	Linear Discriminant Analysis
NSHRF	Nova Scotia Health Research Foundation
OA	Osteoarthritis
OKS	Oxford Knee Score

ORS	Orthopaedic Research Society
PC	Principal component
PCA	Principal Component Analysis
PROM	Patient reported outcome measure
PS	Posterior stabilized
RSA	Radiostereometric Analysis
S or C	Covariance matrix
SF-36	Short Form Health Survey
T	Total sums of squares and cross-products matrix
TKA	Total Knee Arthroplasty
U	Eigenvector
UKA	Unicompartmental Knee Arthroplasty
V	Raw discriminant function coefficients matrix
W	Within-group sum of squares and cross-products matrix
WOMAC	Western Ontario and McMaster Universities Arthritis Index
X	Matrix of variables

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CHAPTER 1 INTRODUCTION

1.1 Introduction

Knee osteoarthritis (OA) is the most prevalent chronic disease of the musculoskeletal system, characterized by pain and reduced function of the knee joint. It is estimated that over 5.6 million Canadians are afflicted with the disease, which is projected to increase to over 10 million by 2040, representing a significant socio-economic burden(Bombardier et al., 2011). Current conservative treatment strategies, primarily pharmaceuticals or knee orthoses, may help with symptom management in the short term but has not been shown to slow disease progression(Crawford et al., 2013). Thus, total knee arthroplasty (TKA) surgery remains the primary treatment option for severe stages of knee OA(Hunter and Felson, 2006). Conventional TKA is a highly invasive orthopaedic procedure involving resection of the degraded bone and bearing surfaces of the knee joint and replacing them typically with a combination of metal and plastic components. The primary goals of the procedure are to reduce knee joint pain and restore knee joint function.

The number of TKA surgeries being performed worldwide, and Canada in particular is increasing. The Canadian Joint Replacement Registry (CJRR) reports that over 60 000 TKA surgeries are performed each year. This is an increase of 20%, over a 5 year span (2010-2015), with the majority (60%) of patients over the age of 65(Canadian Institute for Health Information, 2015). However, there has been a significant increase in the number of younger individuals undergoing the procedure, most notably between the ages of 45 and 54(Canadian Institute for Health Information, 2009; Kurtz et al., 2009). The increasing demand for surgery coupled with limited orthopaedic resources is creating lengthy wait times(Comeau, 2004; Sanmartin et al., 2000). Currently in Nova Scotia, 90% of patients wait over 2 years, on average, to receive a primary knee replacement(Province of Nova Scotia, 2016) and this is the longest provincial wait time in the country, representing a serious socioeconomic burden(Canadian Institute for Health Information, 2016).

TKA is considered highly successful, as most patients report reduced pain and increased function after surgery. A consistent subgroup of patients, however, are dissatisfied due to factors such as persistent pain and unmet functional expectations. Reported rates of patient dissatisfaction have varied between 7-19%(Baker et al., 2007; Bourne et al., 2010; Choi and Ra, 2016; Gustke et al., 2014; Noble et al., 2006; Robertsson et al., 2000). Furthermore, while contemporary implants are associated with a survivorship of 20 years or more(Callaghan et al., 2013; Patil et al., 2015), 7% of all primary TKA procedures require revision surgery at 10 years(Canadian Institute for Health Information, 2015). Revision surgeries are accompanied with increased patient risk and direct and indirect costs. It is currently unclear how the increasing number of younger individuals requiring TKA will affect outcomes due to higher functional demands and requiring longer implant survivorship(Parvizi et al., 2014).

Outcome from TKA surgery is clinically based on patient-reported pain and functional satisfaction after surgery, and at times captured using patient reported outcome measures (PROMs). PROMs are most often used in a research environment, not in standard clinical practice. Measurement of outcome is complex and multifactorial, as such no single PROM has been identified that is able to capture all facets of outcome reliably(Ramkumar et al., 2015). Functional outcome assessed using PROMs is highly subjective, is influenced by patient co-morbidities, and often overestimate functional improvements in response to a large reduction in pain(Boonstra et al., 2008; Dunbar et al., 2004). In addition, PROMs poorly reflect the functional ability of patients, as captured using performance-based measures(Mizner et al., 2011). Performance based measures including timed-walking and sit-to-stand tasks(Konan et al., 2014) are better at capturing global functional ability, but lack in-depth biomechanical assessment, specifically at the joint level. Therefore, knee joint-level function on its own is not currently captured well(Hossain et al., 2015) or often clinically. Current outcome and summary measures cannot provide objective information at the joint-level and it remains unclear if joint-level function is being optimized, specifically on a patient-specific level. This level of information is vital to inform patient management or surgical triage and decision-making.

The use of three-dimensional (3D) gait analysis has provided a means for a more objective and comprehensive biomechanical assessment before and after TKA(Andriacchi et al., 1982; Chao et al., 1980; Simon et al., 1983). Gait analysis has produced evidence suggesting a link between abnormal knee flexion moment patterns and anterior knee pain that persists post-operatively(Smith et al., 2004), a common surgical complaint. Gait analysis has also produced evidence, in conjunction with radiostereometric analysis (RSA), showing that pre-operative knee joint loading patterns may be associated with implant motion post-operatively(Astephen Wilson et al., 2010; Hilding et al., 1996). Implant migration has been associated with future implant loosening, leading to failure and requiring revision surgery(Ryd et al., 1995). These examples highlight the potential role and power of gait analysis in TKA triage. Despite this, its use has primarily remained within the research environment and has received little translational effort to enter the clinic or use by industry for implant design testing and in-vivo evaluation.

Previous studies that have examined 3D knee joint-level biomechanics in TKA have included healthy control cohorts for comparison(Smith et al., 2004; Wilson et al., 1996; Worsley et al., 2013), however it remains unclear what aspects of gait are restored to healthy levels of function for most individuals, and which do not. Previous studies have included small sample sizes and/or often report rather simplistic measures (i.e. subjective discrete measures) and are generally limited to the sagittal plane(Levinger et al., 2013; Milner, 2009; Urwin et al., 2014). Because previous studies have mostly focused on understanding gait improvements from pre-to post-TKA(Hatfield et al., 2011; Xu et al., 2010), it has not been quantified what level of function is achieved post-TKA with respect to the spectrum of functional decline through the disease process of knee OA(Astephen et al., 2008a). Through population averages, TKA has been shown to improve some, but not all, aspects of knee joint biomechanics during walking gait, although functional deficits do remain relative to healthy cohorts, and with significant person-to-person variability(McClelland et al., 2007; Milner, 2009; Sosdian et al., 2014). This has been shown across implant designs, resulting in a lack of evidence to suggest one design is preferred for restoring knee joint function during gait post-operatively(Bolanos et al., 1998; Dorr et al., 1988; Joglekar et al., 2012; Urwin et al., 2014). Patient variability drives the need to further understand the effect of TKA on knee joint biomechanics, not just on average, but on a person-specific level, to more comprehensively capture what the current standard of care (in TKA) is capable of in terms of restoration of knee joint-level biomechanics. And while there seems to be a link between preoperative values of joint function with postoperative values(Smith et al., 2006), it is unclear how the variability in preoperative functional state influences the amount of functional improvement post-operatively.

To understand how to target functional improvements with TKA, it is important to be able to summarize the current standard of care in TKA in terms of function restoration. Few have summarized the multiple changes that occur, often simultaneously, throughout the stages of treatment with TKA, into less complex assessment tools(Chao et al., 1980; Laughman et al., 1984). Multivariate approaches have been utilized previously by our research team to distill information from large datasets to understand differences in biomechanical factors that distinguish between levels of severity along the spectrum of knee OA and progression of the disease to TKA(Astephen et al., 2008b; Hatfield et al., 2015). Through identifying an optimal set of joint-level functional metrics that best separate pre- and post-TKA gait from age-matched healthy knee joint function, as well as the functional metrics that are most targeted by current standard of care TKA, we can begin to distill important and clinically relevant information from the multitude of correlated data that is often presented, into a single ‘functional’ score. This way we can quantify the functional gap in knee joint level biomechanics as summarized by key features of joint-level functional deficits throughout triage, surgery, and post-operative management for individuals presenting for TKA surgery.

The results from this thesis will further our understanding of the changes in knee joint level biomechanics in individuals before and after primary TKA surgery during walking gait. This information will provide an evidence-based framework for an objective clinical assessment tool, which can help in the decision-making process and surrounding management strategies with TKA, including pre- and re-habilitation regimes, surgical decision making, and implant design innovation.

1.2 Objectives

1.2.1 Objective 1: Variability in Knee Joint-Level Biomechanics from Before to After Total Knee Arthroplasty

Objective 1 aims to examine the variability of improvement in knee joint level biomechanics during walking gait of participants immediately before to one year after TKA, as well as investigate how the status of knee joint-level biomechanics before TKA influences the amount of joint-level functional improvement after TKA. A sub-objective is to examine on a participant-specific level whether knee joint-level biomechanics during gait, both before and after TKA, are more similar to healthy controls, those with moderate knee OA, or their own cohort before TKA. This was examined to understand on a participant-specific level where along the functional continuum of knee osteoarthritis severity does knee joint-level function return, if at all, after TKA surgery.

1.2.2 Objective 1 Hypotheses

i) The amount of improvement in knee joint level biomechanics during gait with primary conventional TKA surgery will be highly variable between participants.

ii) The status of knee joint-level biomechanics before TKA will highly influence the amount of improvement in these biomechanics after TKA.

iii) Before and after TKA, participants will have knee joint-level biomechanics during walking gait most like their own cohort before TKA or a moderate osteoarthritis cohort, indicating some improvement in function post-TKA for most patients, but not full joint-level function restoration to levels of an asymptomatic, healthy age-matched cohort.

1.2.3 Objective 2: Hierarchy of Knee Joint-Level Biomechanics in Total Knee Arthroplasty

The purpose of this objective was to investigate which combination of knee joint-level biomechanical features during walking gait best separate participants before TKA from healthy age-matched controls, participants before TKA from one year after TKA, and participants one year after TKA from healthy controls.

1.2.4 Objective 2 Hypotheses

i) Based on previous work showing discriminatory features between individuals with severe knee OA and healthy controls(Astephen et al., 2008b), knee joint-level biomechanics during walking gait that best separate participants before TKA from healthy controls will be sagittal plane knee angle and joint moments, as well as frontal plane knee joint loading features.

ii) Previous work has shown knee joint-level improvements pre- to post-TKA in frontal plane features(Hatfield et al., 2011) and current conventional TKA procedures target frontal plane alignment. Therefore, it was hypothesized that knee joint-level biomechanics during walking gait that best separate participants before TKA from one year after TKA will be frontal plane joint moment features.

iii) Deficits in sagittal plane biomechanics have been shown after TKA relative to healthy controls(Andriacchi et al., 1982). Therefore, it was hypothesized knee joint level biomechanics during walking gait that best separate participants one year after TKA from healthy controls will be sagittal plane knee angle and joint moment features.

CHAPTER 2 BACKGROUND

2.1 Knee Osteoarthritis

Osteoarthritis (OA) is a chronic disease affecting joints of the human body, characterized by joint pain and stiffness, resulting in significant disability and reduced quality of life. OA is the most common form of musculoskeletal disease in Canada, affecting more than 5.6 million(Bombardier et al., 2011), with an overall estimated prevalence near 11% (8.9% for males and 12.6% for females)(Kopec et al., 2007). The large number of individuals afflicted with OA creates an estimated total economic burden (direct and indirect costs) of $27.5 billion in Canada. The number of individuals, and the costs associated, are estimated to increase substantially over the next 30 years(Bombardier et al., 2011).

The knee is one of the most commonly affected joints. Knee OA is often considered a ‘wear and tear’ disease, although it may better be described as the failing repair of joint damage(Kwoh and Hwang, 2014). Damage results from abnormal extra and intra-articular processes, through a variety of pathways including biomechanical, biochemical, and their combination(Andriacchi and Favre, 2014). The exact cause of knee OA is not completely understood, although a growing body of evidence suggests that mechanical factors such as increased physical forces or damaging joint insult is almost always involved in its initiation and progression(Englund, 2010; Felson, 2013). Risk factors include obesity, traumatic joint injury, older age, and gender (female)(Johnson and Hunter, 2014).

The disease process of knee OA involves degradation of knee joint structures. Thinning and fissuring of the articular cartilage covering both the distal end of the femur and tibial plateau result in exposed subchondral bone. The reduction in cartilage volume and narrowing of the joint space condenses subchondral bone, promoting osteophyte formation. Changes also occur to the joint capsule, ligaments, synovium, and muscles surrounding the joint.

Classification of disease severity is determined by radiographic and clinical symptoms. Standing anteroposterior radiographs (x-ray) and the Kellgren-Lawrence scale are used to score structural severity from 0-4, with higher scores coinciding with increased severity based on joint space narrowing and osteophyte formation(Kellgren and Lawrence, 1957). Clinical symptoms, like pain and reduced joint function, are often captured through patient-reported outcome measures (PROMs), including the Likert Western Ontario and McMaster Universities Arthritis Index (WOMAC). These subjective self-reports capture patient activity levels and quality of life, alongside pain and function(Bellamy et al., 1988; Roos and Lohmander, 2003). Severity classification remains complex, however, as there can be discord between structural severity and clinical symptoms(Hannan et al., 2000; Lawrence et al., 1966), depending on the measurement tool(Neogi et al., 2009).

Different treatment options exist targeting various aspects of knee OA, with the goal to reduce symptoms and mitigate its progression. Conservative treatment options include pharmaceuticals, physical therapy, gait modification, knee bracing and orthoses, and weight loss. These conservative strategies are accompanied with varying levels of success in terms of symptom relief in the short-term, but have not been shown to halt further progression of the disease(Bennell et al., 2016; Crawford et al., 2013). Once conservative options have been exhausted and the disease reaches severe stages, surgical interventions remain the primary management option. These include high tibial osteotomy (HTO), unicompartmental knee arthroplasty (UKA), and total knee arthroplasty (TKA). HTO predominately targets alignment deformities to balance joint loading, while UKA aims to replace localized areas of joint degradation; both considered more conservative surgical management as they retain more native joint structure and tissue. Ultimately, TKA surgery is the surgical intervention of choice to provide relief of symptoms associated with severe knee OA, involving the whole replacement of the entire knee joint.

2.2 Total Knee Arthroplasty

Ninety-eight (98%) percent of all total knee arthroplasty (TKA) surgeries are performed in Canada as treatment for knee osteoarthritis(Canadian Institute for Health Information, 2015). The primary objectives of the procedure are to reduce joint pain and increase joint function, increasing mobility and quality of life. Conventional TKA surgery is a highly invasive orthopaedic procedure, requiring surgical incision of the knee joint to resect degraded bone and bearing surfaces of the femur and tibia, which are then replaced with artificial implants. Contemporary implants have been associated with overall survivorship rates as high as 87 - 91% after 20 to 25 years(Callaghan et al., 2013; Patil et al., 2015).

2.2.1 Demand

TKA is a high-volume procedure and demand is increasing worldwide(Kurtz et al., 2011). The Canadian Joint Replacement Registry (CJRR) reports over 60 000 TKA surgeries are performed each year in Canada. This number has increased by 20% over a 5-year span (2010 – 2015)(Canadian Institute for Health Information, 2015). For comparison, TKA surgeries are the most performed operating room procedure in US hospitals, with over 700 000 performed annually, almost doubling since 2001(Weiss and Elixhauser, 2014). While most surgeries are performed on individuals over the age of 65, there has been a significant increase in the number of younger individuals undergoing the procedure, most notably between the ages of 45 and 54(Canadian Institute for Health Information, 2015; Kurtz et al., 2009). The increasing demand coupled with limited orthopaedic resources, has created lengthy wait times in Canada(Comeau, 2004; Sanmartin et al., 2000). In Nova Scotia, 90% of patients wait almost 2 years to receive primary TKA(Province of Nova Scotia, 2016). This is the longest provincial wait time in the country, well over the national benchmark of 182 days(Canadian Institute for Health Information, 2016). While TKA may be a cost-effective treatment option for severe stages of knee OA(Waimann et al., 2014), current and increasing demand along with long wait times make it a substantial socioeconomic burden(Canadian Institute for Health Information, 2015; Stokes and Somerville, 2008).

2.2.2 Demographics

The majority of individuals receiving TKA in Canada are between the ages of 65-74 (37%)(Canadian Institute for Health Information, 2015), with the average individual being 70 years of age(Robertsson et al., 2000; Scott et al., 2010). Females are at higher risk of developing OA(Zhang and Jordan, 2010), and are therefore receiving more TKA procedures than men(Canadian Institute for Health Information, 2015; Franklin et al., 2017).

The majority of individuals receiving TKA have also been reported to have at least one or more comorbidities including cardiac and metabolic diseases, as well as limitations in physical function and presence of significant pain(Franklin et al., 2017; van Dijk et al., 2008). Obesity is prevalent in TKA recipients as only 11% of males and 14% of females are normal weight (BMI between 18.5 and 24.9), 89% of males and 86% of females are either overweight(BMI between 25.0 and 29.9) or obese (BMI > 30)(Canadian Institute for Health Information, 2014). Demographics can vary based on geographical location, but remain similar globally(Franklin et al., 2017).

2.2.3 Standard of Care

Triage for TKA surgery begins once an individual is referred to an orthoapedic surgeon for consultation. In Nova Scotia, 90% of individuals receive consultation within 267 days(Province of Nova Scotia, 2016). The decision to proceed with surgery is based on static 2D radiographs, patient reported symptoms, including pain and function, and a few simple clinical observations including walking down a hall or passive knee range of motion. Ultimately, the decision to operate is determined through patient-surgeon agreement. Then, particularly in Nova Scotia, the patient is put on a wait list for surgery, waiting as long as 3 years from the date of consultation(Province of Nova Scotia, 2016). Educational material and support on topics such as pre- and post-surgery physical therapy and nutrition are available in some parts of the province, but are not mandatory(Nova Scotia Department of Health and Wellness, 2017).

Postoperatively, all individuals receive standardized inpatient care. Generally, the patient is immobilized for the first day, but begins a standardized physiotherapy protocol as soon as possible. This includes immediate full weight bearing, encouraged joint movement, and quadriceps strengthening. The median in-hospital length of stay in Canada is 3 days (interquartile range: 2 days)(Canadian Institute for Health Information, 2015). Discharge is based on adequate pain management and ability to ambulate (i.e. rise from a chair, and ascend and descend stairs, independently). Patients are given standardized postoperative rehabilitation guidance, as well as information on physiotherapy services, either outpatient clinic at the hospital or private practice, to be attended at their own discretion. A follow-up appointment is scheduled and patients meet with the orthopaedic surgeon 2-6 weeks after surgery for evaluation. Postoperative evaluation is typically based on radiographs and patient report of symptoms.

2.2.4 Surgical Procedure

Standard of care primary TKA surgery protocol will vary slightly between cases and surgeons. Most often a standard medial parapatellar approach is used. Intramedullary alignment is performed with a 5° valgus distal femoral cut and a neutral (0°) tibial cut. The anterior and posterior cruciate ligaments are resected based on implant design, with the majority of patellae resurfaced using an inset patellar button. The measured resection technique is used to obtain a balanced flexion and extension gap, with a minimum of 110° flexion and full extension. The goal of conventional TKA is neutral alignment of 0 ± 3 degrees(Vandekerckhove et al., 2016).

2.2.5 Implant Designs

While a variety of implant designs exist, selection is generally based on surgeon preference and hospital resources. Contemporary implant designs aim to recreate native knee joint function through various design features. The basic components of contemporary implant designs include: a femoral component, tibial component, a tibia insert, and a patellar button.

Some implant designs aim to reproduce natural knee motion through ligament preservation such as cruciate retaining (CR) designs. Designs that sacrifice knee joint ligaments aim to achieve mechanical joint stabilization through a post and cam mechanism, known as posterior stabilized (PS) implant systems(Tanzer et al., 2002). The medial pivot and mobile bearing designs were developed to address the internal/external rotational component of knee joint motion, in hopes to reduce polyethylene wear. Wear particle formation contributes to osteolysis, resulting in a failure of the bone-implant interfaces causing aseptic loosening of the implant(Abu-Amer et al., 2007) and is the number one reason for revision surgery(Canadian Institute for Health Information, 2015). Polyethylene wear and particle formation has been associated with the relative motion and loading of the articulating surface of the artificial knee implants(D’Lima et al., 2001; Harman et al., 2001). Medial pivot designs guide tibial rotation through asymmetrical geometries of the articular surfaces(Atzori et al., 2008), while mobile bearing designs allow for tibial rotation by allowing the tibial insert to rotate freely(Huang et al., 2007). Unfortunately, current implant design choices, to date, have not proven to be able to fully restore the complex nature of the knee joint. No one design has been shown through population averages to be optimal over any other(Ahmad et al., 2015; Harrington et al., 2009; Jiang et al., 2016). The use of a patient-specific approach may improve our ability to better match individual joints and function to a design, yielding improved results.

An analysis was performed on a sub-group of TKA recipients used in this thesis, the results of which were presented as a poster at the 2016 meeting of the ORS (Appendix A.1). The objective was to examine pre- and post-operatively, along with the change due to the surgery, knee joint-level biomechanical differences during gait between CR and PS knees. Seventy-three participants were included in this analysis and received one of four implant systems (non-randomized design) including: NexGen PS (n=34) (Zimmer, Warsaw, Indiana), Triathlon PS (n=14) (Stryker Orthopedics, Kalamazoo, MI), Triathlon CR (n=11), and Medial Pivot CR system (n=14) (Wright Medical, Memphis, TN). Patients were grouped by global PS (n=48) or CR design (n = 25). In summary, there were no statistically significant differences in knee joint-level biomechanics between participants receiving either implant design, either before or after surgery, or in terms of change from pre-to post-operatively.

2.3 Surgical Outcome

Historically, outcome after TKA surgery had been measured using patient or implant survival as an end-point(Carr et al., 1993). Despite reports of increased survival rates(Roberts et al., 2007), 7% of all primary TKA surgeries require revision, representing a significant burden to the patient and healthcare system(Canadian Institute for Health Information, 2015). In longer-term scenarios void of revision surgery, using implant failure or death as an end-point may underplay other problems associated with TKA. Outcome measures of pain, function, activity, and general health have been considered a better measure of success in these scenarios(Price et al., 2010). Currently, outcome assessment is not formally a part of standard of care in TKA, with the majority of assessment being conducted within a research capacity.

A major aspect of contemporary outcome assessment is through administered self (patient)- reported outcome measures (PROMs), in questionnaire or survey form. Popular PROMs include the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index, Short Form Health Survey (SF-36), and the Oxford Knee Score (OKS)(da Silva et al., 2014). Many PROMs were created to capture specific facets of certain pathologies, and not necessarily designed or validated for use in TKA outcome assessment(Carr et al., 2012). Despite this, PROMs capture most TKA recipients seeing significant reductions in pain and increased function, activity, and quality of life after TKA(Bourne, 2008; Huch et al., 2005; Jones et al., 2001; Naili et al., 2016; Wright et al., 2004), over the short and long term(Shan et al., 2015).

Satisfaction is a popular outcome measure, and is high for most individuals after TKA(Robertsson et al., 2000). A consistent subgroup of individuals, however, remain dissatisfied due to factors such as persistent pain and unmet expectations(Choi and Ra, 2016), with dissatisfaction rates varying between 7-19%(Baker et al., 2007; Bourne et al., 2010; Gustke et al., 2014; Noble et al., 2006; Robertsson et al., 2000). Satisfaction is difficult to measure as it encompasses multiple sub-metrics (symptoms) and psychological factors(Dunbar et al., 2013). Due to the complex nature of outcome assessment, no single PROM has been identified that is able to capture all facets of outcome reliably(Ramkumar et al., 2015), additionally PROMs are not generally part of the standard of care for TKA.

2.3.1 Knee Joint Function

Restoration of knee joint function is a primary objective of TKA. It is important to the individuals undergoing the procedure, and is considered a factor in patient expectation and satisfaction(Mahomed et al., 2002). Questions such as: "*How mobile will I be after my surgery?*' and "*When will I be able to walk normally again?*" are ranked as some of the most important by patients(Macario et al., 2003).

Approximately 90% of individuals are satisfied with the overall functioning of their knees and with their ability to perform normal activities of daily living (ADL) after TKA(Parvizi et al., 2014). Knee joint function is often considered in context to its role with other aspects of outcome, such as pain and satisfaction, and therefore is not captured well on its own(Hossain et al., 2015). Functional assessment using PROMs is highly subjective, is influenced by co-morbidities, and often overestimates joint function improvements in response to large reductions in pain(Boonstra et al., 2008; Dunbar et al., 2004; Terwee et al., 2006). Furthermore, while PROMs are easier to administer, they poorly reflect the actual functional ability of patients that are captured using performance-based measures(Mizner et al., 2011). Performance-based measures range from simple knee range of motion tests, to more demanding functional tasks such as the 6-minute walk test or timed up and go. Performance-based measures, and PROMs, have both shown improvements in function after TKA on population average, but function remains low compared to those absent of knee pathology(Bade et al., 2010), beyond the functional decline due to age(Noble et al., 2005). While performance-based measures are more objective than PROMs and better capture global functional ability, they do lack in-depth biomechanical evaluation, specifically at the knee joint-level which is necessary for informed innovation in patient-specific treatment and management.

Understanding knee function at the joint-level has proven highly important for the success of TKA. In 1968, Dr. Frank Gunston implanted his first Polycentric knee design. This implant design was based on the biomechanical principles of healthy knee joint motion(Gunston, 1971), as adopted from his mentor Dr. John Charnley(Charnley, 1972) from hip arthroplasty; initiating the modern era of successful implant designs. Aiming to recreate healthy knee joint biomechanics, more modern designs evolved from information garnered through in-depth biomechanical analyses(Andriacchi and Hurwitz, 1997). While cadaver and knee simulators are the go-to for ex-vivo testing, gait analysis was adopted as a model for in-vivo testing as it is a unique tool able to quantify, dynamically, the motion as well as the loading of the knee joint during common daily function, inclusive of surrounding tissue and musculature(Morrison, 1970). Despite this, innovation is more valued than evaluation, with new designs and surgical techniques able to enter the market or clinical practice without undergoing rigorous in-vivo functional testing(Carr et al., 1993). Thus, the use of gait analysis has primarily remained within the research environment, receiving little translational effort to enter the clinic, or by industry, for use as a function evaluation tool. In the research setting, gait analysis has shown that despite significant improvements in clinical measures, aspects of knee joint motion and loading after TKA remain abnormal relative to healthy joint function(Milner, 2009; Sosdian et al., 2014). Links between these abnormal gait patterns have been made to increased risk of implant failure and persistent pain after TKA(Astephen Wilson et al., 2010; Hilding et al., 1996; Smith et al., 2004).

2.4 Gait Analysis and TKA

Gait analysis is a powerful tool to objectively measure knee joint function during walking, providing a more in depth functional assessment than patient reported outcomes or performance-based measures. Modern gait analysis systems typically use optoelectronic motion capture technologies capable of acquiring three-dimensional (3D) motion data, and force platforms providing 3D foot-ground reaction force data, to biomechanically model the musculoskeletal system(Vaughan et al., 1992). Limb segment kinematics and Cardan-Euler rotations are used to calculate 3D joint angles, often expressed in a clinically meaningful anatomical reference frame(Grood and Suntay, 1983). Net resultant external joint moments and forces are calculated by solving an inverse dynamics problem, modeling the lower limb as linked segments, starting at the ground(Li et al., 1993; Morrison, 1970). Simultaneous collection of muscle activity during gait is also becoming more common, using electromyography(Hubley-Kozey et al., 2006). Kinematic, kinetic, and electromyographical data obtained from gait analysis have bene shown to be repeatable within and between day collections for healthy individuals(Kadaba et al., 1989). Futhermore, specific to the gait collection protocol conducted in the Dynamics of Human Motion Laboratory at Dalhousie University, repeatability of both discrete and waveform parameters (PCs) have been examined for kinematic, kinetic and electromyography data in a moderate knee OA population. Knee flexion angle and adduction moment parameters are associated with high intraclass correlation coefficients (ICC) (0.74 – 0.94), representing high repeatability, while knee internal/external rotation angles and moments as well as adduction/abduction angles are associated with lower repeatability, requiring caution when examining(Robbins et al., 2013). Caution should also be used when interpreting the peak knee flexion moment using discrete parameters, as it has shown lower repeatability, as compared to waveforms features captured using principal component analysis(Robbins et al., 2013).

2.4.1 Spatiotemporal Parameters

While not considered joint-level biomechanics, spatiotemporal parameters, such as gait velocity and percent time spent in stance and swing phase of gait, are valuable as summary metrics of functional outcome and comparing participant cohorts. While they been shown to have the potential power to characterize and discriminate between patient groups on their own(Levinger et al., 2009), they lack specificity in terms of diagnostic information around actual knee joint-level function. Gait velocity is a commonly reported spatiotemporal parameter, and can provide an understanding of global function, inherent to performance based measures(Mizner et al., 2011). In general, gait velocity increases through treatment, with individuals walking at a slower self-selected velocity, increasing post-TKA(Hatfield et al., 2011). Post-TKA gait velocity, however, remains significantly slower than healthy controls for most patients(Alnahdi et al., 2011; Mandeville et al., 2007). An inherent relationship exists between gait velocity and knee joint-level biomechanics during walking that needs to be considered during interpretation(Andriacchi et al., 1982; Astephen Wilson, 2012).

2.4.2 Knee Kinematics and Kinetics

Frontal plane kinematics capture the adduction-abduction motion of the knee joint during walking, also known as varus-valgus motion. The overall magnitude and range of this angle is typically small, particularly during stance phase, given the congruency of the knee joint in this plane both anatomically and in terms of implant design. While studies have investigated frontal plane kinematic changes pre- to post-TKA(Apostolopoulos et al., 2011; Orishimo et al., 2012; Wegrzyn et al., 2013) and compared to controls(Abdel et al., 2014; Alnahdi et al., 2011; Mandeville et al., 2008; Milner and O'Bryan, 2008; Urwin et al., 2014; Xu et al., 2010), the results are conflicted. This may be attributed to the variability in kinematics of the frontal plane(Mandeville et al., 2008), inherent error in magnitude depending on anatomical axis definition(Graci and Salsich, 2016) or if angles have been normalized to a static pose. Despite this, post-TKA individuals tend to walk on average with a smaller knee adduction angle compared to pre-TKA(Abdel et al., 2014; Orishimo et al., 2012; Wegrzyn et al., 2013), similar to healthy controls(Alnahdi et al., 2011; Mandeville et al., 2008; Milner and O'Bryan, 2008). This is most likely a reflection of conventional TKA targeting the correction of varus deformity of the joint to a more neutral alignment(Orishimo et al., 2012).

The knee adduction moment (KAM) is one of the most popular metrics characterizing gait in individuals with varying degrees of knee OA severity. The KAM is suggested to be a surrogate measure for the ratio of medial to lateral loading of the knee joint during gait(Hurwitz et al., 1998; Schipplein and Andriacchi, 1991; Zhao et al., 2007), with high KAM being correlated to increased joint space narrowing of the medial compartment of the knee(Miyazaki et al., 2002). Pre-TKA candidates have been shown to have a higher peak KAM as compared to healthy controls(Astephen et al., 2008a; Mandeville et al., 2008). High pre-TKA KAM in conjunction with high BMI, has been associated with an increased risk of implant migration at six months post-TKA(Astephen Wilson et al., 2010). Early migration has been shown to be predictive of implant loosening, leading to possible failure and requiring revision surgery(Ryd et al., 1995). KAM metrics decrease pre- to post-TKA for the majority of individuals(Hatfield et al., 2011; Hilding et al., 1995; Mandeville et al., 2008; Orishimo et al., 2012; Wegrzyn et al., 2013; Worsley et al., 2013), indicative of reduced medial compartment loading. Values of KAM post-TKA have been shown to be similar to healthy controls(Alnahdi et al., 2011; Milner and O'Bryan, 2008; Worsley et al., 2013).

Evidence has not convincingly shown static radiographic alignment of TKA recipients to be correlated with the knee adduction moment(Brugioni et al., 1990) or medial compartment loading(Halder et al., 2014; Kutzner et al., 2013), with other work finding no relationship(Miller et al., 2014; Orishimo et al., 2012). Data investigating passive-dynamic frontal plane alignment captured intraoperatively has been shown to be related to dynamic frontal plane loading pre- and post-TKA during gait(Roda et al., 2012; Young, 2013). Dynamic loading of the knee joint in the frontal plane is affected by more than just static alignment alone(Andriacchi, 1994; Harrington, 1983; Johnson et al., 1980).

Abnormal gait patterns in the sagittal plane (knee flexion-extension) have previously been observed in TKA recipients(Andriacchi et al., 1982; Benedetti et al., 1999; Dorr et al., 1988). Pre-TKA individuals tend to have a reduced range of motion, with decreased peak extension angles during stance phase and decreased peak flexion angles during swing phase of gait(Astephen et al., 2008a; Levinger et al., 2013). Inconsistent results are reported pre- to post-TKA, due to differences in discrete parameter selection. Despite this, post-TKA individuals maintain similar patterns of reduced range of motion during stance phase, with a flexed knee during initial contact with the ground, as well as similar levels of maximum knee flexion during swing(Apostolopoulos et al., 2011; Brugioni et al., 1990; Levinger et al., 2013; Liebensteiner et al., 2008; Orishimo et al., 2012; Smith et al., 2004; Tibesku et al., 2011). As a result, the few studies that directly compare post-TKA gait to healthy controls report reduced range of motion during stance and reduced maximum flexion angles during swing phase(Benedetti et al., 2003; Fuchs et al., 2002; Urwin et al., 2014; Wilson et al., 1996).

TKA candidates tend to have abnormal knee flexion moment patterns pre-TKA, with reduced peak flexion moments during early stance and extension moments during late stance, compared to healthy controls(Astephen et al., 2008a; Levinger et al., 2013; Vahtrik et al., 2014). Post-TKA subgroups of knee flexion moment patterns have consistently been identified including: normal biphasic pattern, flexor dominant pattern, and extensor dominant pattern(Andriacchi et al., 1982; Catani et al., 2009; Levinger et al., 2012; Simon et al., 1983; Smith et al., 2004; Wilson et al., 1996). These perhaps lead to the inconsistent reports of either increased knee flexion(Levinger et al., 2013), increased peak extension(Smith et al., 2004), or a more biphasic flexion to extension pattern, depending on subgroup distributions(Hatfield et al., 2011). Other studies report no significant differences in extension moment parameters between pre- and post-TKA(Apostolopoulos et al., 2011; Levinger et al., 2013). There has been some evidence to suggest that muscle activity differences during gait shown pre- to post-TKA(Hubley-Kozey et al., 2010) are also linked to the subgroups of flexion moment patterns(Catani et al., 2009), perhaps in the form of learned neuromuscular patterns pre-TKA(Andriacchi et al., 1982) in compensation to pain(Smith et al., 2004). Compared to healthy controls, results are variable, with some reporting post-TKA individuals having similar peak flexion moments(Worsley et al., 2013), while others report both reduced peak flexion moments(Mandeville et al., 2007; Smith et al., 2004) or extension moments(Benedetti et al., 2003; Levinger et al., 2013).

Very little is reported in the literature regarding transverse plane knee joint rotation angles(el Nahass et al., 1991) and moments, despite internal-external rotation being an implant design feature of interest(Huang et al., 2007). Additionally, gait studies investigating implant design have neglected to report on transverse plane differences(Tibesku et al., 2011; Urwin et al., 2014). Simon et al. (1983) report no difference between post-TKA knee rotation angles and healthy controls. Brugioni et al. (1990) report no difference in internal or external rotation moments compared to healthy controls. Hatfield et al. (2011) report a significant decrease in the internal rotation moment in early stance post-TKA compared to pre-TKA. Caution is generally taken when measuring off-plane rotations using gait analysis techniques due to small angle magnitudes, as they are on the order similar to error introduced from kinematic crosstalk and skin motion artefact(Manal et al., 2003; Piazza and Cavanagh, 2000). Although, it has been suggested that the high variability seen in transverse plane rotation of TKA implants, as measured in-vivo using video fluoroscopy, could also be attributed to other factors including implant design, surgical procedure, and patient anatomical variability(Dennis et al., 2004).

2.4.3 Summary

This body of research aims to explain globally what happens biomechanically at the knee joint-level pre- to post-TKA during gait. While, in general it can be said that TKA improves symptoms and function when biomechanics are reported as group averages, there is significant variability in improvement, with abnormalities remaining during gait that may be linked to risk of poorer outcome (i.e. dissatisfaction, reduced longevity, and postoperative pain). Many of these differences have been shown on average in these samples, and therefore it is unclear how biomechanics change on a person-specific level. While TKA may not restore all aspects of healthy knee joint function, it has not been quantified what level of function is achieved post-TKA along the spectrum of functional decline through the disease process of knee OA. There is also a lack of knowledge into which gait biomechanics are optimal at describing the multiple changes in knee joint-level biomechanics from pre- to post-TKA. This thesis will provide the basis for which parameters are most important to capture, specific to TKA. To begin to translate research findings to the clinical environment, a more comprehensive analysis of the variability in biomechanical changes pre- to post-TKA is required, including identifying the level of functional restoration possible with TKA and the biomechanics most targeted by the procedure.

2.5 Methodological Considerations

The differences in gait analysis methodologies and variability in cohort selection may contribute to inconsistent results, making interpretation and consensus across studies difficult(McClelland et al., 2007). A common gait analysis methodological consideration that contributes to inconsistencies across gait studies is biomechanical data reduction and parameter (variables) selection. 3D gait analysis results in high dimensional and highly variable biomechanical data that requires reduction for interpretation. Biomechanical data is multivariate by nature, with multiple, simultaneous, and often correlated, biomechanical changes occurring over time. Parameters are most often selected from resultant kinematic and kinetic waveforms at subjectively selected times during the gait cycle, generally being peak maximum or minimum values (i.e. peak flexion angle at 80% of the gait cycle)(Astephen et al., 2008a; Chao et al., 1980; Mandeville et al., 2008; Tibesku et al., 2011). These are known as discrete waveform parameters or discrete metrics. While discrete waveform parameter selection is easier to implement programmatically, they ignore the overall shape characteristics of these waveforms, containing valuable magnitude and temporal information. This can result in selecting parameters that do not capture the same biomechanical parameter between individual waveforms and may not be the best parameter to characterize a specific biomechanical feature.

To accommodate the multivariate nature of gait data, some researchers have turned to multivariate statistical techniques. Many traditional multivariate techniques exist and have been applied to gait data(Chau, 2001a) including: principal component analysis(Deluzio et al., 1999; Olney et al., 1998), factor analysis(Davis and Vaughan, 1993; Helwig et al., 2012), and multiple correspondence analysis(Bonnefoy-Mazure et al., 2013; Loslever et al., 1994). A variety of other techniques have been explored including fuzzy systems, neural networks, and wavelet analysis(Chau, 2001a, 2001b;

Simon, 2004). The choice in technique is determined based on the goal of the analysis, leveraging each technique's advantages while understanding limitations.

2.5.1 Principal Component Analysis

Principal component analysis (PCA) was chosen for use in this thesis because of its ability to explicitly deal with variability within data, as well as its underlying correlation structure, without requirement of an abundance of training data (required for robustness in neural networks). This is of importance in this thesis because of the variance between individuals, but also the variance introduced by multiple groups of individuals (i.e. healthy individuals combined with pre-TKA individuals). PCA is also able to capture and summarize the temporal and magnitude information of the entire gait waveform into a single principal component score, greatly reducing the dimensionality of the dataset. The resultant principal components are able to be visualized for interpretation(Brandon et al., 2013), and have shown practicality in providing interpretation of gait in individuals with moderate osteoarthritis(Landry et al., 2007) and knee arthroplasty(Astephen Wilson et al., 2015; Deluzio et al., 1999) populations, as well as healthy individuals(Deluzio et al., 1997). Gait features captured using PCA have been shown to be reliable in knee OA populations(Robbins et al., 2013), and robust to choice of coordinate system convention(Brandon and Deluzio, 2011).

Applied to gait kinematic and kinetic data, PCA is typically applied to each waveform separately by constructing an n by p data matrix (X), where n is the total number of participants and p is the number of normalized data points of the gait cycle (101). X is centered by subtracting its mean ($X^* = X - \bar{X}$). The eigenvectors (U) calculated from the covariance matrix (S) of the centered data (X^*) are then referred to as principal components (PCs). PCs capture the principal patterns of variability found within the original waveform data, with the first extracted PC representing the pattern contributing to the largest amount of variability, the second PC contributing to the second largest amount of variability and so on. A set of discrete participant PC scores for each PC are calculated ($PCscores = X^* \cdot U$). PC scores represent the degree to which each participant's individual waveform projects onto each principal component. Only important principal components that explain the majority of variability in each original waveform are retained. Scree plot analyses(Deluzio, 1997), as well as previously reported PCs shown to be important in end stage knee OA based on existing literature(Astephen et al., 2008b; Deluzio and Astephen, 2007; Hatfield et al., 2011; Landry et al., 2007; Smith et al., 2004) help in determining the number of features to retain. A combination of examining principal component eigenvector plots, gait waveforms associated with high (95th percentile) and low (5th percentile) PC scores, and single component reconstruction is used to interpret the principal components retained(Brandon et al., 2013; Deluzio and Astephen, 2007).

2.6 Multivariate Separation

A common objective when characterizing differences in gait patterns is to then be able to classify individuals based on these differences. A variety of classification techniques have been employed on gait analysis data of both knee osteoarthritic and TKA gait including nearest neighbor classifiers(Mezghani et al., 2008), Dempster-Shafer theory(Jones et al., 2006), support vector machines(Levinger et al., 2009; Phinyomark et al., 2016), and linear discriminant analysis(Astephen et al., 2008b). The objective of this thesis was not to investigate or use classification techniques to directly classify individuals, but to identify the features that best characterize and separate groups best on their clinical status.

2.6.1 Mahalanobis Distance

The Mahalanobis distance is the multivariate generalization of measuring the distance an observation is away from the centroid of a group(Mahalanobis, 1936). Mahalanobis first developed the distance when investigating the differences and similarities between various known castes and tribes in India using multiple anthropometric variables, each with different scales and variability. The result was the development of a single distance measure that considers not only the standard deviations of each variable but also the correlations between variables. Group assignment can be determined by identifying the smallest Mahalanobis distance between an observation and each group's centroid. This method lends itself well to gait data, due to the inherent variability and correlation between gait variables, and has been used in the development of various gait indices(Agostini et al., 2015; Schutte et al., 2000; Tingley et al., 2002). Tingley et al.

(2000) developed an index to classify gait of young children as normal, unusual or abnormal using 11 gait parameters and the distance at which each individual was from group means. Agostini et al. (2015) utilized the Mahalonobis distance to determine improvements in the gait of patients with idiopathic normal pressure hydrocephalus (INPH) after a tap test intervention. Patients were deemed responders if their post-operative Mahalanobis distance to the control centroid decreased relative to their pre-operative distance.

With g groups and p variables, a vector of mean values ($\bar{x}_i'$) for the variables from the ith group and a pooled sample covariance matrix C can be constructed. The Mahalanobis distance (D_i^2) from observation (x') to the centroid of group i can be estimated using:

$$D_i^2 = (x - \bar{x}_i)'C^{-1}(x - \bar{x}_i)$$

D_i^2 is estimated for all groups i. The observation is then classified as belonging to (or closest to) the group with the smallest D_i^2(Manly, 1994).

2.6.2 Discriminant Analysis

Linear discriminant analysis (LDA) is used to investigate the differences between two groups based on observed values of several continuous variables. Linear functions are constructed using a set of discriminating variables for group classification. An attractive advantage of using this method, beyond classification, is the added insight into how well the set of discriminant variables can separate two groups and which discriminant variables contribute the most to this separation. Using the linear functions, a discriminant score can be calculated for each observation to quantify where along the continuum each observation lies. Furthermore, when used in conjunction with a stepwise approach to variable selection, only variables that contribute the most to group separation are retained for function development and interpretation, resulting in an optimal variable set for group separation.

Astephen et al. (2008) investigated the multivariate relationship of gait biomechanics using a combination of PCA and LDA as they relate to knee OA severity, including moderate OA, severe OA, and healthy controls, but did not investigate the separation between pre- and post-TKA individuals(Astephen et al., 2008b). Astephen et al. (2008)

found a combination of kinematic and kinetics features in all three planes and muscle activation patterns of lower extremity muscles that could optimally separate these groups. Features of the knee flexion, adduction and internal rotation moments along with knee flexion angle were found to be important in the discrimination model separating severe OA participants from asymptomatic participants. Mandeville et al. (2009) investigated the multivariate relationship between a combination of self-reported outcome measures and gait variables during level walking and stair ascent between pre-TKA and healthy individuals, as well as six months post-TKA and healthy individuals. A combination of self-reported measures of function, pain and stiffness as well as the knee adduction moment were best at discriminating between pre-TKA and asymptomatic individuals, whereas the total moment of support, the ankle plantarflexion moment, and knee flexion angle, all during stair ascent, were best at discriminating between post-TKA and asymptomatic individuals(Mandeville et al., 2009). A discriminant model was not developed to separate the pre- and post-TKA groups.

2.6.2.1 Canonical discriminant analysis

Canonical discriminant analysis is used to construct the discriminant functions. With p number of discriminant variables (X) retained after stepwise selection, a discriminant function is constructed with coefficients (u) to calculate each observation's (k) discriminant score (f_k).

$$f_k = u_0 + u_1X_1 + u_2X_2 + \cdots + u_pX_p$$

Before the function coefficients are computed, the general eigenvalue problem below is solved, where B is the between-group sum of squares and cross-products matrix and W is the within-group sum of squares and cross-products matrix. The solution to the eigenvalue problem results in a constant λ and a matrix V containing raw discriminant function coefficients, solved to maximize group separation(Klecka, 1980).

$$\mathrm{B}V = \lambda WV$$

The raw coefficients (V) are not valuable for interpretation and the calculated discriminant score would be meaningless, as no constraints are placed on the origin of the discriminant space or the units to which the distance between groups can be measured.

Adjusting the raw coefficients so that the origin of the discriminant function coincides with the grand centroid (the point in space where all discriminant variables have their average values), results in more meaningful discriminant scores. Discriminant scores will have units of standard deviations from the origin (grand centroid). This allows for the immediate understanding of where an observation lies with respect to the centroid of each group, as well as the grand centroid. The adjusted coefficients (u) are calculated by multiplying the raw coefficients (v) by the square root of the number of groups (g) subtracted from the total number of observations (N).

$$u_i = v_i * \sqrt{N - g}$$

The values of discriminant variables can now be entered to the discriminant function, with the adjusted coefficients (u), to calculate discriminant scores (f_k). Group classification can be performed using the origin of the function (grand centroid) as a cut-off value. Observations are classified into either group based on whether their discriminant score is above or below the cut-off value.

Unfortunately, the adjusted coefficients only provide each discriminant variable's absolute contribution to the discriminant function; they do not provide the relative contribution of each discriminant variable to group separation. This is because the meaning of one unit change may be different for each of the discriminating variables (i.e. the standard deviation for each variable may be different). Standardizing the coefficients allows for the relative contribution of each discriminant variable to group separation to be determined, with larger absolute magnitudes contributing more than lower magnitudes. Standardized coefficients (c) are calculated by multiplying each adjusted coefficient (u) by the square root of the discriminant variable's standard deviation (σ^2) divided by the number of groups (g) subtracted from the total number of observations (N).

$$c_i \; = \; u_i * \sqrt{\frac{\sigma_i^2}{N - g}}$$

Note: if all data were standardized (i.e. standard deviation equal to one) before canonical discriminant analysis was performed, the adjusted coefficients (u) would not need standardization and could be used for relative contribution interpretation.

2.6.2.2 Variable Selection

Forward stepwise and backward stepwise are two procedures employed for optimal discriminant variable selection. Forward stepwise procedures start by selecting the single discriminant variable that provides the greatest univariate discrimination and is entered into the selection model. Next, each remaining variable is entered to the model, one by one, and checked for its ability to improve the model's discriminatory ability. The variable that improves discrimination the most is then added to the selection model. This procedure is repeated until no remaining variables provide improvement in discriminatory ability, or if all variables are selected. The combination of variables contained within the model provides the greatest discriminatory ability. Backward stepwise algorithms proceed in the opposite direction. The procedure begins with all variables in the model, then one by one, each variable is removed and the model is checked for improved discriminatory ability. Variables remain outside the model if their exclusion increased the model's discriminatory ability. Only the combination of variables that provide the greatest discriminatory ability are retained.

Many modern statistical packages use a combination of forward and backward selection, such as the statistical package used for this thesis (IBM SPSS Statistics 21, IBM Corp., Armonk, NY)(IBM Corporation, 2014). This combination takes the form of a forward stepwise approach (i.e. successively adding variables that increase discriminatory ability) but at the beginning of each successive step all variables are reviewed, one by one, for their continued contribution to improving the model's discriminatory ability. Variables that no longer sufficiently contribute are discarded, although are eligible for future selection. This scenario may happen when a variable uniquely contributes to improved discrimination, but a future combination of variables within the model duplicates it's singular contribution, making it a candidate for removal(Klecka, 1980). Similarly, the order in which variables are entered could influence final variable selection if multiple variables contribute equally to group separation (highly correlated). To help minimize these effect, it is important to understand the correlation structure of the predictor variables. With a small number of variables, another simple method to explore this effect is to run multiple stepwise analyses, differing the order of the variables in question that the researcher may have flagged.

Wilks’ Lambda (also known as the likelihood ratio test) is used for determining discriminatory ability, as it is a multivariate measure of group differences over multiple variables(Field, 2009). Wilks’ Lambda is the ratio of the determinant of the within-group sum of squares and cross-products matrix (W) to the determinant of the total sums of squares and cross-products matrix (T)(Johnson and Wichern, 2007).

$$\Lambda = \frac{\det(W)}{\det(T)}$$

It takes into consideration not only the differences between groups means (centroids) but also the degree of how close observations are to their own group means. Wilks’ Lambda is an inverse statistic, ranging from 0 to 1, with values closer to 0 denoting high discrimination and values closer to 1 denoting less discrimination (i.e. group centroids are close together)(Klecka, 1980). At each step of the stepwise procedure this statistic is calculated, with inclusion/exclusion of the discriminant variable based on the Wilks’ Lambda value.

CHAPTER 3 VARIABILITY IN KNEE JOINT-LEVEL BIOMECHANICS FROM PRE-TO POST TOTAL KNEE ARTHROPLASTY

3.1 Introduction

Total knee arthroplasty (TKA) remains the hallmark in current standard of care for management of end-stage severe knee osteoarthritis (OA). It is considered highly successful in terms of self-report pain and function, and contemporary implants are associated with a survivorship of 20 years or more(Callaghan et al., 2013; Patil et al., 2015). Although, TKA is also associated with a 7% rate of revision at 10 years(Canadian Institute for Health Information, 2015) and dissatisfaction rates near 20% have been reported(Gustke et al., 2014; Robertsson et al., 2000).With the increasing number of younger individuals receiving TKA, it is unknown how these outcome figures will change over the long term and in response to higher functional demands(Parvizi et al., 2014).

Assessment of knee joint function both before and after TKA is predominately based on self-reported information, which are subjective and can overestimate improvements in function in conjunction with substantial improvements in pain, and are highly influenced by patient co-morbidities(Boonstra et al., 2008; Dunbar et al., 2004). Furthermore, self-reported function cannot provide a dynamic and in-depth biomechanical assessment of the knee joint. As such, three-dimensional (3D) gait analysis has been used to obtain a more objective assessment of knee joint level biomechanics of patients before and after TKA, however its use has primarily remained within the research environment and has received little translational effort to enter clinics and decision-making.

Previous studies that have examined 3D knee joint-level biomechanics in TKA have included healthy control cohorts for comparison(Smith et al., 2004; Wilson et al., 1996; Worsley et al., 2013), however it remains unclear what aspects of gait are restored to healthy levels of function for most individuals, and which do not. Previous studies have included small sample sizes and/or often report rather simplistic measures (i.e. subjective discrete parameters) and are generally limited to the sagittal plane(Levinger et al., 2013; Milner, 2009; Urwin et al., 2014). Because previous studies have mostly focused on understanding gait improvements from pre- to post-TKA(Hatfield et al., 2011; Xu et al., 2010), it has not been quantified what level of function is achieved post-TKA with respect to the spectrum of functional decline through the disease process of knee OA(Astephen et al., 2008a). Through population averages, TKA has been shown to improve some, but not all, aspects of knee joint biomechanics during walking gait. Functional deficits do remain relative to healthy cohorts, and with significant person-to-person variability(McClelland et al., 2007; Milner, 2009; Sosdian et al., 2014). This has been shown across implant designs, resulting in a lack of evidence to suggest one design is preferred for restoring knee joint function during gait post-operatively(Bolanos et al., 1998; Dorr et al., 1988; Joglekar et al., 2012; Urwin et al., 2014). This patient variability drives the need to further understand the effect of TKA on knee joint biomechanics, not just on average, but also on a person-specific level, to more comprehensively capture what the current standard of care (TKA) is capable of in terms of restoration of knee joint level biomechanics. And while there seems to be a link between preoperative values of joint function with postoperative values(Smith et al., 2006), it is unclear how the variability in preoperative functional state influences the amount of functional improvement post-operatively.

The objective of this study was to examine the variability in improvement of knee joint level biomechanics during gait of participants from before to 1 year post-TKA. We also aimed to examine whether participants at both pre- and post-TKA timepoints have gait more similar to healthy controls or those with moderate OA, as well as understanding how knee joint-level biomechanics pre-TKA influences the level of improvement post-TKA. Understanding dynamically how the knee joint changes in response to TKA provides the framework to help develop more personalized pre- and post-TKA management strategies, including functional expectation, and to assess innovation in implant design and surgical technique. Moving away from studies that focus solely on population average examinations is important in understanding the variability in functional response to TKA surgery for more tailored treatment strategies.

3.2 Methods

3.2.1 Participants

Seventy-two participants receiving primary total knee arthroplasty (TKA) for severe tibiofemoral knee osteoarthritis (OA) were recruited for this study. All TKA participants were recruited from waitlists of high volume orthopaedic surgeons at the QEII Health Sciences Center in Halifax, Nova Scotia. Knee OA severity and compartment involvement were graded via radiographs using the Kellgren-Lawrence global rating scale(Kellgren and Lawrence, 1957) by a single orthopaedic surgeon within one year pre-TKA. All TKA participants had medial compartment involvement, either predominantly medial compartment knee OA or equally affected medial and lateral compartments. TKA participants were required to be able to walk 6 meters unassisted

Cohorts of 72 asymptomatic individuals and moderate OA individuals were selected to best match the preTKA group for age, sex, and BMI, from a database containing 230 asymptomatic and 365 moderate OA participant data collections. Factors such as age, sex, and BMI have been shown to affect gait both independent of OA, but also with OA and TKA(Astephen Wilson et al., 2015; Harding et al., 2012; Ko et al., 2011; McKean et al., 2007). These participant cohorts are from this study but also previous companion studies funded by the Canadian Institutes of Health Research (CIHR) and the Nova Scotia Health Research Foundation (NSHRF). All asymptomatic individuals were recruited from the general public with no known symptoms or history of knee OA. Diagnosis of individuals with moderate OA was done by orthopaedic surgeons based on clinical signs and symptoms, consistent with the American College of Rheumatology criteria(Altman et al., 1986), and were not surgical candidates for TKA. All moderate OA participants had medial compartment involvement, either predominantly medial compartment or equally affected medial and lateral compartments. Asymptomatic and moderate OA participants were able to ascend stairs in a reciprocal fashion, walk a city block and jog 6 meters.

Participants were excluded if they had any major surgery or trauma to the lower extremities (within a year prior to TKA surgery) and screened for any neurological or pathological conditions that could affect walking gait. Participants were also screened for other inflammatory diseases such as rheumatoid arthritis. No exclusion criteria were placed on implant type as long as it fit within the standard of care provided by the surgeons. Informed consent, in accordance with the Nova Scotia Health Authority Research Ethics Board and Dalhousie University Ethics Review Board, was obtained from all participants.

3.2.2 Gait Analysis

All gait analyses took place in the Dynamics of Human Motion Laboratory, Dalhousie University. TKA participants had their surgical limb analyzed approximately one week before (preTKA) and again one year after receiving TKA (postTKA). Moderate OA participants had their most affected limb analyzed, while limb selection was randomized for the asymptomatic participants.

Participants walked shod at their self-selected speed over a 6-meter walkway while three-dimensional (3D) kinematics were captured at 100 Hz using an optoelectronic motion capture system (Northern Digital Inc., Waterloo) with ground reaction forces being collected simultaneously at 2000 Hz using a floor embedded force platform (AMTI, Watertown, Mass.). Kinematic and ground reaction force data was filtered using a double-pass 2nd order butterworth filter with a cutoff frequency of 8 Hz and 60 Hz, respectively.

A total of 16 infrared light emitting diode (IRED) markers were tracked during walking trials. Single markers were fixed to the shoulder, greater trochanter, lateral epicondyle of the femur, and lateral malleolus(Li et al., 1993). Four rigid tracking clusters each comprised of three non-collinear IRED markers were fixed to the pelvis, thigh, shank, and foot(Cappozzo et al., 1996). Virtual markers were identified during static calibration trials using an infrared digitizing pointer at the right and left anterior superior iliac spines, medial epicondyle of the femur, tibial tuberosity, fibular head, medial malleolus, head of the second metatarsal, and posterior aspect of the calcaneus(Hatfield et al., 2011; Landry et al., 2007). Bone embedded segment coordinate systems were defined using marker locations during standing calibration and reconstructed during motion using a least-squares optimization technique(Challis, 1995).

An inverse dynamics procedure was implemented using custom MATLAB (MathWorks Inc., Natick, MA) code to calculate net external knee joint reaction moments(Li et al., 1993), with inertial properties calculated using equations from Vaughan et al. (1992). Knee joint angles and moments were expressed following the conventions of the joint coordinate system(Grood and Suntay, 1983) resulting in knee flexion about the medial-lateral axis of the thigh, knee internal rotation about the long axis of the shank, and knee adduction about a floating axis perpendicular to the plane created by the flexion axis and internal rotation axis. Moments were normalized to body mass (Nm/kg).

Gait events were determined using a heel strike and toe-off algorithm using force and kinematic data(Hreljac and Marshall, 2000). First heel strike (start of gait cycle) was determined at the capture frame in which the vertical component of the ground reaction force past a threshold of 5N, while toe-off was determined at the capture frame in which the vertical component of the ground reaction force fell below the 5N threshold. Second heel strike (symbolizing the end of a complete gait cycle) was found kinematically, at the capture frame in which there was a local maximum in the vertical component of acceleration of the lateral malleolus marker. This was identified when the derivative of acceleration (jerk) was equal to zero. 3D joint angles and moments were time normalized to stance phase of gait, with 0% representing first heel-strike and 100% toe-off (101 data points); knee flexion angle data was normalized to the full gait cycle, i.e. 0% being first heel-strike and 100% being second heel strike (101 data points). Data was collected for at least 5 gait cycles per visit and ensemble averaged. Muscle activity of 7 lower extremity muscle sites were also collected (2000 Hz) simultaneously during all gait trials but will not be presented as part of this study(Hubley-Kozey et al., 2010).

3.2.3 Discrete Parameters

Discrete parameter selection from angle and moment gait waveforms was based on previous studies summarizing changes in knee joint function during walking gait associated with knee OA including healthy controls and individuals receiving TKA(Astephen et al., 2008a; Smith et al., 2004). These parameters have shown to have good to excellent day-to-day reliability in moderate knee OA populations(Robbins et al., 2013) and were extracted for each subject using a custom MATLAB script.

Ten discrete parameters were extracted from four knee waveforms (Figure 3.1), as well as gait speed, as described in Table 3.1. Parameters include peak flexion angle during stance and swing, range of the flexion angle over the full gait cycle, peak flexion moment, peak extension moment during early and late stance, the first and second peak of the adduction moment as well as at mid stance, and peak internal rotation moment.

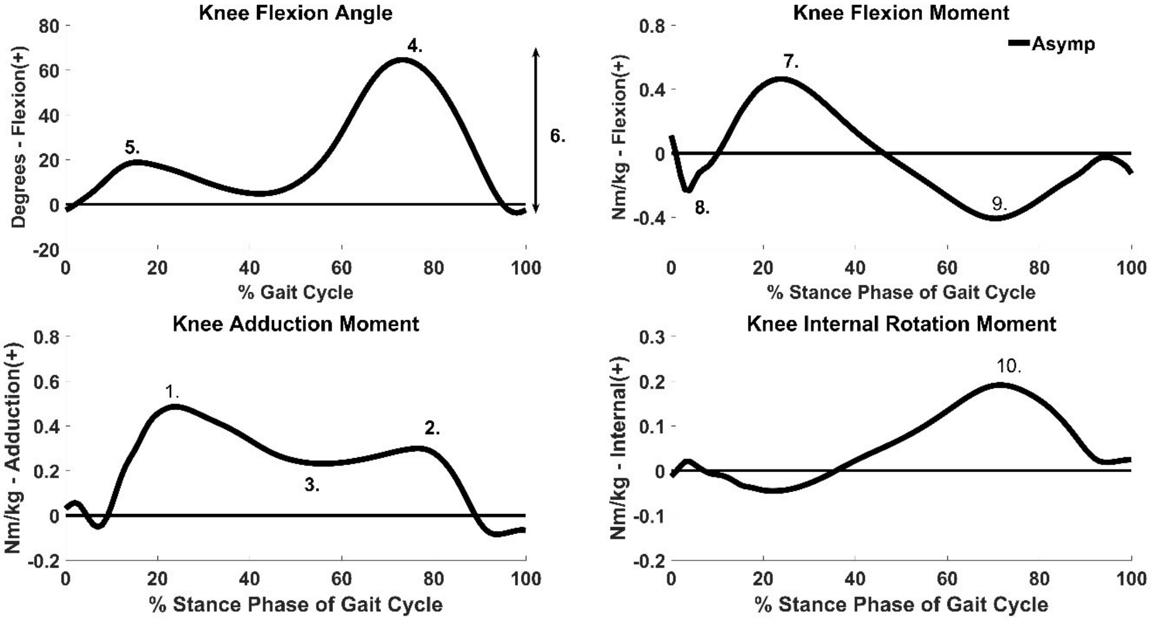

Figure 3.1 Location of knee waveform discrete parameters, for knee flexion angle (top left), flexion moment (top right), adduction moment (bottom left), and internal rotation moment (bottom right). See Table 3.1 for parameter descriptions by waveform label.

Table 3.1. Discrete parameters descriptions. See Figure 3.1 for graphical description of discrete parameter using the number attached to each parameter.

Discrete Parameter	Description	Waveform Label
Adduction Moment First Peak (Nm/kg)	Maximum adduction moment (0-25%) of gait cycle	1
Adduction Moment Second Peak (Nm/kg)	Maximum adduction moment (40-62%) of gait cycle	2
Adduction Moment Mid-stance (Nm/kg)	Minimum adduction moment (20-40%) of gait cycle	3
Peak Flexion Angle (°)	Maximum flexion angle (0-100%) of gait cycle	4

Discrete Parameter	**Description**	**Waveform Label**
Peak Flexion Angle Stance (°)	Maximum flexion angle between 0-45% of gait cycle	5
Flexion Angle Range (°)	Max. flexion angle – min. angle between 0-100% of gait cycle	6
Peak Flexion Moment (Nm/kg)	Maximum flexion moment (0-100%) of gait cycle	7
Peak Extension Moment Early Stance (Nm/kg)	Minimum flexion moment between 0-10% of gait cycle	8
Peak Extension Moment Late Stance (Nm/kg)	Minimum flexion moment between 40-62% of gait cycle	9
Peak Internal Rotation Moment (Nm/kg)	Maximum internal rotation moment (0-100%) of gait cycle	10

3.2.4 Principal Component Analysis

Principal component analysis (PCA) was used to extract magnitude and shape features from the gait waveforms(Deluzio and Astephen, 2007). PCA was applied to each waveform separately by constructing an n by p data matrix (X), where n is the total number of participants (288) and p is the number of normalized data points of the gait cycle (101). X was centered by subtracting its mean ($X^* = X - \bar{X}$). The eigenvectors (U) calculated from the covariance matrix (S) of the centered data (X^*) are herein referred to as principal components (PCs). PCs capture the principal patterns of variability found within the original waveform data, with the first extracted PC representing the pattern contributing to the largest amount of variability, the second PC contributing to the second largest amount of variability and so on. A set of discrete subject PC scores for each PC were calculated($PC\ scores = X^* \cdot U$). PC scores represent the degree to which each subject's individual waveform projects on to each principal component. Important principal components that explained the majority of variability in each original waveform were identified and retained first based on scree plot analyses(Deluzio, 1997), and then included if they have been previously reported to be important in end stage knee OA based on existing literature(Deluzio and Astephen, 2007; Hatfield et al., 2011; Landry et al., 2007; Smith et al., 2004). The goal in this paper was not to identify new features of importance to end stage knee OA, but to understand the rate of improvement in these features in a large cohort of TKA recipients relative to large cohorts of individuals with no or earlier levels of OA.

3.2.5 Data Analysis

The change in parameter values for each TKA participant were calculated for all parameters by subtracting the preTKA values from postTKA values. Two-tailed Pearson correlation coefficients and R^2 values were calculated using SPSS (IBM Corp., Armonk, NY) to examine significant linear associations ($\alpha < 0.05$) between preTKA knee joint gait parameters (both discrete and waveform PCs) and their associated change.

Asymptomatic and moderate OA targets of ± 1 standard deviation from respective group means for both the discrete parameters and waveform PCs were calculated. The percentage of participants whose preTKA and postTKA parameter values were within these targets were calculated and presented.

The Mahalanobis distance (MD) statistic was calculated using retained PCs in Minitab 17 (Minitab Inc., State College, PA). This multivariate distance was used to determine which group centroid each participant was closest to (statistical distance) in terms of their knee joint function, both pre- and post-TKA, taking into account the correlation structure between the retained waveform PCs used to calculate the distance(Mahalanobis, 1936; Manly, 1994). The asymptomatic cohort was used to define a high function centroid, the moderate OA cohort was used to define a moderate function centroid, and the preTKA group was used to define a low function centroid. TKA participants at both preTKA and postTKA timepoints were classified as either high, moderate, or low function determined by the smallest Mahalanobis distance(Manly, 1994).

3.3 Results

3.3.1 Participants

There were no significant differences in age, body mass, or body mass index (BMI) between participants preTKA, postTKA, or the moderate OA group, with the asymptomatic group being significantly younger (mean difference ~ 7 years) and having smaller body mass (mean difference ~ 16 kg) and BMI (mean difference ~ 6 kg/m^2) than all other groups ($p < 0.05$). Subject demographics are in Table 3.2. There was a statistically significant decrease in gait speed with severity, as asymptomatic walked the fastest, followed by the moderate OA group, the postTKA group, and the preTKA group ($p < 0.05$). This was also the case for stride length, with stride length decreasing with severity ($p < 0.05$). The asymptomatic group spent statistically significant less time in stance phase than all other groups ($p < 0.05$). PreTKA spent more time in stance phase than the postTKA and moderate OA groups ($p < 0.05$), although there was no difference between postTKA and moderate OA groups ($p > 0.05$).

Table 3.2. Participant demographics and spatiotemporal parameters. Presented as mean (standard deviation).

	PreTKA	**PostTKA**	**Asymptomatic**	**Mod OA**
N	72	72	72	72
Females	41	41	41	41
Age (years)	64 (7)^{A}	65 (7)^{A}	57 (5)	63 (7)^{A}
Mass (kg)	93.1 (18.7)^{A}	93.2 (18.5)^{A}	76.7 (16.1)	92.2 (19.4)^{A}
BMI (kg/m^2)	33.2 (6.0)^{A}	33.2 (5.9)^{A}	26.7 (4.6)	32.2 (5.6)^{A}
Speed (m/s)	0.89 (0.22)^{T}	1.08 (0.20)^{T}	1.34 (0.16)^{T}	1.19 (0.19)^{T}
Stride length (m)	1.12 (0.17)^{T}	1.24 (0.16)^{T}	1.42 (0.13)^{T}	1.32 (0.14)^{T}
Stance time (s)	0.86 (0.15)^{T}	0.77 (0.09)^{T}	0.68 (0.06)^{T}	0.73 (0.08)^{T*}

^{A} Significant difference with asymptomatic ($p < 0.05$)
^{T} Significant difference across all groups ($p < 0.05$)
* No statistical difference with postTKA ($p < 0.05$)

3.3.2 Principal Component Analysis

Ten principal component waveform PC parameters were retained in total. The first 3 PCs of the knee flexion angle and knee adduction moment, and the first 2 PCs of the knee flexion moment and knee internal rotation moment, cumulatively explained 89% to 92% of each original waveform data. Again, PC retention was based on a combination of Scree analysis and only those features previously described as important to end stage knee OA. Principal component eigenvector plots, gait waveforms associated with high (95th percentile) and low (5th percentile) PC scores (Figure 3.2), as well as single component reconstruction were used to interpret principal components extracted(Brandon et al., 2013; Deluzio and Astephen, 2007), see Appendix B for all eigenvector plots.

Descriptions to help with interpretation of each waveform PC are provided in Table 3.3. Figure 3.3 contains ensemble group averages for all knee joint angles and moments.

Table 3.3. Principal component descriptions, including variability explained by each PC.

Waveform	PC	% Variance Explained	High PC Score Description
Knee Flexion Angle (°)	1	66.8	High overall knee flexion angle magnitude during entire gait cycle
	2	13.9	Difference between stance (smaller) and swing phase (larger) knee flexion angle
	3	10.8	Difference between late-stance (smaller) and mid-swing (larger) knee flexion angle
Knee Adduction Moment (Nm/kg)	1	59.1	High overall knee adduction moment magnitude during stance
	2	23.1	Difference between early (larger) and mid-stance (smaller) knee adduction moment
	3	8.4	Difference between mid (smaller) and late-stance (larger) knee adduction moment
Knee Flexion Moment (Nm/kg)	1	59.2	High overall knee flexion moment magnitude during stance
	2	29.8	Difference between early (larger) and late stance (smaller) knee flexion moment
Knee Internal Rotation Moment (Nm/kg)	1	60.9	High overall knee internal rotation moment magnitude during stance
	2	31.0	Difference between early (smaller) and late stance (larger) knee internal rotation moment

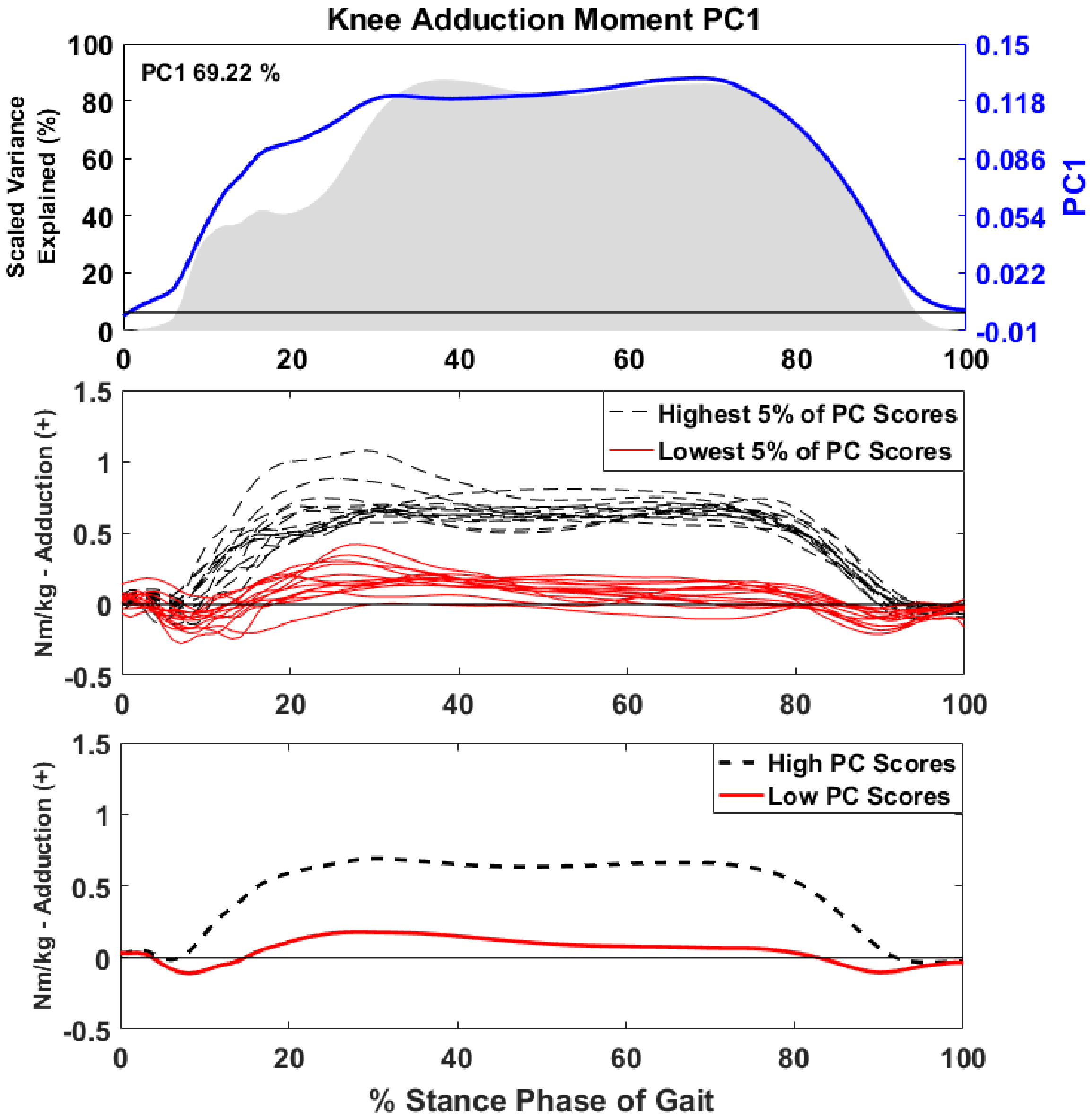

Figure 3.2 Principal component eigenvector plot for knee adduction moment PC1, with eigenvector and variance explained (top row), waveforms associated with high (95th percentile) and low (5th percentile) PC scores (middle row), and mean 95th percentile and 5th percentile PC scores (bottom row).

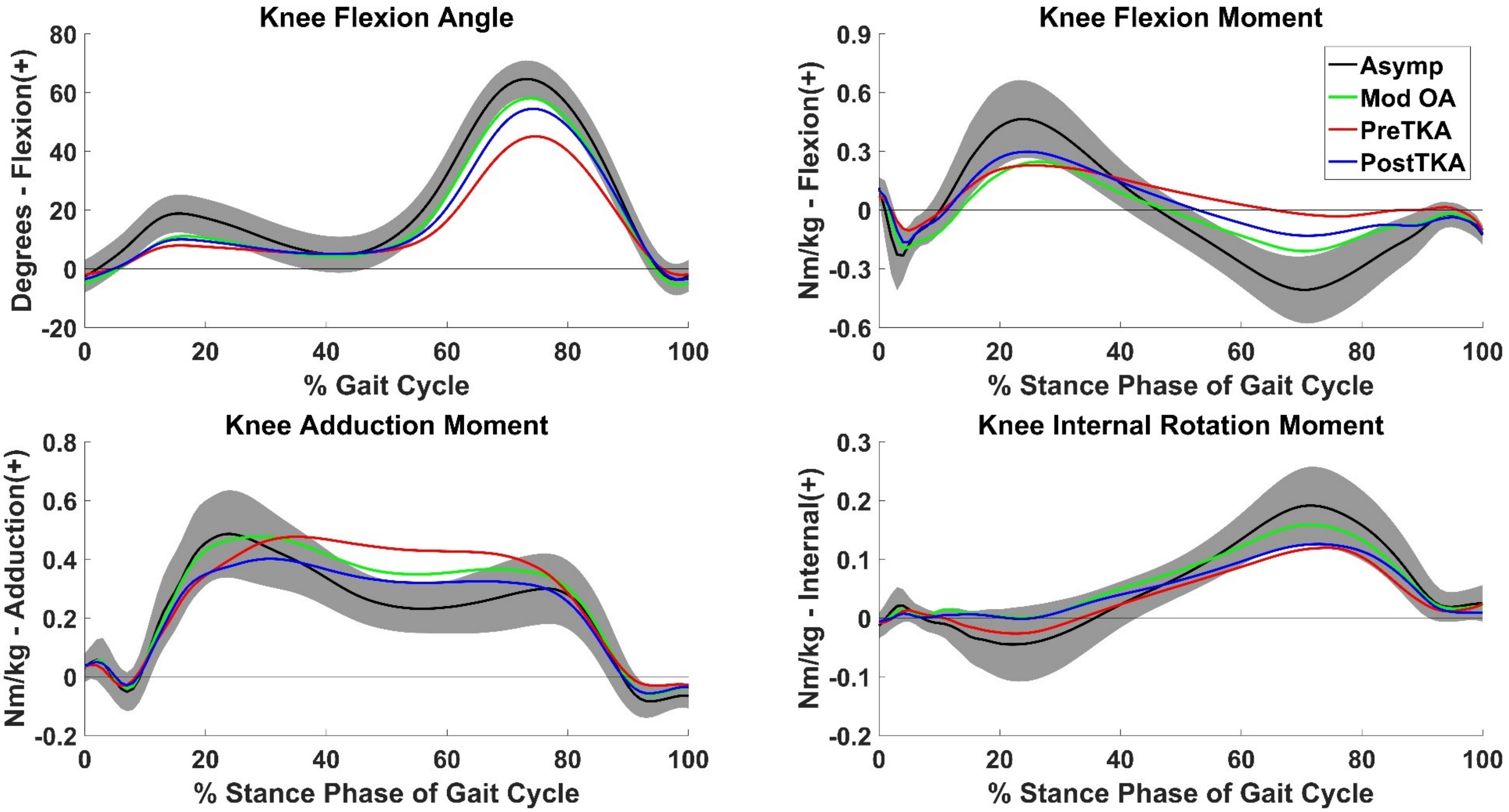

Figure 3.3. Ensemble average waveforms for knee flexion angle (top-left), knee flexion moment (top-right), knee adduction moment (bottom-left), and knee internal rotation moment (bottom-right), including a one deviation reference band (shaded grey) from the asymptomatic group. PreTKA in red, postTKA in blue, moderate OA (Mod OA) in green, and asymptomatic (Asymp) in black.

3.3.3 Change Score Correlation

Significant and negative correlations were found between all preTKA parameters and their associated change from preTKA to postTKA ($p < 0.01$) (Table 3.4). While some mean changes are associated with a negative value, all changes were improvements from the preTKA value, (i.e. the change in PC1 of the knee adduction moment (KAM) from pre-to post-TKA resulted in a negative mean change value -0.61, this signifies a reduced KAM on average which is interpreted as an improvement, Figure 3.4), with the exception of PC2 of the knee rotation moment. The overall magnitude of the internal rotation moment (PC1), the peak flexion angle during swing phase, and the adduction moment minimum during mid-stance were among the parameters with the highest R^2 values, between 0.65 and 0.62.

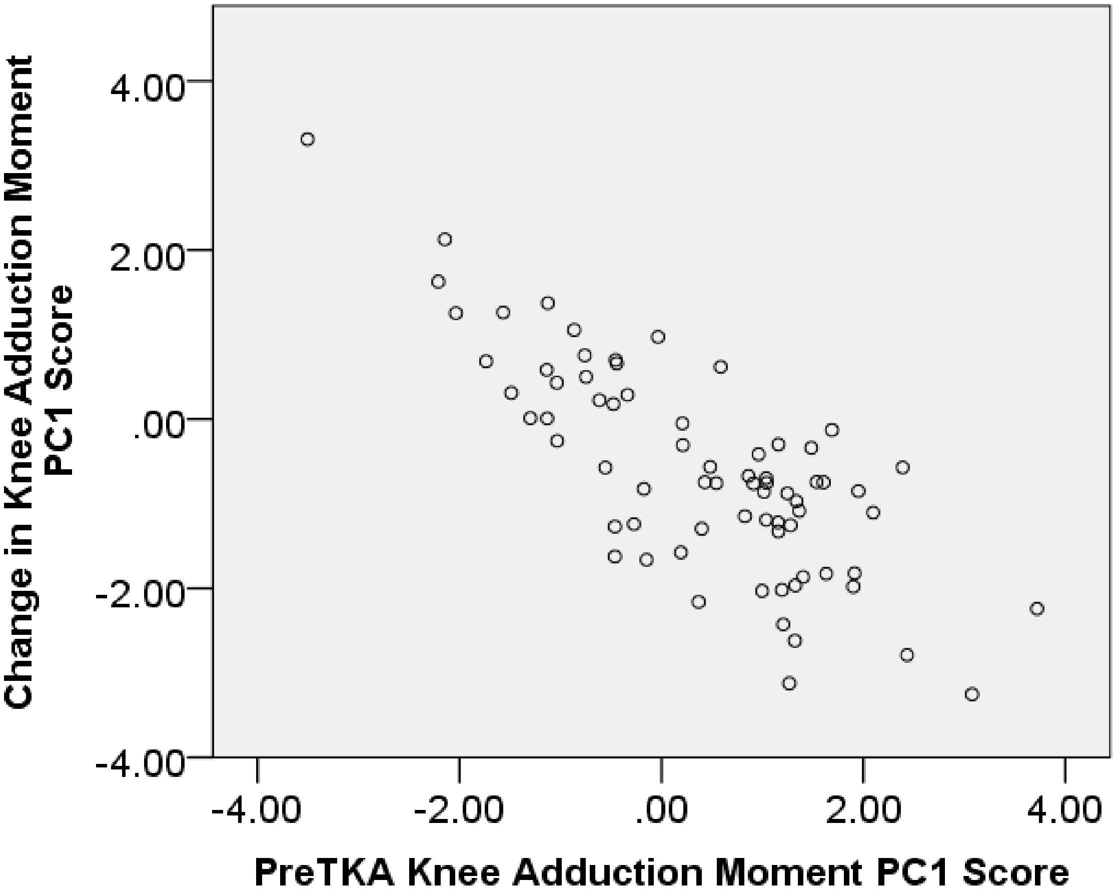

Figure 3.4 Relationship between preTKA knee adduction moment PC1 score and the change in this parameter from pre- to post-TKA. Larger PC1 scores preTKA are associated with larger decreases in this value postTKA.

Table 3.4 Relationship of preTKA parameter values and parameter change (postTKA – preTKA) quantified with R^2 values and Pearson correlation (r) coefficients. All relationships were statistically significant with $p < 0.01$. Bold = not a pre- to post-TKA improvement.

	Group Mean (SD)		**Mean Change**	
Parameter	**PreTKA**	**PostTKA**		**R^2 (Pearson-r)**
Gait Speed (m/s)	0.89 (0.22)	1.08 (0.20)	0.19 (0.18)	0.29 (-0.54)
Discrete Parameters				
Adduction Moment 1st Peak (Nm/kg)	0.50 (0.17)	0.43 (0.13)	-0.06 (0.18)	0.52 (-0.72)
Adduction Moment 2nd Peak (Nm/kg)	0.44 (0.18)	0.34 (0.12)	-0.09 (0.16)	0.58 (-0.76)
Adduction Moment Mid-stance (Nm/kg)	0.38 (0.17)	0.30 (0.10)	-0.09 (0.15)	0.62 (-0.79)
Peak Flexion Angle Swing (°)	46.2 (14.6)	55.1 (9.8)	8.8 (15.8)	0.63 (-0.80)
Peak Flexion Angle Stance (°)	8.9 (5.2)	10.5 (5.6)	1.7 (7.6)	0.46 (-0.68)
Flexion Angle Range (°)	49.1 (14.9)	59.5 (9.6)	10.5 (14.2)	0.61 (-0.78)
Peak Flexion Moment (Nm/kg)	0.28 (0.24)	0.32 (0.20)	0.04 (0.27)	0.48 (-0.70)
Peak Extension Moment Early-stance (Nm/kg)	-0.15 (0.08)	-0.21 (0.10)	-0.06 (0.10)	0.09 (-0.30)
Peak Extension Moment Late-stance (Nm/kg)	-0.12 (0.18)	-0.19 (0.17)	-0.07 (0.19)	0.34 (-0.58)
Peak Internal Rotation Moment (Nm/kg)	0.13 (0.08)	0.13 (0.06)	0.00 (0.07)	0.50 (-0.71)
Waveform PCs				
Adduction Moment PC1	0.38 (1.34)	-0.23 (0.87)	-0.61 (1.25)	0.61 (-0.78)
Adduction Moment PC2	-0.37 (0.45)	-0.1 (0.44)	0.26 (0.48)	0.31 (-0.56)
Adduction Moment PC3	-0.15 (0.28)	0.01 (0.26)	0.16 (0.26)	0.31 (-0.55)
Flexion Angle PC1	-50.40 (65.12)	-10.04 (57.53)	40.36 (81.66)	0.51 (-0.71)
Flexion Angle PC2	-11.68 (37.82)	5.46 (25.58)	17.14 (38.01)	0.60 (-0.77)
Flexion Angle PC3	-13.48 (26.4)	-6.62 (25.76)	6.86 (29.06)	0.33 (-0.57)
Flexion Moment PC1	0.67 (1.84)	0.23 (1.31)	-0.43 (1.81)	0.55 (-0.74)
Flexion Moment PC2	-0.59 (0.74)	-0.15 (0.77)	0.44 (0.89)	0.33 (-0.57)
Rotation Moment PC1	-0.15 (0.61)	-0.03 (0.37)	0.12 (0.58)	0.65 (-0.81)
Rotation Moment PC2	-0.05 (0.24)	-0.11 (0.27)	**-0.06 (0.3)**	0.28 (-0.53)

3.3.4 Percent within Asymptomatic and Moderate OA Standard Deviations

Asymptomatic and moderate OA targets of ± 1 standard deviation from respective group means for both the discrete parameters and waveform PCs were calculated (Table 3.5). The percentage of participants whose preTKA and postTKA parameter values were within these targets were calculated to determine which target captured more individuals (Table 3.6).

In general, higher percentages of individuals pre- and post-TKA had discrete parameter and waveform PC values within a one standard deviation moderate OA target, as compared to an asymptomatic target. Sagittal plane kinetic parameters including peak knee flexion moment, peak knee extension moment during late-stance and PC1 and PC2 of the knee flexion moment were parameters with low percentages (19% to 33%) of post-TKA participants within the asymptomatic target. These percentages were higher (42% to 82%) when using the moderate OA target, but were still among the lowest percentages for either target. While PC2 of the knee flexion moment had the highest percentage of participants within the moderate target postTKA, this was a small negative change (-1%) from preTKA, despite this parameter seeing an 18% increase using the asymptomatic target. PostTKA individuals had higher PC scores for this parameter compared to moderate OA individuals (Table 3.5), suggesting that postTKA individuals may be falling between the moderate and asymptomatic targets. This was not the case for the peak knee flexion moment that saw a negative change (-2%) pre- to post-TKA in the asymptomatic target, but improvements in the moderate target, despite the postTKA mean for this parameter being higher than moderate OA. The reliability of capturing this discrete parameter has been shown to be low(Robbins et al., 2013), and the means of the preTKA, postTKA, and moderate OA cohorts were similar making interpretation complex.

Frontal plane parameters were among the parameters with higher percentages of participants within asymptomatic and moderate OA targets, and had higher changes pre- to post-TKA. The first peak of the knee adduction moment, however, had similar percentages of individuals within asymptomatic and moderate OA targets, and did not change pre- to post-TKA for either target (Table 3.6). This is likely due to the targets overlapping and therefore capturing the same percentage of individuals (Table 3.5).

PC2 of the knee rotation moment saw negatives changes in both the asymptomatic (-8%) and moderate targets (-7%), despite relatively higher percentages overall compared to other parameters for both targets. This is most likely an artefact of this feature being the only feature that did not see improvement after TKA, with preTKA individuals having more asymptomatic PC scores than postTKA (Table 3.5, Figure 3.2). This may be a mechanical constraint imposed on the joint due to implant design. Caution is taken when interpreting waveform PCs in the transverse plane as they have been shown to have poor reliability(Robbins et al., 2013).

Discrete parameters saw, in general, smaller percentages of participants within asymptomatic and moderate OA targets compared to waveform PCs. This may be due to waveform PCs being able capture both magnitude and shape features, while discrete parameters subjectively capture magnitude information at a single point in the gait cycle.

While the focus of this sub-objective was not to interpret mean changes between groups, interpretation of the complex changes was aided by examining group differences. A post hoc examination of group means for all discrete parameters and waveform PCs was performed using a one-way analysis of variance (ANOVA), with Bonferroni post-hoc analyses ($\alpha = 0.05$), but is not presented here but can be found in Appendix B.

The complexity of interpreting the multiple simultaneous changes across all parameters prompted the decision to use a multivariate approach (Mahalanobis distance) to incorporate multiple biomechanical parameters, as well as the relationships between them, to aid in interpretation. The number of parameters used in the multivariate approach, however, was first reduced by examining the redundancy between discrete parameters and waveform PCs, grouped by plane and metric (i.e. angle or moment). The results of this examination can be found in Appendix B. Only waveform PCs were chosen for the multivariate approach as significant correlations were found between discrete parameters and waveform PCs, with the exception of PC3 of the knee flexion angle which was not correlated with any sagittal plane angle discrete parameter ($p > 0.05$). PC1 of the knee adduction moment, flexion angle, and internal rotation moment were either very strong or strongly correlated with all discrete parameters of their respectively planes ($R^2 > 0.50$). The peak extension moment during early stance was the only discrete parameter to not have a strong correlation with either PCs of the knee flexion moment, but was found to be moderately correlated to PC1 of the knee flexion moment ($R^2 = 0.23$, $p < 0.0001$).

Table 3.5 Group means (SD) for preTKA, postTKA, asymptomatic, and moderate OA groups, for all discrete parameters and waveform PCs.

	Group Means (SD)			
Parameter	**PreTKA**	**PostTKA**	**Asymptomatic**	**Moderate OA**
Gait Speed (m/s)	0.89 (0.22)	1.08 (0.2)	1.34 (0.16)	1.19 (0.19)
Discrete Parameters				
Adduction Moment 1st Peak (Nm/kg)	0.50 (0.17)	0.43 (0.13)	0.51 (0.15)	0.51 (0.15)
Adduction Moment 2nd Peak (Nm/kg)	0.44 (0.18)	0.34 (0.12)	0.31 (0.12)	0.39 (0.14)
Adduction Moment Mid-stance (Nm/kg)	0.38 (0.17)	0.30 (0.10)	0.22 (0.09)	0.33 (0.13)
Peak Flexion Angle Swing (°)	46.2 (14.61)	55.1 (9.8)	65.0 (6.34)	58.6 (7.69)
Peak Flexion Angle Stance (°)	8.9 (5.24)	10.5 (5.59)	19.0 (6.55)	12.0 (7.00)
Flexion Angle Range (°)	49.1 (14.89)	59.5 (9.64)	69.3 (4.55)	64.9 (6.38)
Peak Flexion Moment (Nm/kg)	0.28 (0.24)	0.32 (0.20)	0.48 (0.21)	0.27 (0.25)
Peak Extension Moment Early-stance (Nm/kg)	-0.15 (0.08)	-0.21 (0.10)	-0.29 (0.14)	-0.25 (0.12)
Peak Extension Moment Late-stance (Nm/kg)	-0.12 (0.18)	-0.19 (0.17)	-0.42 (0.17)	-0.26 (0.20)
Peak Internal Rotation Moment (Nm/kg)	0.13 (0.08)	0.13 (0.06)	0.19 (0.06)	0.17 (0.07)
Waveform PCs				
Adduction Moment PC1	0.38 (1.34)	-0.23 (0.87)	-0.35 (0.79)	0.19 (1.09)
Adduction Moment PC2	-0.37 (0.45)	-0.10 (0.44)	0.41 (0.44)	0.06 (0.41)
Adduction Moment PC3	-0.15 (0.28)	0.01 (0.26)	0.14 (0.34)	0.00 (0.32)
Flexion Angle PC1	-50.40 (65.12)	-10.04 (57.53)	54.40 (50.24)	6.05 (51.25)
Flexion Angle PC2	-11.68 (37.82)	5.46 (25.58)	-2.63 (28.23)	8.85 (26.67)
Flexion Angle PC3	-13.48 (26.4)	-6.62 (25.76)	11.85 (21.47)	8.25 (26.85)
Flexion Moment PC1	0.67 (1.84)	0.23 (1.31)	-0.62 (0.96)	-0.28 (1.47)
Flexion Moment PC2	-0.59 (0.74)	-0.15 (0.77)	1.02 (0.82)	-0.29 (1.14)
Rotation Moment PC1	-0.15 (0.61)	-0.03 (0.37)	0.08 (0.30)	0.11 (0.44)
Rotation Moment PC2	-0.05 (0.24)	-0.11 (0.27)	0.21 (0.32)	-0.05 (0.36)

Table 3.6 Percent of participants with discrete parameter and waveform PC values within asymptomatic and moderate OA targets (+/- 1 standard deviation from group mean). Bold = decrease or no change in number of participants pre- to post-TKA.

	Asymptomatic Target		Change	Moderate OA Target		Change
Parameter	**PreTKA**	**PostTKA**		**PreTKA**	**PostTKA**	
Gait Speed (m/s)	7%	17%	10%	17%	42%	25%
Discrete Parameters						
Adduction Moment 1st Peak (Nm/kg)	44%	43%	**-1%**	44%	44%	**0%**
Adduction Moment 2nd Peak (Nm/kg)	21%	46%	25%	33%	46%	13%
Adduction Moment Mid-stance (Nm/kg)	17%	36%	19%	32%	49%	17%
Peak Flexion Angle Swing (°)	13%	28%	15%	28%	43%	15%
Peak Flexion Angle Stance (°)	13%	29%	16%	42%	47%	5%
Flexion Angle Range (°)	6%	18%	12%	22%	38%	16%
Peak Flexion Moment (Nm/kg)	31%	29%	**-2%**	44%	54%	10%
Peak Extension Moment Early-stance (Nm/kg)	24%	42%	18%	35%	42%	7%
Peak Extension Moment Late-stance (Nm/kg)	14%	19%	5%	32%	43%	11%
Peak Internal Rotation Moment (Nm/kg)	19%	29%	10%	26%	40%	14%
Waveform PCs						
Adduction Moment PC1	35%	67%	32%	57%	72%	15%
Adduction Moment PC2	15%	42%	27%	40%	57%	17%
Adduction Moment PC3	53%	72%	19%	63%	79%	16%
Flexion Angle PC1	24%	43%	19%	43%	65%	22%
Flexion Angle PC2	56%	71%	15%	56%	69%	13%
Flexion Angle PC3	51%	53%	2%	58%	68%	10%
Flexion Moment PC1	31%	33%	2%	53%	67%	14%
Flexion Moment PC2	13%	31%	18%	83%	82%	**-1%**
Rotation Moment PC1	36%	57%	21%	49%	81%	32%
Rotation Moment PC2	51%	43%	**-8%**	88%	81%	**-7%**

3.3.5 Mahalanobis distances

Group classification results based on Mahalanobis distances are in Table 3.7. The majority of participants preoperatively (69%) were classified as low function, with 25% closest to moderate function, and 6% being closest to high function. Postoperatively, over half (53%) of the participants were closest to moderate function, while 13% were closest to high function. The remaining 35% remained as low function after surgery.

Table 3.7 Function classification using Mahalanobis distances preTKA and postTKA. Functional levels were defined by the centroids of the preTKA group (low function), moderate OA group (moderate function) and asymptomatic group (high function).

Group	PreTKA (N = 72)		PostTKA (N = 72)	
	N	Percent	N	Percent
Low Function	50	69%	25	35%
Moderate Function	18	25%	38	53%
High Function	4	6%	9	13%

Changes in group classification using Mahalanobis distances are in Table 3.8. Forty three percent of the participants improved from pre- to post-operatively, as observed through a change in function classification. Improvement was interpreted as a change from a low function classification to higher function classification. Of the participants who improved, 77% were classified as low function before surgery and moderate function postTKA. Four participants improved to high function classification postoperatively from low function, and 3 improved from moderate function to high function. Half of the participants did not change function classification, with the majority (61%) of these participants being classified as low function at both pre- and postoperative time points. Five participants declined in terms of classification, with 3 participants changing from moderate function to low function and 2 participants changing from high to moderate function. No participants who were classified high function preoperatively declined to the low function postoperatively.

Table 3.8 The change in participant function classification from preTKA to postTKA, with improvement representing a change to a higher functional classification postoperatively, decline representing a change to less functional classification postoperatively, and no change representing the same function classification at both time points.

Change	N	Total (% of 72 Participants)
Improved from low to moderate function	24	31 (43%)
Improved from low to high function	4	
Improved from moderate to high function	3	
Stayed low function	22	36 (50%)
Stayed moderate function	12	
Stayed high function	2	
Declined from moderate to low function	3	5 (7%)
Declined from high to low function	0	
Declined from high to moderate function	2	

3.4 Discussion

The majority of knee joint biomechanics, including both kinematic and kinetic parameters, remained deficient for a large percentage of post-TKA participants in this study. These findings agree with previous literature that have captured similar results on population averages(McClelland et al., 2007; Milner, 2009; Sosdian et al., 2014), although previous studies have only compared TKA recipients, pre- and post-surgery, to asymptomatic cohorts. No previous studies have investigated these deficiencies relative to other populations across the functional severity spectrum of progressive knee osteoarthritis. The results from this study support that while some aspects of knee joint-level biomechanics during walking gait do improve one year post-TKA(Hatfield et al., 2011), functional deficits do remain relative to an asymptomatic population, but these deficits resemble functional adaptations similar to those with moderate levels of knee OA.

The main objectives of TKA are commonly stated to be the reduction of pain in the knee joint and increase function. The actual functional target for the knee joint post-TKA is unknown, but is implied to be of “normal” function(Noble et al., 2005). This study provides a comprehensive and objective assessment of the level of function attained and the variability in improvement across participants post-TKA, on a person-specific level. Over half (53%) of the post-TKA gait patterns in the current study were classified as moderate level of function using a multivariate method of classification, with the majority (33%) of these improving in classification from low level of function. Only 19% of gait patterns were classified as high function post-TKA. This suggests that post-TKA participants are more similar in terms of knee joint-level function during gait to those with moderate levels of knee OA than those with no symptoms (asymptomatic), and perhaps levels of moderate OA function are a more reasonable target for functional expectation post-TKA with current standard of care surgery.

Interestingly, almost one third of pre-TKA participants had gait patterns classified as either moderate or high level of function. This further highlights the functional variability among those presenting for and triaged to primary TKA, including a subset with fairly high functioning joints who may not see large improvements in knee joint function post-TKA. Further improvement of participants classified as higher functioning pre-TKA (either moderate or high) was observed in a small number (3) of subjects post-TKA, with most staying at their pre-TKA functional classification (14), or in a few cases (5) declining to a lower function classification. This may be due to the influence of pre-TKA functional state on improvement post-TKA(Smith et al., 2006, 2004), and a ceiling effect in that, in general, moderate OA-level function looks to be the highest obtainable functional level post-TKA for the majority of participants. Significant and negative associations were shown between pre-TKA values of knee joint level biomechanics and the change in these biomechanics from pre- to post-TKA. This suggests that the pre-TKA functional status of the joint has a strong influence on the degree of functional improvement post-TKA. The directionality of these associations support the intuition that participants with poor knee function pre-TKA have the potential to improve the most post-TKA, as compared to higher functioning pre-TKA participants who may have less to gain functionally from the surgery(Laughman et al., 1984). Strategies incorporating realistic functional outcome potential based on pre-TKA knee joint functional status may help to better manage patient and surgeon expectation. It is important to note that joint function was summarized and classified using parameters of knee joint mechanics that have been previously shown to characterize knee OA across severity levels. These parameters may not be all encompassing and could be further improved by incorporating other biomechanical markers such as knee joint musculature activity(Benedetti et al., 2003; Hubley-Kozey et al., 2010; Wilson et al., 1996).

We showed here that frontal plane loading parameters had higher percentages of post-TKA subjects within a standard deviation of asymptomatic values (42% - 72%) compared to other parameters, such as sagittal plane loading, and also saw some of the largest increases in percentages from pre- to post-TKA (25% - 32%). The overall reduction of the knee adduction moment magnitude from pre- to post-TKA is consistent with previous investigations(Hatfield et al., 2011; Hilding et al., 1995; Mandeville et al., 2008; Orishimo et al., 2012; Wegrzyn et al., 2013; Worsley et al., 2013), with some evidence that post-TKA values of the knee adduction moment are similar to those of healthy controls(Alnahdi et al., 2011; Milner and O’Bryan, 2008; Worsley et al., 2013). The current findings suggest that some aspects of frontal plane loading during gait seem to be among the most altered or improved parameters by current end stage treatment of knee OA. As the knee adduction moment has been suggested as a surrogate measure for the ratio of loading between the medial and lateral compartments of the knee joint(Schipplein and Andriacchi, 1991), a reduced and/or more-balanced dynamic loading of the medial and lateral compartments of the tibial component post-TKA may be beneficial for implant longevity(Andriacchi, 1988). Our group has also shown lower knee adduction moment patterns pre-TKA, that often persist post-TKA, are associated with reduced tibial component migration post-TKA(Astephen Wilson et al., 2010). While there was an overall reduction in the adduction moment magnitude and peak, most post-TKA participants maintained the inability to “unload” the medial compartment of the knee joint during stance (captured with PC2), which has been associated with more severe levels of knee OA and increased risk of further progression(Astephen et al., 2008a; Hatfield et al., 2015).

This study also showed that, in general, sagittal plane kinetic parameters improved very little with standard of care TKA, with the smallest percentages of post-TKA participants within asymptomatic targets post-TKA. Furthermore, the knee range of motion in the sagittal plane during gait had the smallest percentage of post-TKA subjects within asymptomatic (18%) and moderate OA (38%) targets. These findings agree with previous literature that suggest sagittal plane deficits post-TKA are highly prevalent, representing aspects of gait that TKA does not look to substantially improve(Andriacchi et al., 1982; Benedetti et al., 2003; Levinger et al., 2013; McClelland et al., 2010; Simon et al., 1983; Smith et al., 2004; Wilson et al., 1996). This study additionally showed that sagittal plane deficits look to occur for most individuals on a person-specific level, not just on average. Dynamic kinematic deficits during knee joint use may not be reflective of the passive range of motion capable of the post-TKA participant(Dennis et al., 1998), and may represent potentially modifiable aspects of gait that could be improved with controlled exercise programs, including gait/neuromuscular retraining.

The coupling of reduced knee flexion angles and moments during the stance phase of gait has been characterized as a “stiff knee” gait pattern(Dorr et al., 1988). The potential cause of stiff knee gait for individuals post-TKA is unclear as there are multiple hypotheses including manifestations (learned patterns, ‘functional adaptations’) of abnormal patterns established by individuals pre-TKA(Andriacchi et al., 1982; Metcalfe et al., 2013; Simon et al., 1983; Smith et al., 2004), quadriceps weakness/inhibition and neuromuscular control impairment that is evident both pre- and post-TKA(Benedetti et al., 2003; Hubley-Kozey et al., 2010; Yoshida et al., 2012), and reduced proprioception due to excision of native knee tissue and ligamentous structures(Andriacchi et al., 1982; Barrett et al., 1991; Cash et al., 1996). At moderate levels of OA, most individuals are able to ambulate without much observable disability, despite clinical symptoms of OA and gait deviations (from asymptomatic) shown through altered knee joint loading and neuromuscular patterns(Hubley-Kozey et al., 2006; Landry et al., 2007). These deviations in gait may be an attempt by moderate OA participants to adapt to the diseased knee joint to reduce pain, increase stability, and maintain adequate mobility during activities of daily living. Post-TKA participants could be adopting a compensatory strategy to the artificial knee joint in a similar fashion to those with moderate OA. If pain or loss of proprioception from joint tissue damage were main drivers for these adaptations pre-TKA, perhaps specialized rehabilitation post-TKA, in the absence of pain and diseased tissue, could help to 'unlearn' these patterns and allow TKA recipients to become more confident using their artificial joint.

Intuitively, attainment of normal sagittal plane loading, especially the characteristic biphasic flexion to extension moment pattern, would be beneficial post-TKA. Although there is some evidence that a more biphasic pattern may increase risk of tibial component migration post-TKA(Hilding et al., 1999), which has been linked to early implant failure through aseptic loosening(Ryd et al., 1995). In contrast, research from our group suggests lower magnitude knee flexion moments pre-TKA (possibly even more extension dominated moment patterns) may play a role in higher migration post-TKA(Astephen Wilson et al., 2010). Individuals with a biphasic moment pattern post-TKA have also been shown to display anterior knee pain more often than those with other loading patterns (either flexion or extension dominated patterns)(Smith et al., 2004). Therefore, it seems unclear as to the long term negative outcomes of having abnormal sagittal loading patterns, in terms of implant longevity or pain. However, it is reflective of a stiff knee gait pattern, possibly due to a lack of confidence using the joint dynamically and may have implications for prolonging the burden of functional disability of the disease, including decreased ability during high demand functional activities.

The primary focus in this study was to capture the relationship between pre- and post-TKA function relative to the spectrum of OA severity, and the variability in response to the current standard of care in management of end stage knee OA. As such, no exclusion criteria were set in terms of other joints affected by OA or previous arthroplasties (mechanics were not measured bilaterally), physical therapy or implant design. However, it is important to understand the limitation of interpreting joint level function without regard to these factors. It is difficult to study primary TKA in isolation of these and it would be valuable to move forward by developing multi-factorial models to help predict optimal post-TKA function based on a deeper individual health profile. It remains unclear if gait deficits post-TKA are a reflection of the replaced joint or more a reflection of the general health and comorbidities of the TKA participant. Therefore, it may be important in future multifactorial examinations to include and understand other person-specific factors that may influence joint-level function for a more person-specific model.

TKA surgery is not a poor management strategy for end stage knee OA in general, as it is associated with increased quality of life(Shan et al., 2015) and generally high satisfaction post-TKA(Robertsson et al., 2000). However, the current results suggest that, in terms of joint function, it may not be the optimal or sole solution for all individuals(Wylde et al., 2007). Understanding the changes in knee joint mechanics on a person-specific level could help to better manage potential participants who may not have a positive response to TKA. Through developing a framework that can better quantify and monitor the outcome of current end-stage knee OA management, incorporating knee joint mechanics pre- and post-TKA, we can begin to further improve outcome from TKA.

CHAPTER 4 HIERARCHY OF BIOMECHANICAL GAIT METRICS IN TOTAL KNEE ARTHROPLASTY

4.1 Introduction

Restoring the functional capacity of the knee joint is a primary objective of total knee arthroplasty (TKA) for individuals suffering from end-stage knee osteoarthritis (OA). TKA is considered highly successful, as most individuals report reduced pain and increased function after surgery. A consistent subgroup of individuals, however, are dissatisfied due to factors such as persistent pain and unmet functional expectations(Dunbar et al., 2013). Reported rates of patient dissatisfaction have varied between 7-19%(Baker et al., 2007; Bourne et al., 2010; Choi and Ra, 2016; Gustke et al., 2014; Noble et al., 2006; Robertsson et al., 2000). Furthermore, while contemporary implants are associated with a survivorship of 20 years or more(Callaghan et al., 2013; Patil et al., 2015), 7% of all primary TKA procedures require revision surgery at 10 years(Canadian Institute for Health Information, 2015). Revision surgeries are accompanied with increased patient risk and direct and indirect costs. It is currently unclear how the increasing number of younger individuals requiring TKA will affect outcomes due to higher functional demands and requiring longer implant survivorship(Parvizi et al., 2014).

Knee joint-level function is an important outcome after TKA, although is not captured well on its own(Hossain et al., 2015). Improvement is often overestimated in context to other aspects of outcome such as pain and satisfaction(Boonstra et al., 2008; Naili et al., 2016; Terwee et al., 2006). A lack of objective assessment tools neither exist or are utilized clinically to quantity knee joint-level function before and after TKA surgery. Three-dimensional gait analysis has been used in the research environment to investigate improvements in knee joint-level biomechanics from pre- to post-TKA(Hatfield et al., 2011; Orishimo et al., 2012) and the differences that remain relative to age-matched controls(Levinger et al., 2013; Smith et al., 2004; Wilson et al., 1996). While improvements have been shown through group averages, a comprehensive look at the person-to-person variability in improvement and in the functional deficits that remain is lacking. This information is important both in clinic for more personalized TKA management strategies and in industry for future innovation and evaluation.

Few have summarized the multiple changes that occur, often simultaneously, throughout the stages of TKA triage, into less complex assessment tools(Chao et al., 1980). Multivariate approaches have been employed by our research team in the past to understand the knee joint-level biomechanics that discriminate those with severe knee OA and healthy controls, as well as biomechanics that discriminate those with moderate knee OA that do and do not go on to receive TKA(Astephen et al., 2008b; Hatfield et al., 2015). Neither investigated discriminating features separating pre- and post-TKA individuals. To understand how to target functional improvements with TKA, it is important to be able to summarize the current standard of care of TKA in terms of function restoration. Through identifying an optimal set of joint-level biomechanics that separate pre- and post-TKA gait from age-matched healthy controls, as well as the biomechanics that are most targeted by the surgery, we can begin to distill important and clinically relevant information from the multitude of correlated data that is often presented (*Objective 1 of this thesis*). This way we can quantify the functional gap in walking gait knee biomechanics of TKA patients and identify key features that summarize joint-level functional deficits throughout triage.

The objective of this study was to investigate which multivariate combination of features of three-dimensional knee joint kinematics and kinetics during gait optimally discriminate pre-TKA from aged matched healthy controls, one year post-TKA walking gait from aged matched healthy controls, and pre- from post-TKA. This information could help to make more informed surgical decisions such as preoperative surgical planning, implant design, and rehabilitation regimes, as well as develop a framework to test future innovations aimed at restoring knee joint function with TKA.

4.2 Methods

Some aspects of the methodology for this chapter will overlap with the methods of *Objective 1*.

4.2.1 Participants

Seventy-two participants receiving primary total knee arthroplasty (TKA) for severe knee osteoarthritis (OA) were recruited for this study. All TKA participants were recruited from waitlists of high volume orthopaedic surgeons at the QEII Health Sciences Center in Halifax, Nova Scotia. Knee OA severity and compartment involvement were graded via radiographs using the Kellgren-Lawrence (KL) global rating scale by a single orthopaedic surgeon within one year pre-TKA. All TKA participants had medial compartment involvement, either predominantly medial compartment knee OA or equally affected medial and lateral compartments. TKA participants were required to be able to walk 6 meters unassisted.

A cohort of 72 asymptomatic participants were selected from a database of 230 asymptomatic participant data collections, between the ages of 34 and 77 to best match the preTKA group for age, sex, and BMI. Factors such as age, sex, and BMI have been shown to affect gait both independent of OA, but also with OA and TKA(Astephen Wilson et al., 2015; Harding et al., 2012; Ko et al., 2011; McKean et al., 2007). Asymptomatic participants included those from this study but also previous companion studies funded by the Canadian Institutes of Health Research (CIHR) and the Nova Scotia Health Research Foundation (NSHRF). All asymptomatic participants were recruited from the general public with no known symptoms or history of knee OA (i.e. asymptomatic), able to ascend stairs in a reciprocal fashion, walk a city block and jog 6 meters.

Participants were excluded if they had any major surgery or trauma to the lower extremities (within the last year prior to surgery) and screened for any neurological or pathological conditions that could affect walking gait. Participants were also screened for other inflammatory diseases such as rheumatoid arthritis. No exclusion criteria were placed on implant type as long as it fit within the standard of care provided by the surgeons. Informed consent, in accordance with the Nova Scotia Health Authority Research Ethics Board and Dalhousie University Ethics Review Board, was obtained from all participants.

4.2.2 Gait Analysis

All gait analyses took place in the Dynamics of Human Motion Laboratory, Dalhousie University. TKA participants had their surgical limb analyzed approximately one week before (preTKA) and again one year after receiving TKA (postTKA), while limb selection was randomized for the asymptomatic participants.

Participants walked shod at their self-selected speed over a 6-meter walkway while three-dimensional (3D) kinematics were captured at 100 Hz using an optoelectronic motion capture system (Northern Digital Inc., Waterloo). Ground reaction forces were collected simultaneously at 2000 Hz using a floor embedded force platform (AMTI, Watertown, Mass.). Kinematic and ground reaction force data were filtered using a double-pass 2nd order butterworth filter with cutoff frequencies of 8 Hz and 60 Hz, respectively.

A total of 16 infrared light emitting diode (IRED) markers were tracked during walking trials. Single markers were fixed to the shoulder, greater trochanter, lateral epicondyle of the femur, and lateral malleolus(Li et al., 1993). Four rigid tracking clusters each comprised of three non-collinear IRED markers were fixed to the pelvis, thigh, shank, and foot(Cappozzo et al., 1996). Virtual markers were identified during static calibration trials using an infrared digitizing pointer at the right and left anterior superior iliac spines, medial epicondyle of the femur, tibial tuberosity, fibular head, medial malleolus, head of the second metatarsal, and posterior aspect of the calcaneus(Hatfield et al., 2011; Landry et al., 2007). Bone embedded segment coordinate systems were defined using marker locations during standing calibration and reconstructed during motion using a least-squares optimization technique(Challis, 1995).

An inverse dynamics procedure was implemented using custom MATLAB (MathWorks Inc., Natick, MA) code to calculate net external knee joint reaction moments(Li et al., 1993), with inertial properties calculated using equations from Vaughan et al. (1992). Knee joint angles and moments were expressed following the conventions of the joint coordinate system resulting in knee flexion about the medial-lateral axis of the thigh, knee internal rotation about the long axis of the shank, and knee adduction about a floating axis perpendicular to the plane created by the flexion axis and internal rotation axis(Grood and Suntay, 1983; Wu and Cavanagh, 1995). Moments were normalized to body mass (Nm/kg).

Gait events were determined using a heel strike and toe-off algorithm using force and kinematic data(Hreljac and Marshall, 2000). First heel strike (start of gait cycle) was determined at the capture frame in which the vertical component of the ground reaction force past a threshold of 5N, while toe-off was determined at the capture frame in which the vertical component of the ground reaction force fell below the 5N threshold. Second heel strike (symbolizing the end of a complete gait cycle) was found kinematically, at the capture frame in which there was a local maximum in the vertical component of acceleration of the lateral malleolus marker. This was identified when the derivative of acceleration (jerk) was equal to zero. 3D joint angles and moments were time normalized to stance phase of gait, with 0% representing first heel-strike and 100% toe-off (101 data points); knee flexion angle data was normalized to the full gait cycle, i.e. 0% being first heel-strike and 100% being second heel strike (101 data points). Data was collected for at least 5 gait cycles per visit and ensemble averaged. Muscle activity of 7 lower extremity muscle sites were also collected (2000 Hz) simultaneously during all gait trials but will not be presented as part of this study(Hubley-Kozey et al., 2010).

4.2.3 Principal Component Analysis

Principal component analysis (PCA) was used to extract magnitude and shape features from the gait waveforms(Deluzio et al., 1997). PCA was applied to each gait waveform separately by constructing an n by p data matrix (X), where n is the total number of participants (216) and p is the number of normalized data points of the gait cycle (101). X was centered by subtracting its mean ($X^* = X - \bar{X}$). The eigenvectors (U) calculated from the covariance matrix (S) of the centered data (X^*) are herein referred to as principal components (PCs). PCs capture the principal patterns of variability found within the original waveform data, with the first extracted PC representing the pattern contributing to the largest amount of variability, the second PC contributing to the second largest amount of variability and so on. A set of discrete participant PC scores for each PC were calculated ($PCscores = X^* \cdot U$). PC scores represent the degree to which each participant’s individual waveform projects onto each principal component. Important principal components that explained the majority of variability in each original waveform were identified and retained, first based on scree plot analyses(Deluzio, 1997), and then included if they have been previously reported to be important in end stage knee OA based on existing literature(Astephen et al., 2008b; Deluzio and Astephen, 2007; Hatfield et al., 2011; Landry et al., 2007; Smith et al., 2004). A combination of examining principal component eigenvector plots, gait waveforms associated with high (95th percentile) and low (5th percentile) PC scores, and single component reconstruction was used to interpret the principal components extracted(Brandon et al., 2013; Deluzio, 1997).

4.2.4 Analysis of Optimal Group Separation

Using participant PC scores obtained from principal component analysis, standard statistical tools were employed to examine group differences. A one-way analysis of variance (ANOVA), with Bonferroni post hoc analyses, was used to examine significant differences ($\alpha = 0.05$) between the means of each group for all PC scores and demographic data. This resulted in sets of PC scores that significantly differed between each group.

Three separate stepwise discriminant models were created to identify the combination of PC features that optimally separated preTKA gait from postTKA gait, preTKA gait from asymptomatic gait, and postTKA gait from asymptomatic gait. Only the sets of PC scores that were significantly different between groups were used in these analyses. Each model was built using a stepwise procedure which successively examined each PC for its ability to improve group separation, tested using the Wilks' lambda statistic(Field, 2009; Jennrich, 1960; Klecka, 1980). PC features that failed to reduce the overall model's Wilks' lambda statistic were excluded, resulting in a subset of features that best separated the two groups in each analysis.

Using the PC features selected from the stepwise procedures, linear discriminant functions were built using canonical discriminant analysis(Klecka, 1980). The absolute magnitude of a feature's standardized coefficient within a discriminant function quantified the relative contribution that feature has in group separation, with large relative magnitudes coinciding with large contribution to group separation(Klecka, 1980).

The standardized coefficients were normalized to the largest magnitude coefficient in each function to obtain relative contribution of each feature (normalized coefficient of 1.0 signifies the most contribution). Discriminant scores were calculated for each participant by applying each participant's set of PC scores into each discriminant function. Group classification was performed using a cut-off value calculated as the mid-point (centroid) between the discriminant score means of the two groups used in the analysis. Participants were classified into either group based on whether their discriminant score was above or below the cut-off value. Discriminant function classification rates were calculated using a leave-one-out cross validation classification routine to determine each function's ability to correctly classify a participant's group membership. All discriminant models were developed using IBM SPSS Statistics 21 (IBM Corp., Armonk, NY).

4.2.5 Robustness of Models

As a preliminary exploration of the robustness of the models discriminating preTKA gait from postTKA gait and preTKA gait from asymptomatic gait, discriminant scores were calculated for a new cohort of 41 preTKA participants (New PreTKA). These 41 participants had not yet received their one-year post-TKA gait analysis and were not used in the PCA and discriminant model development. The inclusion criteria for this separate cohort matched that of the original cohort of 72 preTKA participants. PC scores were calculated for each new participant using the PCA model developed from the data of the original 3 groups. Discriminant scores were then calculated for the new preTKA participants by inputting the participant's PC scores into the discriminant functions that separated preTKA gait from postTKA gait and preTKA gait from asymptomatic gait. The ability of each function to properly classify the new preTKA participants as preTKA was examined by calculating percent correct classification rates.

4.3 Results

4.3.1 Participants

There were no significant differences in age, body mass, or body mass index (BMI) between the participants at their pre- and postTKA timepoints. Despite best matching, the asymptomatic group was significantly younger (mean difference: 7 years) and had both smaller body mass (mean difference: 16 kg) and BMI (mean difference: 6.5 kg/m^2) than the TKA cohort at either timepoint ($p < 0.05$). Participant demographics are in Table 4.1. There was a significant average self-selected gait speed difference found between all groups, with the asymptomatic group walking the fastest, followed by postTKA, with preTKA participants walking the slowest ($p < 0.05$). The asymptomatic group had a significantly longer average stride length than preTKA and postTKA, with postTKA having a longer stride length than preTKA ($p < 0.05$). A significant difference in the amount of time spent during the stance phase of gait was found between all groups, with preTKA spending the largest amount of time in stance phase followed by postTK, and finally the asymptomatic group with the least ($p < 0.05$). Participant spatiotemporal parameters are in Table 4.1. No differences were found in any demographic or spatiotemporal parameters between either preTKA groups ($p > 0.05$).

Table 4.1 Participant demographics and spatiotemporal parameters. Presented as mean (standard deviation).

	PreTKA	**PostTKA**	**Asymptomatic**	**Test PreTKA**
N	72	72	72	41
Females	41	41	41	21
Age (years)	64 (7) ^{A}	65 (7) ^{A}	57 (5)	65 (8)
Mass (kg)	93.1 (18.7) ^{A}	93.2 (18.5) ^{A}	76.7 (16.1)	95.8 (24.1)
BMI (kg/m^2)	33.2 (6.0) ^{A}	33.2 (5.9) ^{A}	26.7 (4.6)	33.3 (6.5)
Speed (m/s)	0.89 (0.22) ^{A}	1.08 (0.20) $^{A, T}$	1.34 (0.16)	0.89 (0.19)
Stride length (m)	1.12 (0.17) ^{A}	1.24 (0.16) $^{A, T}$	1.42 (0.13)	1.10 (0.17)
Stance time (s)	0.86 (0.15) ^{A}	0.77 (0.09) $^{A, T}$	0.68 (0.06)	0.85 (0.12)

^{A} Significant difference with Asymptomatic ($p < 0.05$)
^{T} Significant difference with PreTKA ($p < 0.05$)

4.3.2 Principal Component Analysis

Ensemble average waveforms of preTKA, postTKA, and asymptomatic gait data are shown in Figure 4.1. A shaded band representing ± 1 standard deviation of the mean waveforms for the asymptomatic group was also included as a reference for the variability associated with asymptomatic gait patterns and as a visual aid to observe where preTKA and postTKA deviate from these patterns.

Fourteen PCs were retained for data analysis, cumulatively capturing between 81% and 93% of the variability within the original data of each waveform. This included the first 2 PCs of the knee adduction angle, knee internal rotation angle, knee flexion moment and knee internal rotation moment, along with the first 3 PCs of the knee flexion angle and knee adduction moment (KAM). Descriptions to help with interpretation of each waveform parameter are provided in Table 4.2. Only significantly different ($p < 0.05$) PC scores between groups (Table 4.3) were entered in to each respective stepwise procedure before constructing the discriminant functions.

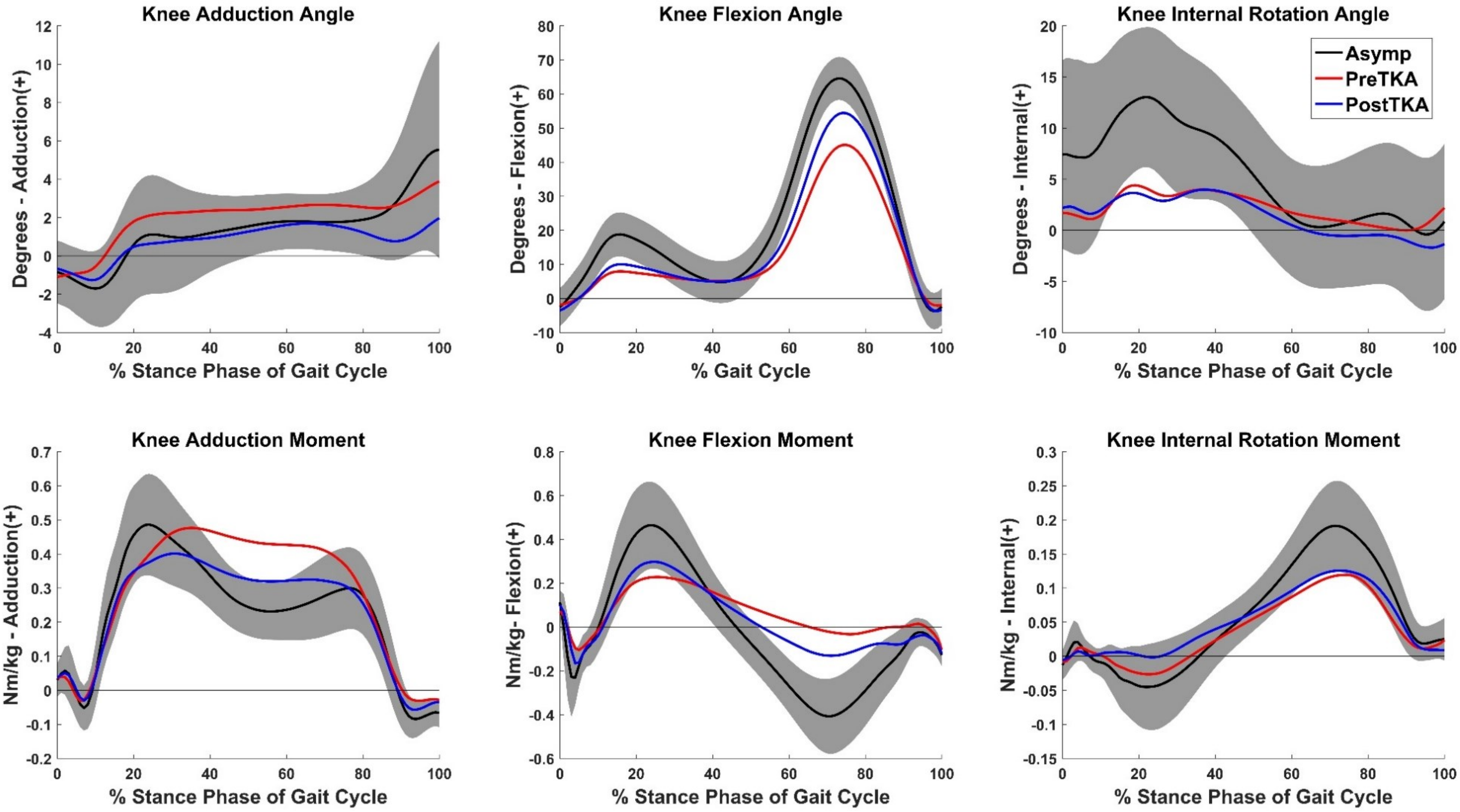

Figure 4.1 Ensemble average gait waveforms of 3D knee joint angles (top row) and net external knee joint moments (bottom row) for preTKA (red), postTKA (blue) and asymptomatic (black). A one standard deviation shaded gray band represents the variability of each measure for the asymptomatic participants.

Table 4.2 PC descriptions and variability explained of gait waveforms for knee joint angles and moments.

Waveform	PC	% Variance Explained	High PC score Description
Knee Adduction Angle (deg)	1	60.4	High overall angle magnitude during stance
	2	21.0	Difference between early (smaller) and late stance (larger)
Knee Flexion Angle (deg)	1	70.2	High overall angle magnitude during entire gait cycle
	2	13.5	Difference between stance (smaller) and swing phase (larger)
	3	9.6	Difference between late-stance (smaller) and mid-swing (larger and earlier)
Knee Internal Rotation Angle (deg)	1	57.2	High overall angle magnitude during stance
	2	23.9	Difference between early (larger) and late stance (smaller)
Knee Adduction Moment (Nm/kg)	1	67.9	High overall moment magnitude during stance
	2	17.6	Difference between early (larger) and mid-stance (smaller)
	3	5.9	Difference between mid (smaller) and late-stance (larger)
Knee Flexion Moment (Nm/kg)	1	60.9	High overall moment magnitude during stance
	2	28.0	Difference between early (larger) and late stance (smaller)
Knee Internal Rotation Moment (Nm/kg)	1	62.5	High overall angle magnitude during stance
	2	29.1	Difference between early (smaller) and late stance (larger)

Table 4.3 Mean (SD) PC scores of preTKA, postTKA, and asymptomatic groups, including Bonferroni corrected P-Values for group comparisons. Bold = statistically significant (α = 0.05). A = asymptomatic.

Waveform	PC	PreTKA	PostTKA	A	PreTKA vs A	PreTKA vs PostTKA	PostTKA vs A
Adduction Angle	1	5.5 (21.2)	-7.4 (20.3)	2.0 (19.9)	0.91	**0.0006**	**0.02**
	2	-3.8 (12.4)	-1.7 (12.0)	5.5 (11.0)	**<0.0001**	0.91	**0.0009**
Flexion Angle	1	-49.0 (65.4)	-7.9 (57.3)	56.9 (49.4)	**<0.0001**	**0.0001**	**<0.0001**
	2	-6.7 (37.2)	8.9 (25.9)	-2.2 (29.1)	1.00	**0.009**	0.10
	3	-9.7 (26.6)	-3.0 (25.8)	12.7 (22.6)	**<0.0001**	0.34	**0.0006**
Rotation Angle	1	-10.2 (43.7)	-16.6 (49.0)	26.9 (53.2)	**<0.0001**	1.00	**<0.0001**
	2	-11.7 (33.3)	-4.2 (25.8)	15.8 (35.6)	**<0.0001**	0.48	**0.0006**
Adduction Moment	1	0.46 (1.34)	-0.16 (0.86)	-0.30 (0.78)	**<0.0001**	**0.001**	1.00
	2	-0.33 (0.45)	-0.09 (0.44)	0.43 (0.45)	**<0.0001**	**0.004**	**<0.0001**
	3	-0.14 (0.28)	0.01 (0.26)	0.12 (0.35)	**<0.0001**	**0.007**	0.08
Flexion Moment	1	0.63 (1.82)	0.16 (1.3)	-0.8 (0.94)	**<0.0001**	0.13	**0.0002**
	2	-0.63 (0.81)	-0.23 (0.79)	0.86 (0.84)	**<0.0001**	**0.009**	**<0.0001**
Internal Rotation Moment	1	-0.12 (0.6)	-0.01 (0.37)	0.13 (0.31)	**0.003**	0.37	0.24
	2	-0.06 (0.24)	-0.13 (0.27)	0.19 (0.32)	**<0.0001**	0.40	**<0.0001**

4.3.3 Discriminant Models

The discriminant function separating preTKA and asymptomatic groups included 6 PC features, dominated by loading features in the sagittal and frontal plane (Table 4.4). PC2 of the knee flexion moment had the highest contribution to the function with a standardized function coefficient of 0.469, followed by PC2 of the knee adduction moment (0.433) (see Appendix C for table of standardized coefficients). The other features included PC1 of both the knee flexion moment and angle, as well as PC1 and PC3 of the knee adduction moment. The preTKA vs asymptomatic function was associated with a cross-validated correct classification rate of 91% (Table 4.7). Group separation based on discriminant score distribution of each group can be visualized in Figure 4.2.

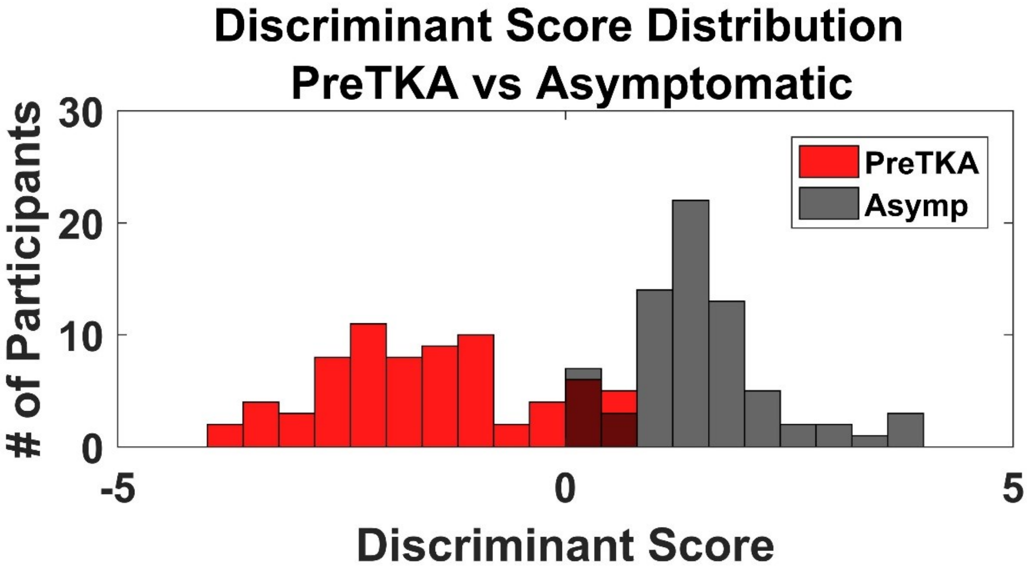

Figure 4.2 PreTKA vs asymptomatic discriminant score distribution. Overlap is visualized as the shaded region.

Table 4.4 PreTKA vs asymptomatic discriminant function summary, including the features selected for this function, their contribution, and interpretation.

PC Feature	Normalized Coefficient*	PC Feature Interpretation
Knee Flexion Moment PC2	1.00	PreTKA had lower flexion moment during early stance and extension moment in late stance
Knee Adduction Moment PC2	0.92	PreTKA had small KAM unloading between early and mid-stance (i.e. smaller difference between early- and mid-stance)
Knee Flexion Moment PC1	0.81	PreTKA had a smaller knee flexion moment throughout stance
Knee Flexion Angle PC1	0.74	PreTKA had a smaller knee flexion angle throughout stance
Knee Adduction Moment PC1	0.69	PreTKA had higher KAM throughout stance
Knee Adduction Moment PC3	0.55	PreTKA had small KAM unloading between mid and late-stance (i.e. smaller difference between mid- and late-stance)

* Normalized to the maximum standardized coefficient magnitude. The relative contribution of each PC feature is represented by the magnitude of its coefficient in the discriminant function. 1.0 = highest contribution.

The preTKA and postTKA groups were separated by a discriminant function including 5 PC features. Four of the 5 were features of the frontal plane, with PC2, PC3, and PC1 of the knee adduction moment contributing the most to this function (Table 4.4), having standardized function coefficients of 0.656, 0.515, and -0.508, respectively. The other two features included PC1 of the knee adduction angle and PC2 of the knee flexion angle. The function's ability to correctly classify participants as either preTKA or postTKA was 74% (Table 4.7). Group separation based on discriminant score distribution of each group can be visualized in Figure 4.3.

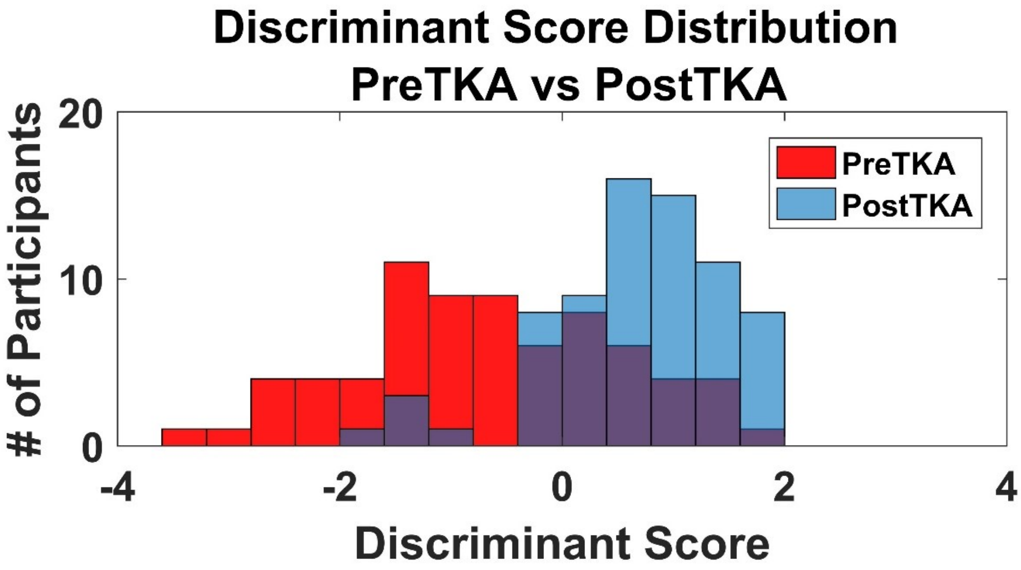

Figure 4.3 PreTKA vs postTKA discriminant score distribution. Overlap is visualized as the shaded region.

Table 4.5 PreTKA vs postTKA discriminant function summary, including the features selected for this function, their contribution, and interpretation.

PC Feature	Normalized Coefficient*	PC Feature Interpretation
Knee Adduction Moment PC2	1.00	PostTKA had larger KAM unloading between early and mid-stance (i.e. larger difference between early and midstance)
Knee Adduction Moment PC3	0.79	PostTKA had larger difference between mid and late-stance (i.e. lower mid-stance and higher late-stance, more characteristic of a healthy KAM pattern)
Knee Adduction Moment PC1	0.77	PostTKA had lower KAM throughout stance
Knee Adduction Angle PC1	0.61	PostTKA had a lower adduction angle throughout stance
Knee Flexion Angle PC2	0.50	PostTKA had larger difference in flexion angle between stance and swing phase

* Normalized to the maximum standardized coefficient magnitude. The relative contribution of each PC feature is represented by the magnitude of its coefficient in the discriminant function. 1.0 = highest contribution.

Six PC features separated the postTKA and asymptomatic groups (Table 4.5). Of the six, four were features of the sagittal plane, with the overall magnitude of the knee flexion angle (PC1) contributing most to this discriminant function, with a standardized function coefficient of 0.663. PC1 and PC2 of the knee flexion moment and PC3 of the knee flexion angle were the other sagittal plane features included in this function. The two non-sagittal plane features were PC2 of the knee internal rotation moment and PC2 of the knee adduction angle. The correct classification rate associated with this function was 88% (Table 4.6). Group separation based on discriminant score distribution of each group can be visualized in Figure 4.4.

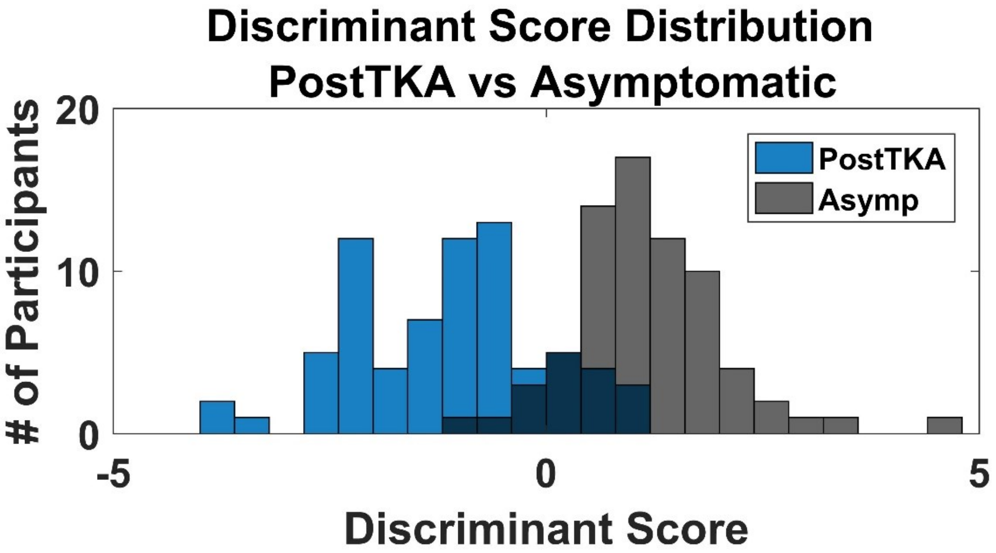

Figure 4.4 PostTKA vs asymptomatic discriminant score distribution. Overlap is visualized as the shaded region.

Table 4.6 PostTKA vs asymptomatic discriminant function summary, including the features selected for this function, their contribution, and interpretation.

PC Feature	Normalized Coefficient*	PC Feature Interpretation
Knee Flexion Angle PC1	1.00	PostTKA had lower flexion angle throughout gait cycle
Knee Flexion Moment PC1	0.57	PostTKA had lower flexion moment throughout stance
Knee Flexion Moment PC2	0.53	PostTKA had smaller biphasic moment pattern (i.e. smaller difference between early and late-stance)
Knee Flexion Angle PC3	0.49	PostTKA had smaller difference between late-stance and mid-swing, with peak swing occurring later in the gait cycle
Knee Internal Rotation Moment PC2	0.49	PostTKA had smaller difference between early to late-stance (i.e. less dynamic rotation pattern)
Knee Adduction Angle PC2	0.37	PostTKA had smaller difference between early to late-stance

* Normalized to the maximum standardized coefficient magnitude. The relative contribution of each PC feature is represented by the magnitude of its coefficient in the discriminant function. 1.0 = highest contribution.

Table 4.7 Correctly predicted group membership rates using original discriminant functions and cross validated correct classification rate using a leave-one-out routine.

Discriminant Function	Original Group Membership	Predicted Group Membership		Correct Classification Rate
		PreTKA	Asymptomatic	
PreTKA vs Asymptomatic	PreTKA	61 (84.7%)	11 (15.3%)	91.0%
	Asymptomatic	0 (0.0%)	72 (100%)	
		PreTKA	PostTKA	
PreTKA vs PostTKA	PreTKA	49 (68.1%)	23 (31.9%)	74.3%
	PostTKA	13 (18.1%)	59 (81.9%)	
		PostTKA	Asymptomatic	
PostTKA vs Asymptomatic	PostTKA	60 (83.3%)	12 (16.7%)	88.2%
	Asymptomatic	5 (6.9%)	67 (93.1%)	

Exploring the preTKA vs asymptomatic discriminant function using 41 "test" preTKA participants resulted in 92.7% (38/41) of the preTKA participants being correctly classified. Inputting this test cohort of preTKA participants into the preTKA vs postTKA discriminant function resulted in only 51.2% (21/41) of participants correctly classified. Figure 4.5 shows the average ensemble waveform differences of the original preTKA and the test preTKA groups for the waveforms that were contained within the preTKA vs. postTKA discriminant function. While the knee adduction moment patterns look similar between the original preTKA and the test preTKA groups (Figure 4.5), their knee adduction angle patterns after early stance look to deviate, with the test group walking less adducted through the remainder of stance. In terms of the adduction angle PC1 feature that is part of the discriminant function separating preTKA and postTKA, this would translate in the test group potentially having a more "postTKA-like" pattern as postTKA individuals walked less adducted throughout stance, and thus this pattern would give the participants in the test preTKA higher discriminant scores. Additionally, while the patterns during swing phase of the knee flexion angle between preTKA groups looks similar, there does look to be a slight deviation in the angle during stance, with the test group having a smaller knee flexion angle during stance compared to the original preTKA group. This could potentially have the test group scoring higher on the knee flexion angle PC2 feature, which captures a difference between the knee flexion angle during stance and swing phase (higher scores = larger difference), contributing to a higher discriminant score in the preTKA vs. postTKA discriminant function. Differences in PC features between the original preTKA and test preTKA were not statistically tested. In addition, the reduced classification rate highlights the need to test statistical models using independent test sets to understand the dynamics of these models when used on new or different cohorts than those used during model construction.

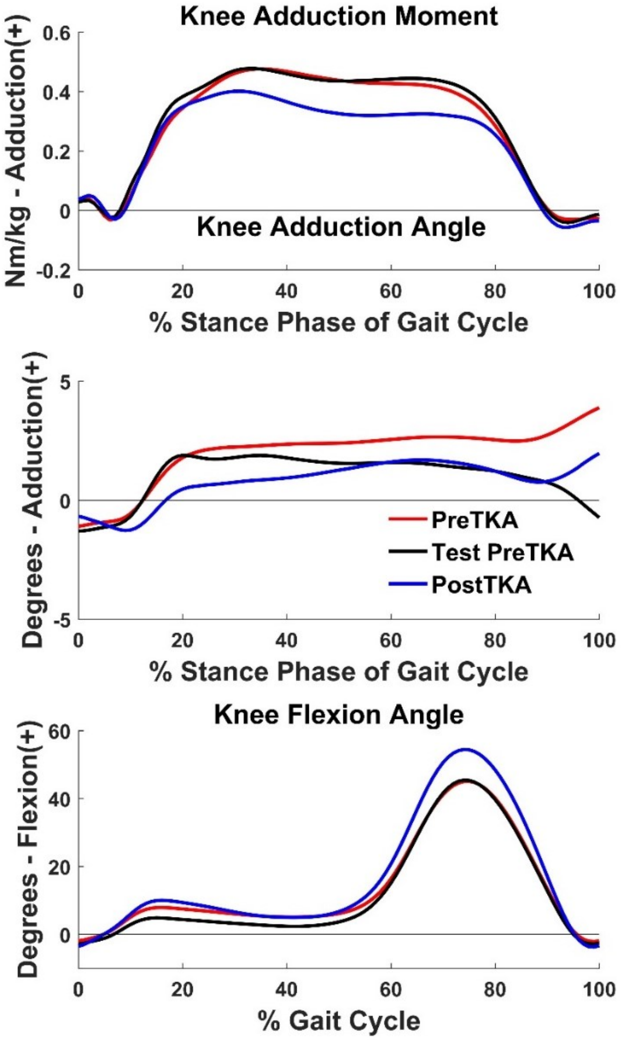

Figure 4.5 Ensemble average gait waveforms of the PCs that were contained within the preTKA vs. postTKA discriminant function. PreTKA (red), postTKA (blue) and test preTKA (black).

4.4 Discussion

Determining the success of total knee arthroplasty (TKA) in restoring function to an impaired knee joint requires a tool that can handle the high dimensional space of human gait. Using a discriminant model, a quantification of the remaining gait deficits following surgical intervention was possible and for the first-time insight into the strengths and limitations of the current standard of care from a functional and biomechanical perspective was achieved. The results of this study showed that the current TKA procedure has predominately altered frontal plane gait mechanics, and a relatively large deficit in sagittal plane knee joint function between the surgical recipients and asymptomatic participants remained.

Abnormal gait patterns linked to the degenerative processes of OA can be characterized by a set of biomechanical features in both the frontal and sagittal plane. Previous studies have focused on the role of the knee adduction moment as it is regarded as a surrogate measure for the ratio of medial and lateral compartment loading(Schipplein and Andriacchi, 1991), where higher adduction moments coincide with higher levels of medial joint loading. For example, it has been shown that higher peak and sustained knee adduction moment patterns during stance phase of gait are characteristic of individuals with severe levels of medial compartment knee OA(Astephen et al., 2008a; Rutherford et al., 2008). Abnormal sagittal plane loading patterns coupled with reduced knee flexion angles have also been reported(Astephen et al., 2008a), and is often described as a 'stiff knee' gait pattern(Dorr et al., 1988). It is unclear what exactly causes severe OA individuals to adopt a 'stiff knee' gait pattern, although as a response to pain and/or lack of confidence in the joint is plausible.

The features that discriminated pre-TKA gait from asymptomatic gait captured the difference in the loading patterns between these two groups in both the frontal and sagittal plane. The discriminating feature set included the overall magnitudes of these moments (PC1), as well as the dynamic patterns of these moments throughout stance (PC2 and PC3 of the knee adduction moment). Separation of pre-TKA gait from asymptomatic gait was quite distinct in this study, shown by the 91% correct classification rate. When this discriminant model was tested using a separate cohort of pre-TKA participants, 93% of these participants were classified correctly. This provides a level of confidence that these are highly discriminatory features that are robust in other cohorts of pre-TKA participants and not an over-fitted explanation of the specific differences in one cohort.

The discriminant function separating pre-TKA from post-TKA was almost solely comprised of frontal plane loading features, with the second, third and first principal components of the knee adduction moment contributing the most (in descending order) to the separation of these groups. The standard TKA procedure includes augmentation of the articulating surfaces of the knee joint and alignment of the tibial component to achieve a neutral mechanical axis of 0 (± 3) degrees. This practice is driven by the hypothesis that a neutrally aligned tibial component will result in a more equally distributed load between the medial and lateral compartments, and subsequently, a reduced knee adduction moment, leading to improved longevity and function postoperatively(Andriacchi et al., 1986). Because altering the frontal plane alignment is a primary objective of the TKA procedure, it is intuitive that the dynamic frontal plane features would be the most affected. The rationale for altering the static alignment of the knee during the TKA procedure is not well supported with evidence(Vandekerckhove et al., 2016), as it has not convincingly been shown that that static alignment is correlated with the knee adduction moment(Brugioni et al., 1990) or medial compartment loading(Halder et al., 2014; Kutzner et al., 2013), with other work finding no relationship(Miller et al., 2014; Orishimo et al., 2012). Although, data investigating passive-dynamic frontal plane alignment captured intraoperatively has been shown to be related to dynamic frontal plane loading pre- and post-TKA during gait(Roda et al., 2012; Young, 2013). It is suggested that dynamic loading of the knee joint in the frontal plane, the dominate features discriminating between pre- and post-TKA, is affected by more than just static alignment(Andriacchi, 1994; Harrington, 1983; Johnson et al., 1980).

Interestingly, no features of the knee flexion moment and only one feature of the knee flexion angle (PC2) were contained in the discriminant function despite the relatively high contribution of sagittal plane features in discriminating pre-TKA joint function from that of asymptomatic knee joints during gait. When this discriminant model was tested using a separate cohort of pre-TKA participants only 51% of these participants were classified correctly, this may have been due to the test group having some aspects of the features in this function being more similar to postTKA, causing higher discriminant scores or because the participants in the test set were not used in the original model development. These models provide valuable information regarding important variables for group separation, however future rigorous testing, including resampling and use of independent tests sets, is required to understand model dynamics, most importantly before deployment as a tool in the clinical environment.

Separation of post-TKA participants from those with asymptomatic knee joints was quite distinct (classification rate of 88 %), with the dominant contributors again comprised of sagittal plane motion and loading features. The features separating pre- and post-TKA gait from asymptomatic gait were similar, suggesting that the current standard of care for TKA, including its surrounding management, is not appropriately targeting functional deficits of the knee joint relative to a cohort of age-matched healthy participants. This information has implications for both pre- and re-habilitation management, with potential targets being those that contribute to ‘stiff knee’ gait, both pre- and post-TKA. This information may also suggest there needs to be a shift in focus of TKA surgical planning to include 3D joint structure and dynamic joint function and how this may influence or optimize walking mechanics post-surgery

It can be difficult to interpret multiple changes in gait biomechanics simultaneously. Using a tool like discriminant analysis, with a stepwise approach, we were able to summarize these changes using an optimal subset of gait features. This presents the ability to summarize knee joint function into a single ‘functional score’(Chao et al., 1980; Laughman et al., 1984), and provides a framework to objectively quantify outcome from TKA along a spectrum of knee joint function. It also provides insight into the hierarchy among gait features that separate subject groups. While these models were designed to summarize current standard of care TKA, which contains valuable information regarding what the procedure currently best targets and what remains deficient in terms of knee joint function, it also brings the potential to test or evaluate new innovations in surgical triage against the current standard of care, such as implant design, surgical strategies and techniques, as well as pre- and re-habilitation management.

CHAPTER 5 CONCLUSION

5.1 Overview

Total knee arthroplasty is a successful orthopaedic procedure for most individuals when considered in terms of self-reported improvements in pain and function, and demand is increasing. These results have been obtained using implant designs and surgical rationale that has been altered very little since the 1970s. But, despite reported success, it is unclear based on current tools and clinical monitoring postoperatively if function at the knee joint-level is being optimized, specifically on an individual level. Candidate demographics are changing, shifting to include not just an increased aging population but also a younger and more obese demographic, whose prospective outcome from contemporary TKA management is not yet clear. The drive to understand the variability in individual response at the knee joint-level of this widening demographic is paramount to increasing success with TKA. While abnormal joint-level function has been linked to poorer outcomes of pain, risk of implant failure and patient satisfaction, objective joint-level function needs to be regarded as an important outcome measure on its own for its broader implications on patient care during triage, surgery, and post-operatively. Providing more objective tools to clinicians allows for more informed decision making and evaluation of current standard of care practices in TKA.

The first objective of this thesis aimed to comprehensively capture the variability in knee joint level biomechanics during walking gait of individuals pre- and one year post-TKA, as well as their improvement. This included investigations into how the status of knee joint-level biomechanics before TKA influences the level of improvement after TKA, as well as examining on a person-specific level whether knee joint-level biomechanics during gait, both pre- and post-TKA, are more similar to healthy controls (high function), those with moderate knee OA (moderate function), or those approximately one week before TKA surgery (low function). The majority of individuals post-TKA are more similar in terms of knee joint-level function during gait to those with moderate levels of knee OA than those with no symptoms (healthy controls). Attainment of moderate function was most often an improvement for individuals with lower levels of function before surgery. This was supported by the significant associations between all pre-TKA values of knee joint level biomechanics and the change in these biomechanics from pre- to post-TKA, suggesting that the pre-TKA functional status of the joint has a strong influence on the degree of functional improvement post-TKA. A portion of individuals did have either moderate or higher levels of function before surgery, highlighting the person-specific variability in functional status despite all being triaged to primary TKA for severe knee OA. Furthermore, frontal plane biomechanics had the largest percentages of individuals within healthy values post-TKA, while sagittal plane biomechanics had the lowest, indicating that the surgery in general better targeted frontal plane mechanics than sagittal.

Currently, orthopaedic surgeons are faced with the challenge of strategizing triage and developing surgical plans based on limited assessment tools, almost solely consisting of static 2D joint specific radiographs and interpretation of subjective self-reported pain and function. As a result, conventional TKA management tends to continue to be very much a one size fits all approach, with very little person-specific information used for decision making, and a lack of objective and dynamic joint-level assessment tools to help target functional improvements with TKA and guide innovation in current TKA management strategies. This thesis quantified the functional gap in knee joint-level biomechanics, as summarized by key functional deficits throughout triage for individuals receiving TKA surgery, providing a baseline to understand what the current management is most targeting and what functional deficits remain.

The second objective of this thesis aimed to summarize knee joint-level biomechanical features during walking gait that optimally separate individuals pre-TKA from healthy controls, individuals pre-TKA from one year post-TKA, and individuals one year post-TKA from healthy controls. The features that separated pre- and post-TKA gait from that of healthy controls were similar, suggesting that current conventional TKA, and its surrounding management, is not appropriately targeting some of the key biomechanical functional deficits of the knee joint relative to age-matched healthy individuals. In terms of gait mechanics, current TKA management predominately alters features of the frontal plane, resulting in relatively large deficits in sagittal plane knee joint function between TKA recipients and healthy controls. Separations were quantified using discriminant functions constructed with an optimal subset of biomechanical features. This provides a framework for the development of an objective functional assessment and scoring tool specific to TKA and in vivo dynamic knee joint kinematic/kinetic function.

5.2 Implications of Thesis Results

Previous research investigating changes in knee joint-level biomechanics may have captured, through population averages, that functional improvements are made pre- to post-TKA and that knee joint-level biomechanics post-TKA are different than healthy controls, but this was the first research to comprehensively investigate where along the functional spectrum individuals lie post-TKA, representing critical information to inform the next steps of clinical translation. Some of the key results from *Objective 1* showed that the majority of individuals achieve a level of knee joint function most similar to those with moderate knee OA. Additionally, it was suggested that those with higher levels of function pre-TKA have less to gain from the surgery than those with lower function pre-TKA. Together, this information can have implications for patient and surgeon expectation management as well as person-specific triage and management strategies. Surgeons have not had the data to show quantitatively using objective joint-level metrics that perhaps the best functional outcome that can be expected for the majority of individuals is moderate levels of function, and that those with higher levels of function pre-TKA may have less to gain, or perhaps may decline in function, post-TKA. Unmet expectation has been shown to significantly contribute to dissatisfaction post-TKA(Dunbar et al., 2013), and understanding and managing expectation on a person-specific level has high clinical value. It is possible that individuals with continued high function but triaged for primary TKA may be better served from alternative treatment strategy.

Multiple, simultaneous, changes occurred in joint-level biomechanics in *Objective 1*, making overall interpretation complex. *Objective 2* aimed to reduce this complexity by capturing a subset of biomechanics that optimally separated these groups. One of the main findings suggested that conventional TKA management most targets frontal plane mechanics, leaving sagittal plane deficits post-TKA relative to age-matched healthy joint function. This may be intuitive, as preoperative planning is based on 2D radiographs in the frontal plane, resulting in the procedure focusing heavily on varus-valgus alignment correction. However, this finding has broader implications for surrounding management strategies. Neuromuscular contributions are most often ignored during preoperative planning and the TKA procedure itself. Surrounding management does not incorporate any prior learned neuromuscular adaptations that may persist post-TKA(Hubley-Kozey et al., 2010), that the surgery does not target. These current findings that sagittal plane features are not targeted well by the surgery drives the need to further understand how dynamic muscular patterns influence sagittal plane gait mechanics post-TKA, and if they can be targeted by person-specific pre- or re-habilitation regimes. It also promotes the idea that future TKA innovation should aim to better incorporate three-dimensional mechanics in its approach.

5.3 Limitations and Considerations

It would be negligent to not acknowledge the main modes of error that are inherent to 3D gait analysis. Malalignment of coordinate system axes definitions can result in kinematic error, most noticeably during periods of increased flexion angles. This is known as kinematic crosstalk and results in the bleeding over of rotation from one plane onto another(Piazza and Cavanagh, 2000). Malalignment of the axes can result from improper anatomical landmark identification which can be influenced by participant adiposity. In this study, except for the knee flexion angle, all biomechanical variables were captured during stance phase of gait which results in smaller angles of flexion (<30°), which are less prone to kinematic crosstalk error. Skin motion artefact can further introduce kinematic errors, which can be increased by adiposity(Benoit et al., 2007; Manal et al., 2003). The choice of anatomical reference frame has been shown to influence both the magnitude and amplitude of joint moments, and therefore the ability to detect changes in parameters such as the knee adduction moment and internal rotation moments(Newell et al., 2008; Schache et al., 2007). While, the use of principal component analysis has been shown to capture features in both these planes that are robust to coordinate system selection in knee OA populations(Brandon and Deluzio, 2011; Newell et al., 2008), the choice to not focus heavily on measures of off-plane kinematics (adduction angle and internal/rotation angle) were due to their level of being prone to error and lack of reliability. The standardized protocol developed in the Dynamics of Human Motion laboratory and used for the data collections in this thesis follows the suggested standard for expression of lower-limb joint kinematics and kinetics known as the joint coordinate system(Grood and Suntay, 1983; Wu and Cavanagh, 1995), and shown good day-to-day reliability for the majority of the discrete parameters and PC scores ($ICC_{2,k} > 0.7$) reported in this thesis(Robbins et al., 2013).

All gait analyses were performed unilaterally, only collecting the surgical limb pre-and post-TKA. There were no exclusion criteria set on participants having a previous TKA in the contralateral limb, other than contralateral surgery could not have been received within the year prior to the currently tested surgery limb. While there are an increasing number of studies investigating the effects of TKA on the contralateral limb(Alnahdi et al., 2011; Catani et al., 2009; Metcalfe et al., 2013; Milner, 2008), we did not explore this factor in the analyses of this thesis. Inclusion of information of this type is an example of where the use of the functional scoring tool could be used to investigate subgroups of participants with and without a contralateral TKA. Additionally, pilot data examining the effect of obesity, age, and previous contralateral TKA on knee joint-level mechanics and muscle activity during gait in 149 individuals prior to TKA surgery did not show group differences between individuals with and without contralateral TKA before surgery (see Appendix D.1 for pilot data). The post-TKA data has not yet been fully explored, as a full post-TKA subset with this information is currently being collected.

In a similar vein, no exclusion criteria were set on implant design for individuals participating in this study. While the intuitive goal of different implant designs is to elicit a specific functional response, there is a lack of evidence showing differences in gait between groups receiving different implants designs(Ahmad et al., 2015; Harrington et al., 2009; Jiang et al., 2016). Furthermore, a sub analysis from the TKA cohort used in this thesis, separated by cruciate retaining and posterior stabilized implant designs resulted in no significant differences between groups in walking gait biomechanics, see Appendix A.1. Additionally, inclusion of multiple designs used in the standard of care for TKA could result in better generalizability of the findings in comparison to studies of a single implant design, with the acknowledged caveat of the potential selection bias by the surgeon for some cases.

5.4 Future Work

The discriminant models constructed in *Objective 2* were developed to summarize current standard of care TKA, in terms of knee joint level function, which is valuable in and of itself, but it also provides the possibility of assigning on a person-specific level a 'functional score'. Using this framework for the development of an objective functional scoring tool brings the potential to evaluate future innovations in implant design, surgical decision-making, and surrounding management strategies, against a baseline model of what conventional TKA management is capable of in terms of restoration of dynamic knee joint-level function. Prior to model deployment to the clinical environment, rigorous model testing using independent test sets and resampling procedures is required to understand the dynamics of the models when using new participants.

One avenue in which this objective functional scoring tool could be further utilized is to investigate person-specific characteristics (age, sex, BMI, etc.) and identify subgroups of individuals who improve and those who do not, and where they lie along the spectrum of joint-level function. Preliminary pilot data investigating effects of BMI in pre-TKA and post-TKA participants (Appendix D.2) is currently being extended to include further breakdown of obesity class, as well as examine effects of sex, as recent work from our group has shown that outcome from TKA looks to be sex specific(Astephen Wilson et al., 2015).

The future of this research program lies in the efficient and effective translation of this research into the clinical environment. This will involve leveraging off the shelf technologies able to capture the optimal subgroup of kinematic and kinetic biomechanical variables required to feed the scoring tool, without the use of a fully equipped gait laboratory. After appropriate laboratory validation, this mobile gait assessment device could be utilized in clinic to provide streamlined and time-effective patient-specific evaluation. This type of information could help in patient screening and assessment to better prioritize wait lists.

The participants in this thesis are also part of a companion study funded by the Canadian Institutes of Health Research (CIHR) and the Nova Scotia Health Research Foundation (NSHRF) investigating biomechanical outcome from TKA (3D gait analysis including electromyography) as well as self-reported information (physiotherapy, satisfaction, etc.). Once data collections are complete, data from an overall larger cohort (~100 participants) of pre- and one year post-TKA will be available. A portion of these participants who had received their pre-TKA gait analysis were used as a test set to examine the robustness of the models developed in this thesis. Future work with a larger cohort will allow for further testing of the remaining models and for future model development. There was incomplete patient-reported outcome measurements (PROMs) for the primary participants used in this study, as well as incomplete information on participant comorbidities. This type of information would have allowed for a more accurate description of this patient population for comparison to previous study cohorts and for future exploratory work examining the use of discriminant models.

The use of gait analysis in evaluation and assessment of those receiving TKA may provide a valuable contribution to surgical triage on its own. Its real power, however, may result in combination with other objective measurement tools surrounding TKA management including intraoperative computer assisted surgical navigation data(Roda et al., 2012; Young et al., 2015) and radiostereometric analysis (RSA) to track implant migration post-TKA(Astephen Wilson et al., 2010). Additionally, future work from our research group plans to marry data obtained from these objective tools with other hospital based outcomes (i.e. patient reported outcomes, deeper patient health history, and other metrics collected in surgery) to develop a larger framework encompassing multiple data inputs. A main objective of our research group is to develop these technologies in combination to provide a more objective patient assessment and evaluation regime here in Nova Scotia, with the goal of providing the best possible triage management and outcome from TKA surgery based on objective patient-specific data. The results from this thesis represent a component to the development of such a regime, and for increased clinical uptake and application.

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Appendix A Chapter 2 Supplementary Material

Appendix A.1 Equivalence of Change in Gait Mechanics after Total Knee Arthroplasty Surgery with Cruciate Retaining and Posterior Stabilized Implant Designs

Orthopaedic Research Society 2016 Annual Meeting Orlando, Florida (Poster Presentation)

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ABSTRACT INTRODUCTION: There is inconclusive evidence for the effect of posterior cruciate ligament retaining (CR) versus posterior stabilized (PS) implant designs, particularly in terms of objective measurement of joint-level function post-operatively. The CR surgery retains more native knee tissue, and in theory contributes to more natural knee kinematics with higher levels of proprioception enabled (Kolisek et al., 2009). The CR knee is also more capable of femoral rollback during flexion. Whether these anatomical differences translate into enhanced joint mechanics post-operatively has not been fully explored, and self-report clinical and functional scores have been equivocal (Tanzer et al., 2002; Bolanos et al., 1998, Yoshiya et al., 2005, Kolisek et al., 2009), even in randomized trials (Tanzer et al., 2002). We have previously shown that post-operative joint-level biomechanics move toward asymptomatic levels post-operatively, but remain quite variable (Hatfield et al., 2011), and that the pre-operative joint-level mechanics are highly correlated to the post-operative values (Outerleys et al., ORS 2015), meaning that patient selection in non-randomized studies plays a large role in post-operative outcome comparisons. The objective of this study was to examine the pre-operative knee joint-level biomechanical (kinematic, kinetic) differences during gait between a large cohort of CR and PS knees, and additionally to examine the difference in the effect of each surgery on the change and post-operative values in joint-level kinematics and kinetics during walking gait.

METHODS: Seventy-three patients diagnosed with end stage knee osteoarthritis and scheduled to receive a primary total knee arthroplasty (TKA) surgery were recruited to the study. Patients (non-randomized design) received one of four implant systems including the NexGen PS (n=34) (Zimmer, Warsaw, Indiana), Triathlon PS (n=14) (Stryker Orthopedics, Kalamazoo, MI), Triathlon CR (n=11), and Medial Pivot CR system (n=14) (Wright Medical, Memphis, TN). Patients were grouped by global PS (n=48) or CR design (n = 25). All patients provided informed consent according to the Capital District Health Authority. All patients visited the Dynamics of Human Motion laboratory at Dalhousie University for a three-dimensional gait analysis, both one week prior to and approximately one year after their surgery. Gait testing was performed over ground at self-selected walking speed. Three-dimensional knee angles and net resultant moments during gait were captured with an Optotrak motion capture system (Northern Digital Inc., Waterloo, ON) synchronized with an AMTI force platform embedded within the walkway and modelled according to the joint coordinate system (Grood and Sunay, 1983). Inverse dynamics was performed using a custom Matlab program (Hatfield et al., 2011). Ten discrete parameters were extracted from the gait kinematic and kinetic waveforms for comparison, as previously defined (Astephen et al., 2008), including gait velocity, peak and range of knee flexion angle during the gait cycle, peak knee flexion moment, peak late stance and early stance extension moments, peak internal rotation moment, first and second peak and midstance minimum of knee adduction moment. Independent t-tests were used to compare these discrete metrics pre-operatively, post-operatively (1 year), and as change score due to surgery between the CR and PS groups (alpha=0.05).

RESULTS SECTION: Pre-operative mass and BMI were not statistically significant between the CR and PS groups (P>0.05), although the CR group was marginally younger (62 vs 66 years, P=0.03). There was higher ratio of females in the CR group (0.76) vs the PS group (0.5). Many of the gait parameters changed from pre-to post-operatively, consistent with previous work (Hatfield et al., 2012). However, interestingly, there were no statistically significant differences in the extracted features of the knee joint kinematics, kinetics, or gait speed between the implant groups, pre-operatively, post-operatively, or in terms of the change in these values pre-to post-operatively (all P>0.05).

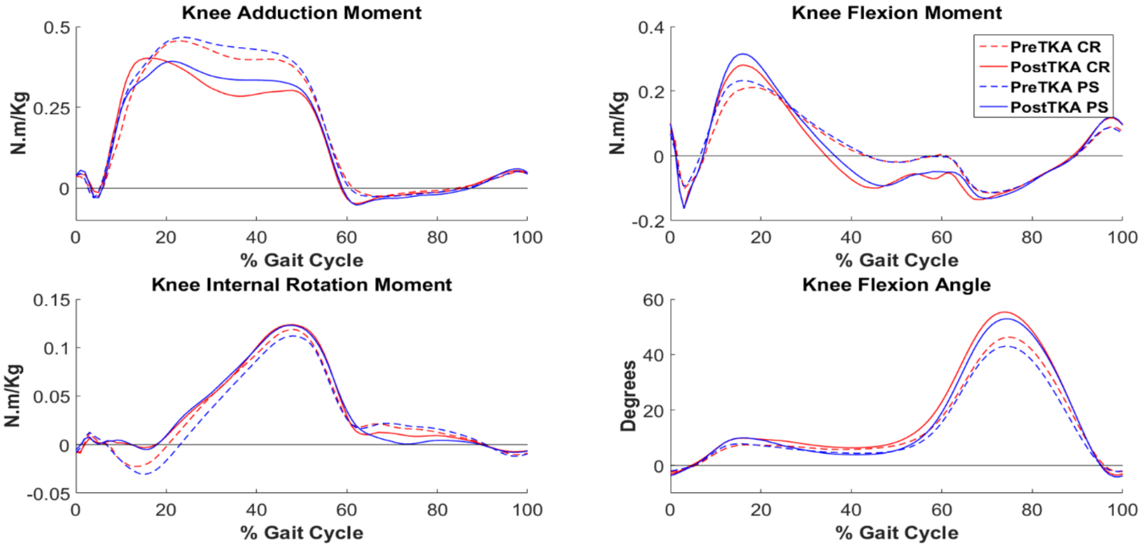

Figure 1. Average knee joint kinematic and kinetic waveforms during walking gait, pre- (dashed) and post-TKA (solid). CR group in red and PS group in blue.

DISCUSSION: Knee joint level biomechanics did not show differences between the PS and CR implant groups at either time-points or in terms of a change from pre-to post-operatively. This is consistent with other studies showing no differences in terms of self-report clinical and functional scores (Tanzer et al. 2002, Kolisek 2009, Urquart et al. 2009), yet provides the additional and objectively measured insight into a similar effect of the surgeries in terms of joint level biomechanics during gait. There have been previous reports of a difference in the knee adduction moment between PS and CR (Medial Pivot only) implant types post-operatively (Urquart et al., 2009), and Yoshiya et al. (2005) showed differences in rollback kinematics between CR and PS implant designs, but with no other differences in gait kinematics. There were no statistically significant differences between the groups in terms of gait speed in the current study, yet post-operatively a small mean difference approached significance (P = 0.07). Three-dimensional gait analysis offers an objective measurement of joint-level function and a powerful tool for examining differences between implant designs and patient-to-patient variability in terms of their response to surgery. Not only should new designs that aim to improve the biomechanics environment of the joint be tested in this way, objective biomechanical analysis can provide important information on the patient-specific joint environment, that we have shown can significantly dictate the functional outcome of surgery (Outerleys et al., 2015).

SIGNIFICANCE: Objective biomechanics analysis of joint dynamics before and after surgery is rarely used to evaluate the added value or effect of new implant designs. Our results show relative equivalence, in terms of group averages, between the CR and PS implant designs in terms of joint-level biomechanics during gait after surgery, and also in terms of change from pre-to post to surgery. This does not mean that individuals with particular knee joint biomechanics environments pre-operatively may not benefit from one design over the other, and more research should address how to use this information to help inform surgical planning, decisions and design.

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Appendix B Chapter 3 Supplementary Material

Principal component eigenvector plots, with eigenvector and variance explained (top row), waveforms associated with 95th and 5th percentile PC scores (middle row), and mean 95th and 5th percentile PC scores (bottom row). Plots were used to interpret PC features and determine high and low scoring features in Chapter 3 (n = 288 participants).

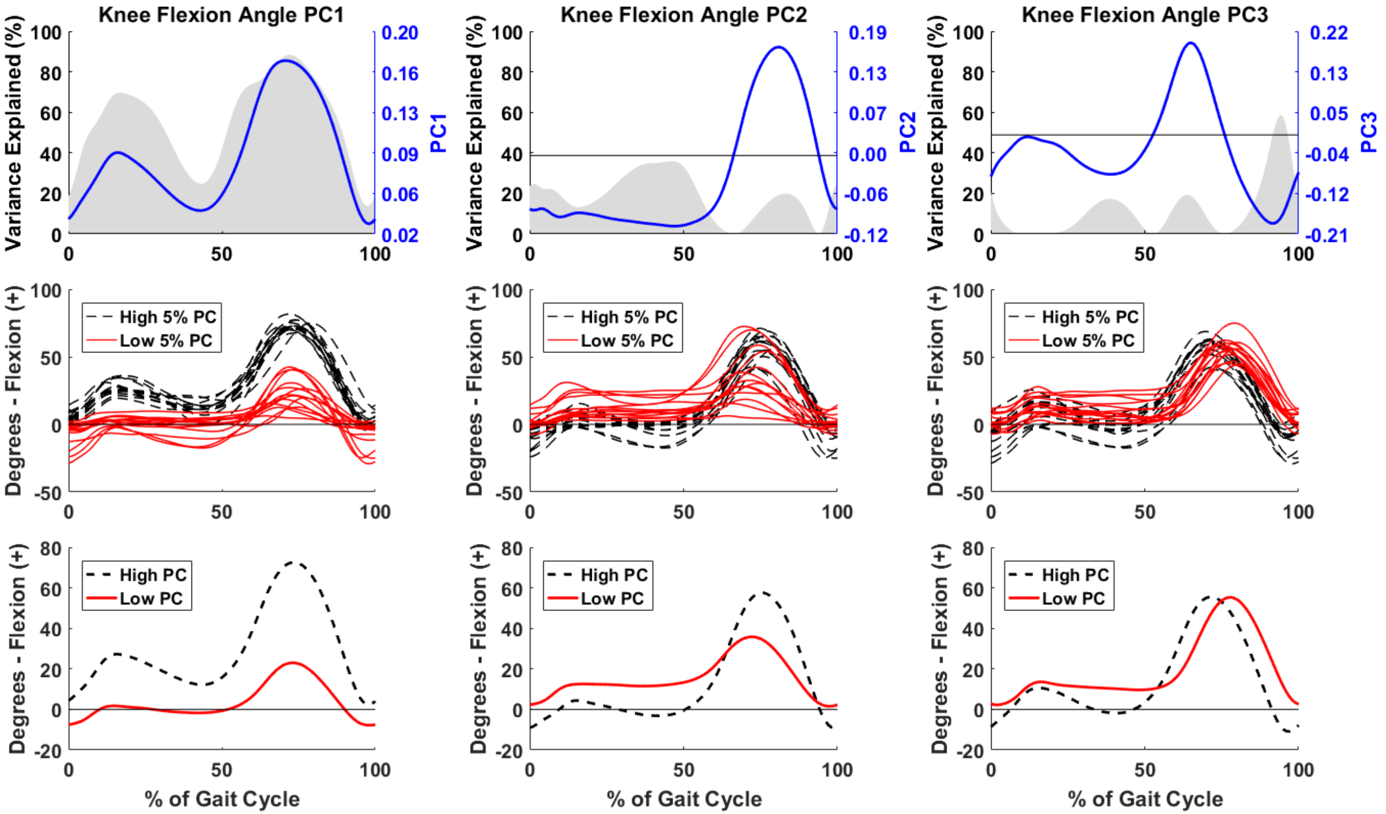

Figure B.1 Knee flexion angle principal component 1 (left), 2 (center), and 3 (right) eigenvector plots.

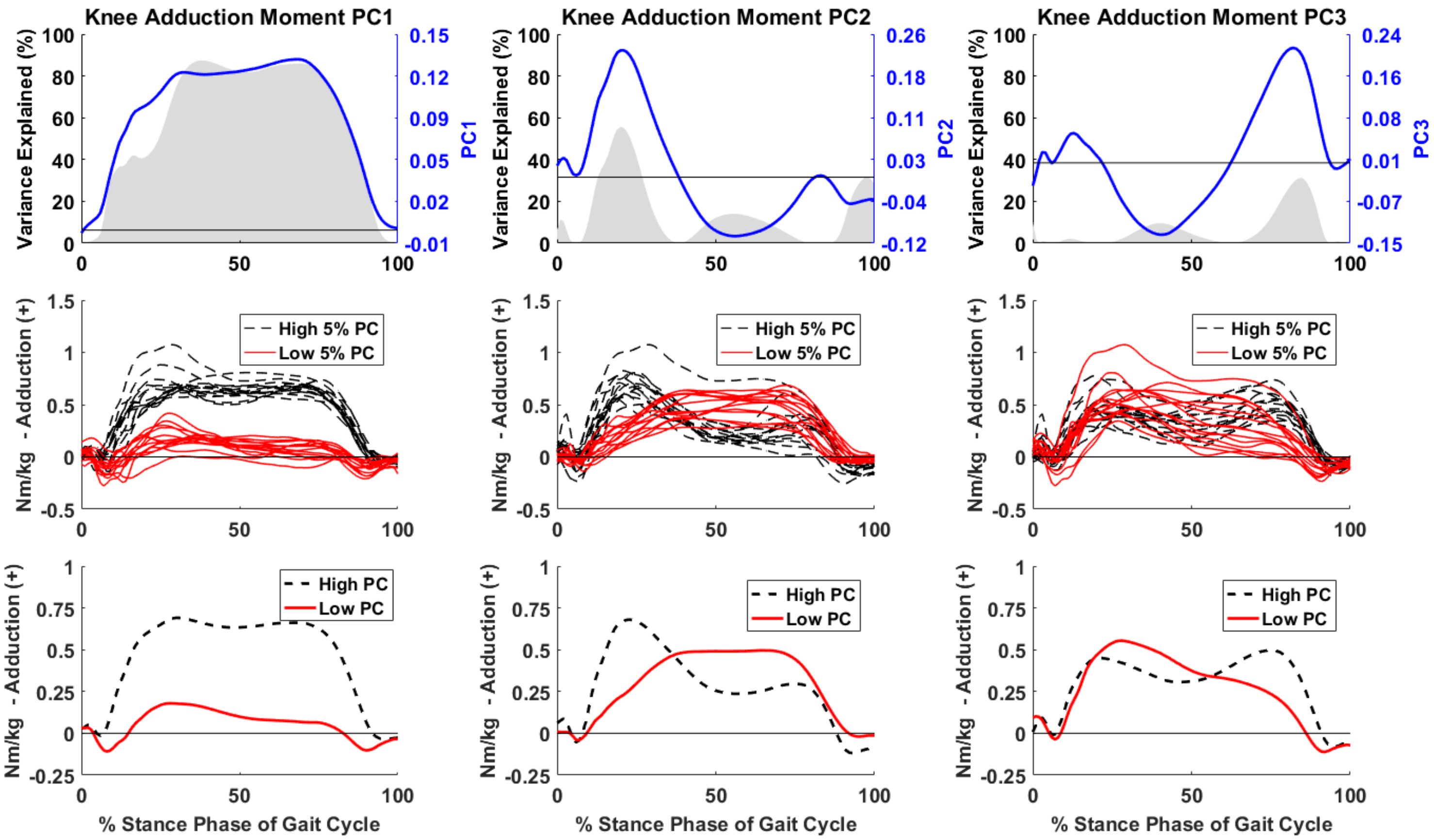

Figure B.2 Knee adduction moment principal component 1 (left), 2 (center), and 3 (right) eigenvector plots.

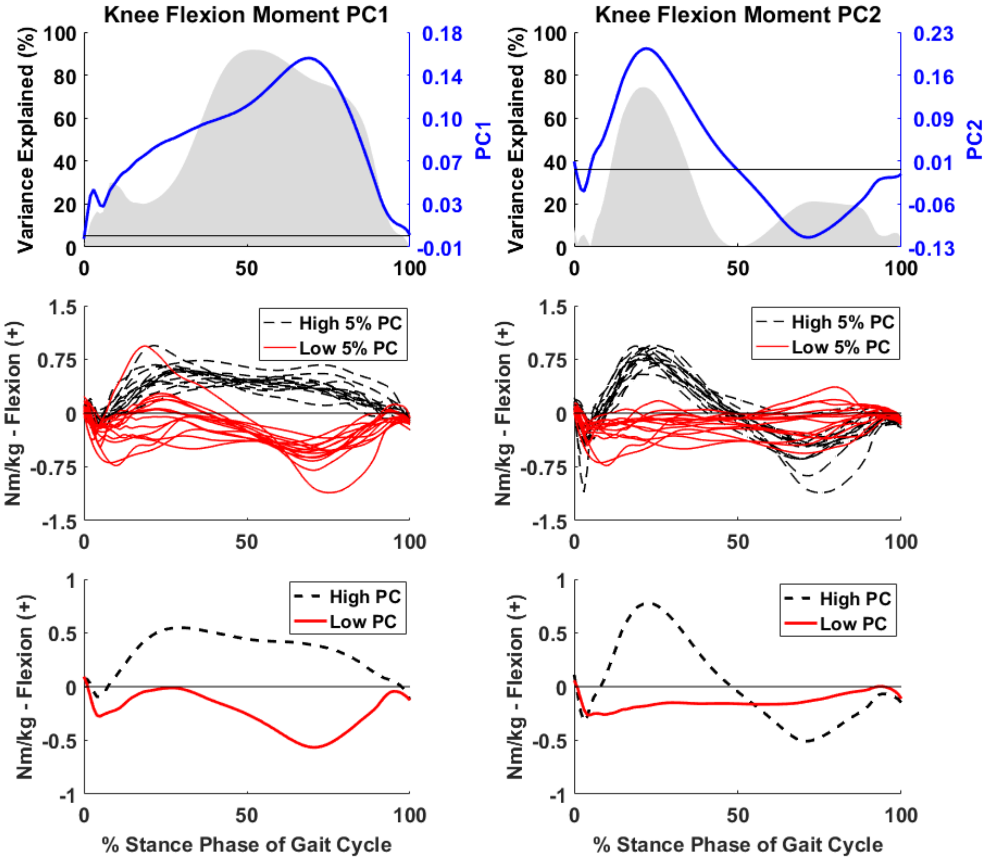

Figure B.3 Knee flexion moment principal component 1 (left) and 2 (right) eigenvector plots.

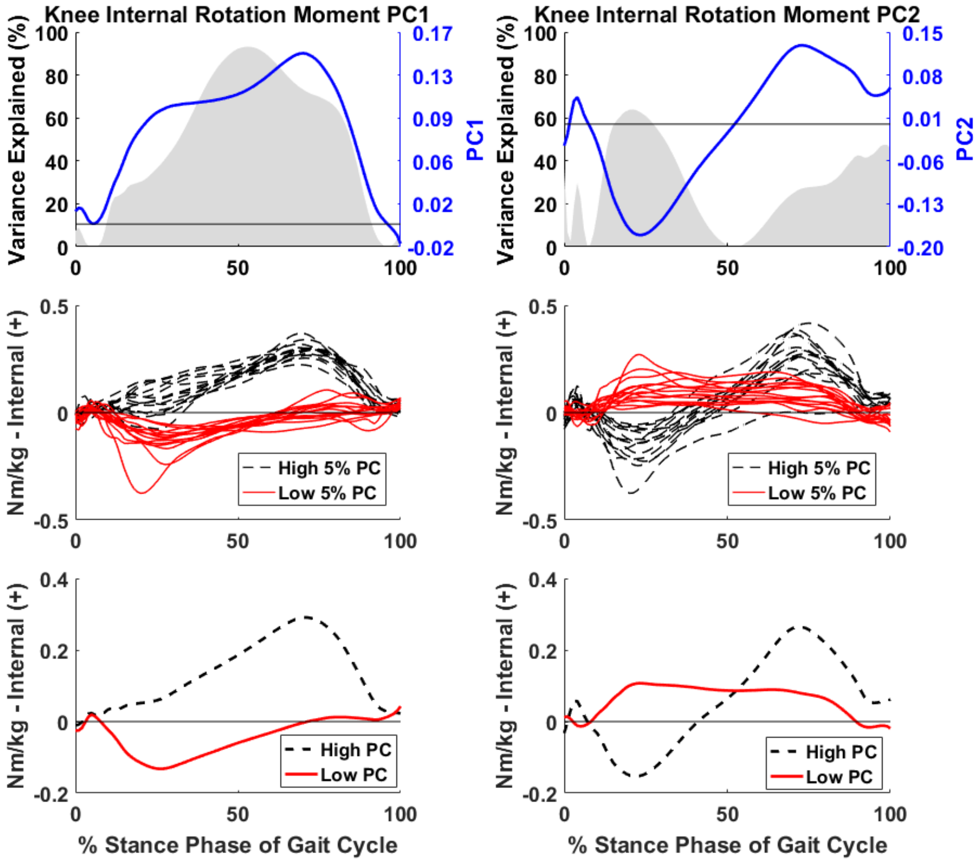

Figure B.4 Knee internal rotation moment principal component 1 (left) and 2 (right) eigenvector plots.

Table B.1 ANOVA results for discrete and waveform PC parameters. Bold = statistically significant (α = 0.05).

	PreTKA	**PostTKA**	**Asymp**	**Mod**	**Pre vs. Post**	**Post vs. A**	**Post vs. Mod**
Gait Speed (m/s)	0.89 (0.22)	1.08 (0.2)	1.34 (0.16)	1.19 (0.19)	< **0.01**	< **0.01**	< **0.01**
Discrete Parameters							
Adduction Moment 1st Peak (Nm/kg)	0.50 (0.17)	0.43 (0.13)	0.51 (0.15)	0.51 (0.15)	0.09	**0.02**	0.03
Adduction Moment 2nd Peak (Nm/kg)	0.44 (0.18)	0.34 (0.12)	0.31 (0.12)	0.39 (0.14)	< **0.01**	1.00	0.46
Adduction Moment Mid-stance (Nm/kg)	0.38 (0.17)	0.30 (0.10)	0.22 (0.09)	0.33 (0.13)	< **0.01**	< **0.01**	0.66
Peak Flexion Angle Swing (°)	46.2 (14.61)	55.1 (9.8)	65.0 (6.34)	58.6 (7.69)	< **0.01**	< **0.01**	0.22
Peak Flexion Angle Stance (°)	8.9 (5.24)	10.5 (5.59)	19.0 (6.55)	12.0 (7.0)	0.62	< **0.01**	0.91
Flexion Angle Range (°)	49.1 (14.89)	59.5 (9.64)	69.3 (4.55)	64.9 (6.38)	< **0.01**	< **0.01**	< **0.01**
Peak Flexion Moment (Nm/kg)	0.28 (0.24)	0.32 (0.20)	0.48 (0.21)	0.27 (0.25)	1.00	< **0.01**	1.00
Peak Extension Moment Early-stance (Nm/kg)	-0.15 (0.08)	-0.21 (0.10)	-0.29 (0.14)	-0.25 (0.12)	< **0.01**	< **0.01**	0.18
Peak Extension Moment Late-stance (Nm/kg)	-0.12 (0.18)	-0.19 (0.17)	-0.42 (0.17)	-0.26 (0.20)	0.15	< **0.01**	0.15
Peak Internal Rotation Moment (Nm/kg)	0.13 (0.08)	0.13 (0.06)	0.19 (0.06)	0.17 (0.07)	1.00	< **0.01**	**0.03**
Waveform PCs							
Adduction Moment PC1	0.38 (1.34)	-0.23 (0.87)	-0.35 (0.79)	0.19 (1.09)	< **0.01**	1.00	0.12
Adduction Moment PC2	-0.37 (0.45)	-0.10 (0.44)	0.41 (0.44)	0.06 (0.41)	< **0.01**	< **0.01**	0.17
Adduction Moment PC3	-0.15 (0.28)	0.01 (0.26)	0.14 (0.34)	0.00 (0.32)	< **0.01**	0.06	1.00
Flexion Angle PC1	-50.40 (65.12)	-10.04 (57.53)	54.40 (50.24)	6.05 (51.25)	< **0.01**	< **0.01**	0.53
Flexion Angle PC2	-11.68 (37.82)	5.46 (25.58)	-2.63 (28.23)	8.85 (26.67)	< **0.01**	0.64	1.00
Flexion Angle PC3	-13.48 (26.4)	-6.62 (25.76)	11.85 (21.47)	8.25 (26.85)	0.62	< **0.01**	< **0.01**
Flexion Moment PC1	0.67 (1.84)	0.23 (1.31)	-0.62 (0.96)	-0.28 (1.47)	0.43	< **0.01**	0.20
Flexion Moment PC2	-0.59 (0.74)	-0.15 (0.77)	1.02 (0.82)	-0.29 (1.14)	**0.02**	< **0.01**	1.00
Rotation Moment PC1	-0.15 (0.61)	-0.03 (0.37)	0.08 (0.3)	0.11 (0.44)	0.68	0.74	0.34
Rotation Moment PC2	-0.05 (0.24)	-0.11 (0.27)	0.21 (0.32)	-0.05 (0.36)	1.00	< **0.01**	1.00

Table B.1 (cont.) ANOVA results for discrete and waveform PC parameters. Bold = statistically significant (α = 0.05).

	PreTKA	**PostTKA**	**Asym**	**Mod**	**Pre vs. M**	**Pre vs. A**	**Mod vs. A**
Gait Speed (m/s)	0.89 (0.22)	1.08 (0.2)	1.34 (0.16)	1.19 (0.19)	**< 0.01**	**< 0.01**	**< 0.01**
Discrete Parameters							
Adduction Moment 1st Peak (Nm/kg)	0.50 (0.17)	0.43 (0.13)	0.51 (0.15)	0.51 (0.15)	1.00	1.00	1.00
Adduction Moment 2nd Peak (Nm/kg)	0.44 (0.18)	0.34 (0.12)	0.31 (0.12)	0.39 (0.14)	0.17	**< 0.01**	**0.01**
Adduction Moment Mid-stance (Nm/kg)	0.38 (0.17)	0.30 (0.10)	0.22 (0.09)	0.33 (0.13)	0.08	**< 0.01**	**< 0.01**
Peak Flexion Angle Swing (°)	46.2 (14.61)	55.1 (9.8)	65.0 (6.34)	58.6 (7.69)	**< 0.01**	**< 0.01**	**< 0.01**
Peak Flexion Angle Stance (°)	8.9 (5.24)	10.5 (5.59)	19.0 (6.55)	12.0 (7.0)	**0.01**	**< 0.01**	**< 0.01**
Flexion Angle Range (°)	49.1 (14.89)	59.5 (9.64)	69.3 (4.55)	64.9 (6.38)	**< 0.01**	**< 0.01**	**0.04**
Peak Flexion Moment (Nm/kg)	0.28 (0.24)	0.32 (0.20)	0.48 (0.21)	0.27 (0.25)	1.00	**< 0.01**	**< 0.01**
Peak Extension Moment Early-stance (Nm/kg)	-0.15 (0.08)	-0.21 (0.10)	-0.29 (0.14)	-0.25 (0.12)	**< 0.01**	**< 0.01**	0.24
Peak Extension Moment Late-stance (Nm/kg)	-0.12 (0.18)	-0.19 (0.17)	-0.42 (0.17)	-0.26 (0.20)	**< 0.01**	**< 0.01**	**< 0.01**
Peak Internal Rotation Moment (Nm/kg)	0.13 (0.08)	0.13 (0.06)	0.19 (0.06)	0.17 (0.07)	**0.01**	**< 0.01**	0.11
Waveform PCs							
Adduction Moment PC1	0.38 (1.34)	-0.23 (0.87)	-0.35 (0.79)	0.19 (1.09)	1.00	**< 0.01**	**0.01**
Adduction Moment PC2	-0.37 (0.45)	-0.10 (0.44)	0.41 (0.44)	0.06 (0.41)	**< 0.01**	**< 0.01**	**< 0.01**
Adduction Moment PC3	-0.15 (0.28)	0.01 (0.26)	0.14 (0.34)	0.00 (0.32)	**0.01**	**< 0.01**	**0.05**
Flexion Angle PC1	-50.40 (65.12)	-10.04 (57.53)	54.40 (50.24)	6.05 (51.25)	**< 0.01**	**< 0.01**	**< 0.01**
Flexion Angle PC2	-11.68 (37.82)	5.46 (25.58)	-2.63 (28.23)	8.85 (26.67)	**< 0.01**	0.43	0.13
Flexion Angle PC3	-13.48 (26.4)	-6.62 (25.76)	11.85 (21.47)	8.25 (26.85)	**< 0.01**	**< 0.01**	1.00
Flexion Moment PC1	0.67 (1.84)	0.23 (1.31)	-0.62 (0.96)	-0.28 (1.47)	**< 0.01**	**< 0.01**	0.89
Flexion Moment PC2	-0.59 (0.74)	-0.15 (0.77)	1.02 (0.82)	-0.29 (1.14)	0.24	**< 0.01**	**< 0.01**
Rotation Moment PC1	-0.15 (0.61)	-0.03 (0.37)	0.08 (0.3)	0.11 (0.44)	**< 0.01**	**0.01**	1.00
Rotation Moment PC2	-0.05 (0.24)	-0.11 (0.27)	0.21 (0.32)	-0.05 (0.36)	1.00	**< 0.01**	**< 0.01**

Table B.2 Associations between discrete parameter and waveform PCs. Strength of associations between discrete and waveform PCs measured with R^2. Bold = strong or very strong correlation ($R^2 > 0.5$). Pearson correlation coefficient (r) and P-value in parentheses.

Waveform PCs	Discrete Parameter		
	Adduction Moment 1st Peak (Nm/kg)	Adduction Moment 2nd Peak (Nm/kg)	Adduction Moment Mid Stance (Nm/kg)
Adduction Moment PC1	**0.69 (r = 0.83, P < 0.0001)**	**0.87 (r = 0.93, P < 0.0001)**	**0.85 (r = 0.92, P < 0.0001)**
Adduction Moment PC2	0.23 (r = 0.48, P < 0.0001)	0.06 (r = -0.25, P < 0.0001)	0.07 (r = -0.26, P < 0.0001)
Adduction Moment PC3	0.02 (r = 0.14, P = 0.01)	0.03 (r = 0.17, P = 0.004)	0.02 (r = -0.15, P = 0.01)
	Peak Flexion Angle Swing (°)	Peak Flexion Angle Stance (°)	Flexion Angle Range (°)
Flexion Angle PC1	**0.88 (r = 0.94, P < 0.0001)**	**0.69 (r = 0.83, P < 0.0001)**	**0.59 (r = 0.77, P < 0.0001)**
Flexion Angle PC2	0.10 (r = 0.31, P < 0.0001)	0.15 (r = -0.39, P < 0.0001)	0.25 (r = 0.50, P < 0.0001)
Flexion Angle PC3	0.00 (r = 0.06, P = 0.3)	0.00 (r = -0.04, P = 0.5)	0.08 (r = 0.28, P < 0.0001)
	Peak Flexion Moment (Nm/kg)	Peak Extension Moment Early Stance (Nm/kg)	Peak Extension Moment Late Stance (Nm/kg)
Flexion Moment PC1	0.28 (r = 0.53, P < 0.0001)	0.23 (r = 0.48, P < 0.0001)	**0.67 (r = 0.82, P < 0.0001)**
Flexion Moment PC2	**0.69 (r = 0.83, P < 0.0001)**	0.04 (r = -0.21, P = 0.0003)	0.23 (r = -0.48, P < 0.0001)
		Peak Internal Rotation Moment (Nm/kg)	
Rotation Moment PC1		**0.67 (r = 0.82, P < 0.0001)**	
Rotation Moment PC2		0.25 (r = 0.50, P < 0.0001)	

Appendix C Chapter 4 Supplementary Material

Principal component eigenvector plots, with eigenvector and variance explained (top row), waveforms associated with 95th and 5th percentile PC scores (middle row), and mean 95th and 5th percentile PC scores (bottom row). Plots were used to interpret PC features and determine high and low scoring features in Chapter 4 (n = 216 participants).

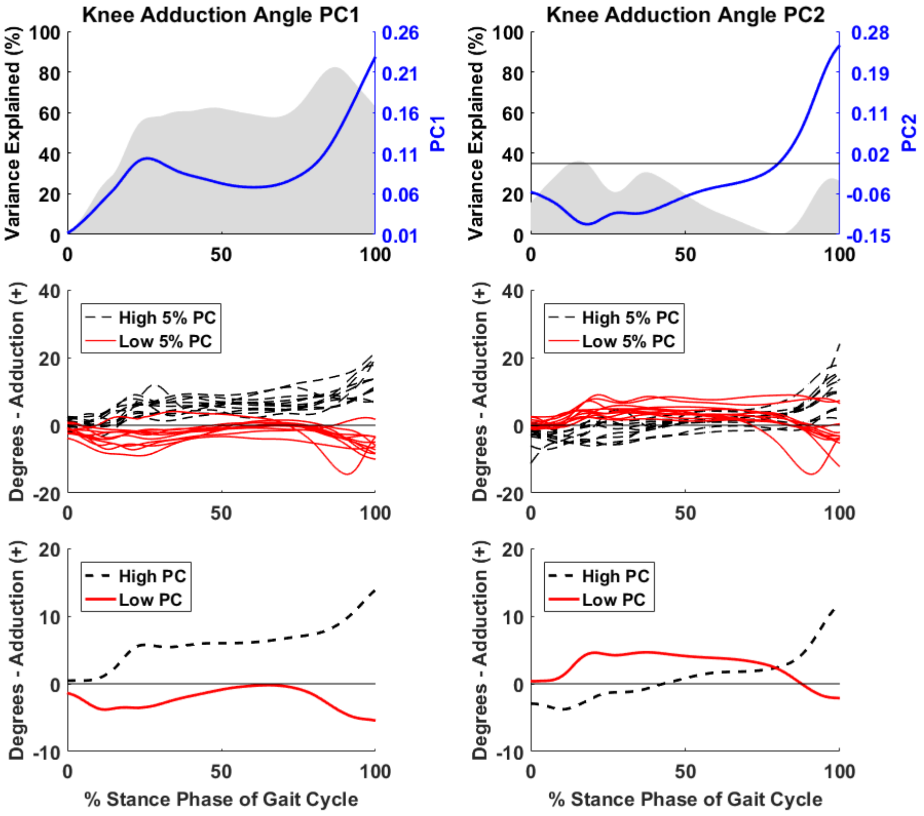

Figure C.1 Knee adduction angle principal component 1 (left) and 2 (right)eigenvector plots.

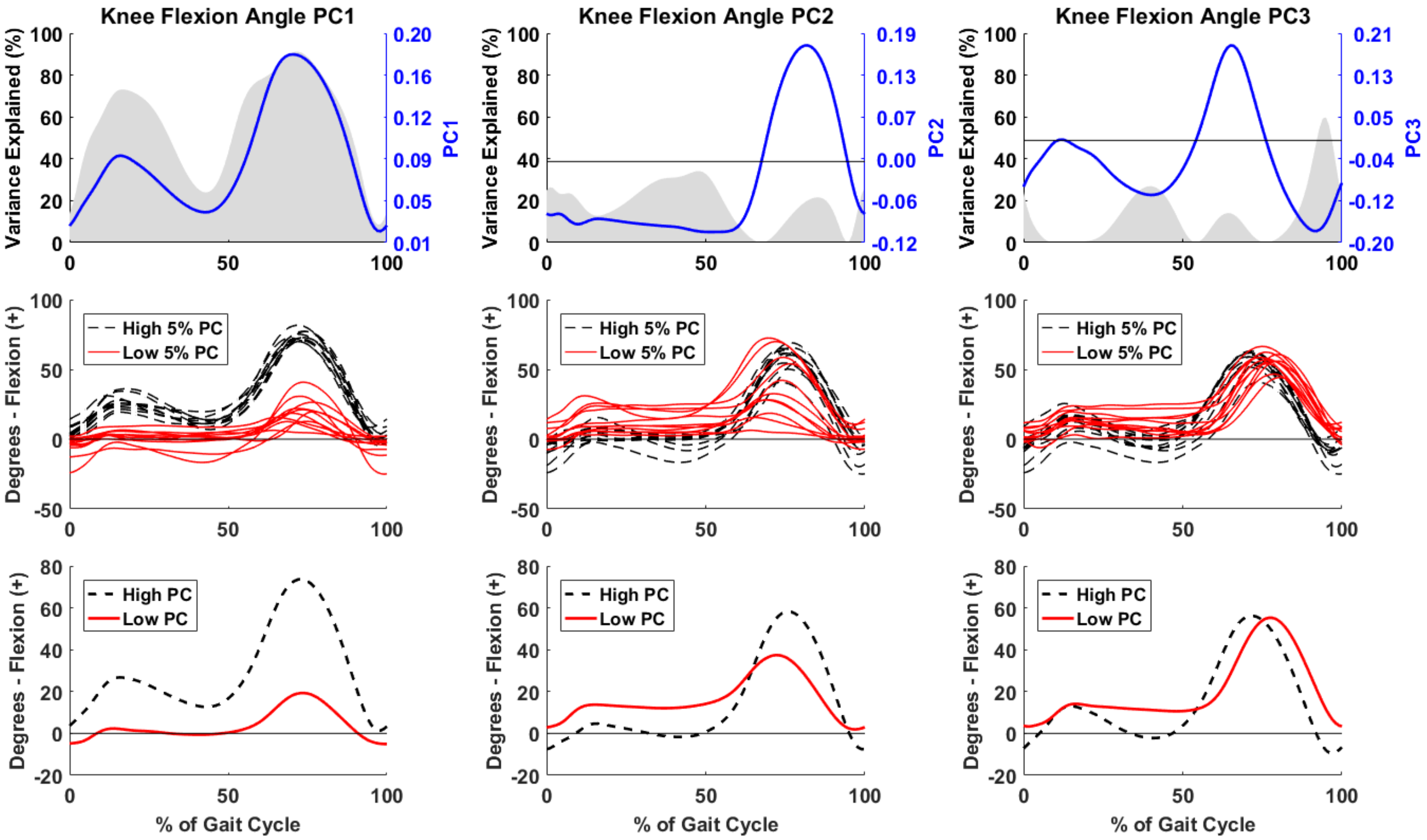

Figure C.2 Knee flexion angle principal component 1 (left), 2 (center), and 3 (right) eigenvector plots.

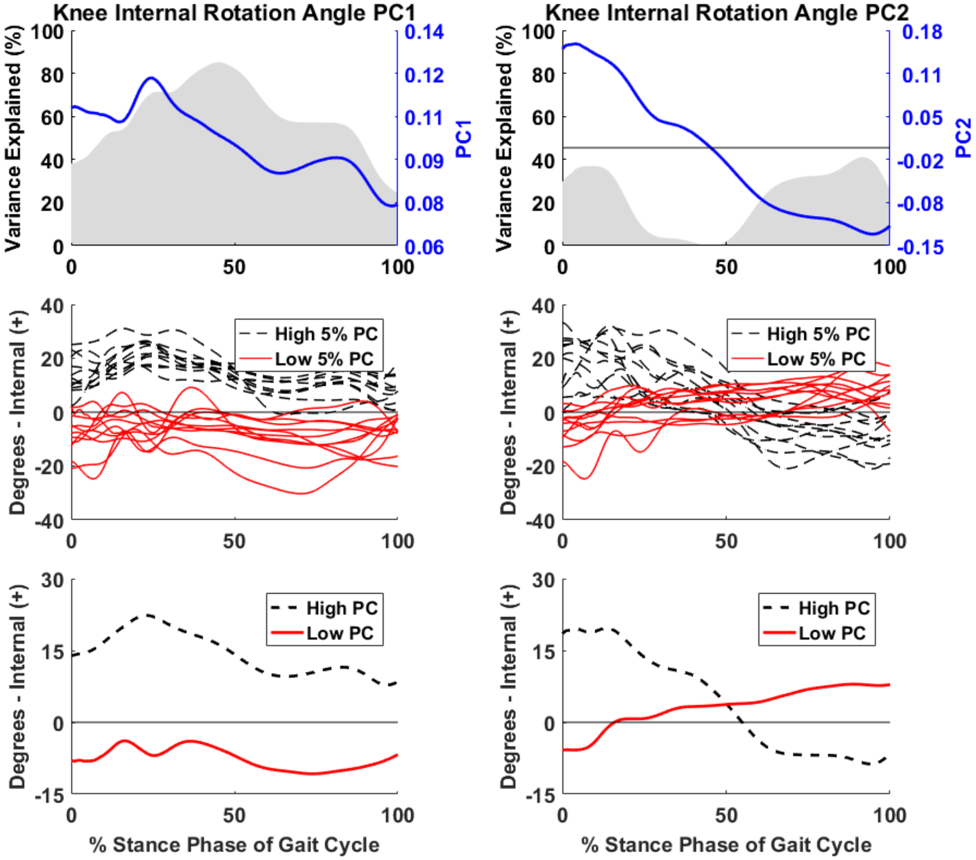

Figure C.3 Knee internal rotation angle principal component 1 (left) and 2 (right)eigenvector plots.

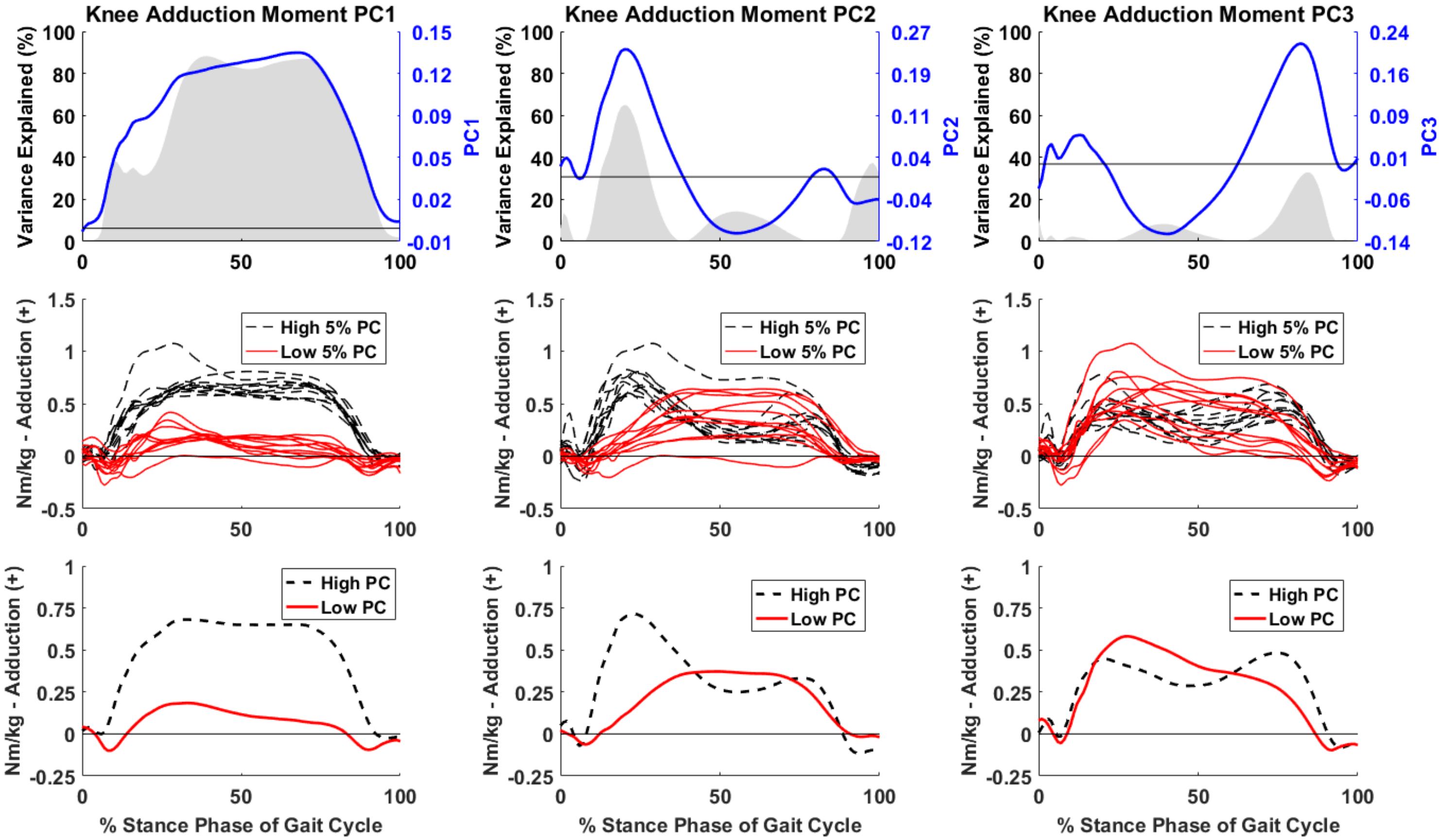

Figure C.4 Knee adduction moment principal component 1 (left), 2 (center), and 3 (right) eigenvector plots.

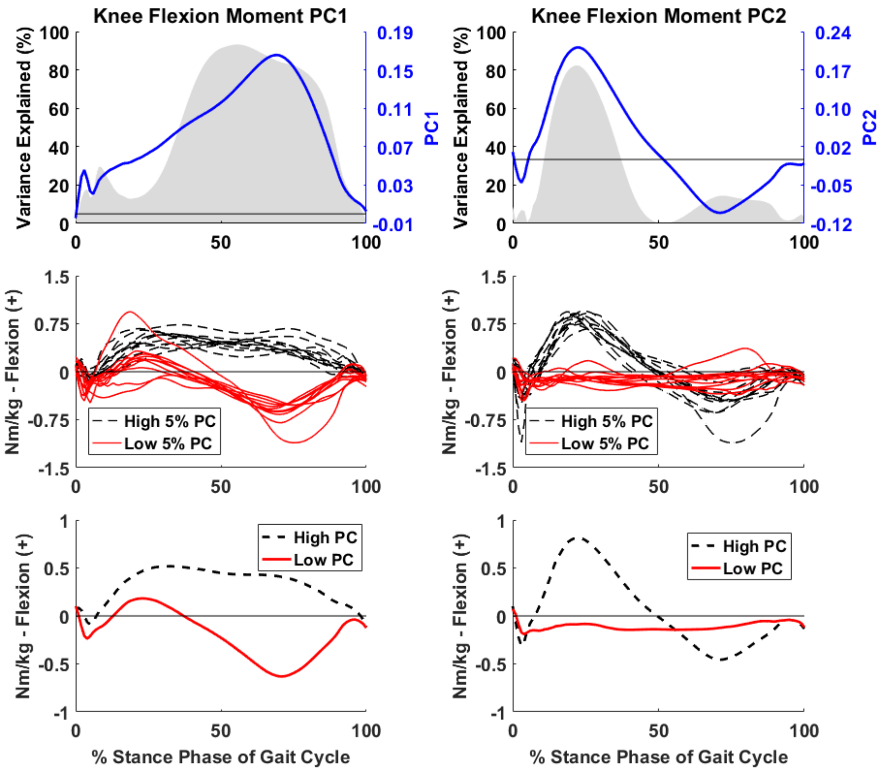

Figure C.5 Knee flexion moment principal component 1 (left) and 2 (right) eigenvector plots.

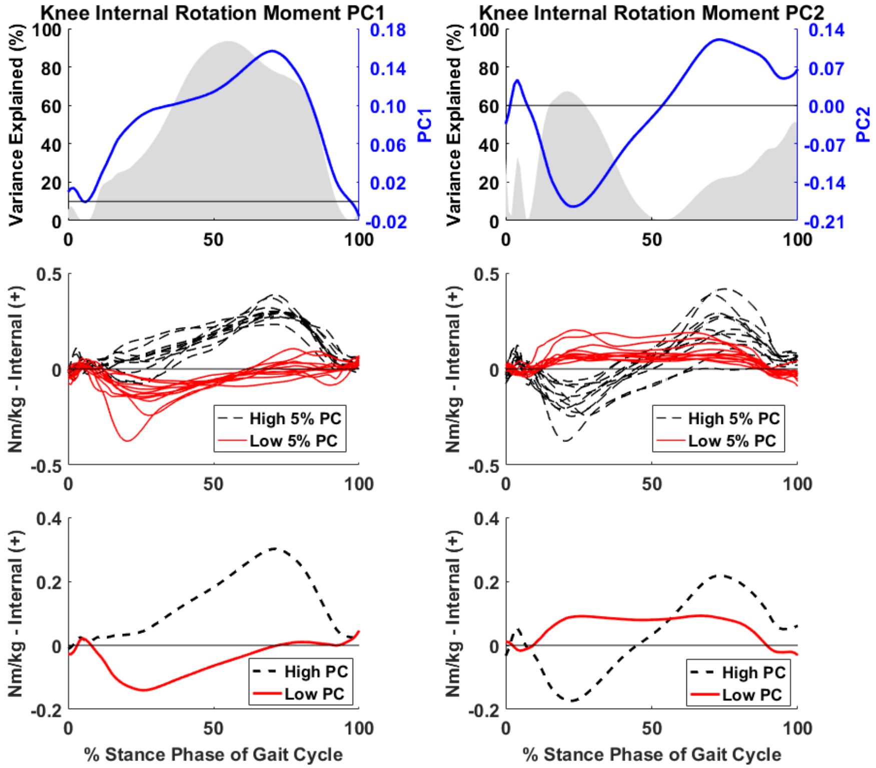

Figure C.6 Knee internal rotation moment principal component 1 (left) and 2 (right) eigenvector plots.

Table C.1 PC features selected for optimal group separation, including standardized discriminant function coefficients (absolute coefficient magnitudes quantify feature contribution to group separation, larger coefficient = larger contribution) and normalized coefficient (coefficients normalized to largest standardized coefficient).

PC Feature	Standardized Canonical Discriminant Function Coefficient	Normalized Coefficient
PreTKA vs Asymptomatic		
Knee Flexion Moment PC2	0.469	1
Knee Adduction Moment PC2	0.433	0.92
Knee Flexion Moment PC1	-0.381	0.81
Knee Flexion Angle PC1	0.345	0.74
Knee Adduction Moment PC1	-0.325	0.69
Knee Adduction Moment PC3	0.256	0.55
PreTKA vs PostTKA		
Knee Adduction Moment PC2	0.656	1
Knee Adduction Moment PC3	0.515	0.79
Knee Adduction Moment PC1	-0.508	0.77
Knee Adduction Angle PC1	-0.397	0.61
Knee Flexion Angle PC2	0.327	0.5
PostTKA vs Asymptomatic		
Knee Flexion Angle PC1	0.663	1
Knee Flexion Moment PC1	-0.378	0.57
Knee Flexion Moment PC2	0.350	0.53
Knee Flexion Angle PC3	0.327	0.49
Knee Internal Rotation Moment PC2	0.326	0.49
Knee Adduction Angle PC2	0.243	0.37

Appendix D Chapter 5 Supplementary Material

Appendix D.1 Obesity has a Larger Effect on Knee Joint Mechanics and Muscle Activity during Walking Prior to Total Knee Arthroplasty (TKA) Surgery than Older Age or Contralateral TKA

Pilot data submitted to 2017 Canadian Orthopaedic Associations/Canadian Orthopaedic Research Society Annual Meeting (2017)

Authors: JL Astephen Wilson, JB Outerleys, DM Ikeda, G Richardson, MJ Dunbar, CL Hubley-Kozey

Abstract:

Introduction: A major predictor of an individual's knee joint function after total knee arthroplasty (TKA) surgery is the functional state of the joint pre-operatively. There is significant demographic variability among individuals presenting for surgery, and our group and others have shown that factors such as obesity and age can affect knee joint function during gait. The objective of the current study was to examine the effect of obesity, age, and previous contralateral TKA on joint mechanics and muscle activity during gait prior to TKA surgery.

Methods: A large cohort of 149 individuals scheduled to receive primary TKA visited the Dynamics of Human Motion lab at Dalhousie University for walking gait testing within the week prior to surgery. We examined statistical differences in features of three-dimensional knee angles, resultant moments, and muscle electromyographic (EMG) patterns captured with principal component analysis between i) obese (BMI >= 30; n=100) and non-obese (n=49), ii) older (age >= 70; n=31) and younger (age <60; n=78), and iii) contralateral TKA (n=27) and not contralateral (n=114) using ANOVA ($\alpha = 0.05$).

Results: A previous contralateral TKA did not significantly affect knee joint function or muscle activity during pre-operative gait. There were minimal differences with older age, but older surgical candidates had less body mass ($P<0.0001$) and higher overall lateral quadriceps activity, likely a reflection of lower knee extension strength ($P=0.013$). Significant differences ($P<0.05$) with obesity included higher mid-stance knee adduction

moments, more constant flexion/extension and rotation moments and some muscle activity differences including higher overall activation of the quadriceps and hamstrings despite no strength deficits.

Conclusions/Significance: The pre-surgical candidate who is obese represents a different patient in terms of knee joint function, with less mid-stance unloading of the medial compartment of the knee, a stiffer knee joint in terms of sagittal and transverse plane loading, and higher activity of the quadriceps and hamstrings muscles during gait. Older age and a previous contralateral TKA had minimal effect on knee joint function pre-TKA.

Appendix D.2 The Effect of Body Mass Index on Gait Mechanics and Muscle Activity Before and After Total Knee Arthroplasty Surgery

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(Abstract Submission)

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INTRODUCTION

Total knee arthroplasty (TKA) is the primary treatment for end stage knee osteoarthritis (OA). While it is suggested that obesity is related to poorer outcome from TKA using self-report measures, the literature is conflicted [1]. TKA in general has been shown to improve knee joint biomechanics, but with large person-to-person variability in response and evidence that functional outcome is influenced by demographic factors such as sex [2,3]. Furthermore, there is evidence to suggest altered gait patterns before TKA in conjunction with higher BMI may increase risk of early implant loosening [4]. Obesity in the presence of earlier stages of knee OA has been associated with altered knee joint mechanics and muscle activity patterns [5,6], but it is unclear if these relationships persist with end stage knee OA or influence functional response to TKA. The purpose of this study was to examine differences in knee joint level biomechanics and muscle activity during walking gait before and after TKA surgery between those with class II obesity and overweight or healthy-weight individuals.

METHODS

Seventy-one participants receiving primary standard-of-care TKA surgery for end stage knee OA underwent 3D gait analysis approximately one week before and one year after surgery. Optoelectronic motion capture (NDI, 100Hz) and synchronized floor-embedded force platform (AMTI, 2000Hz) collected motion and forces during walking at self-selected speed. Knee moments calculated using inverse dynamics, expressed in ISB coordinate axes, were normalized to body mass. Synchronized surface electromyography (sEMG) data of medial (MG) and lateral gastrocnemius, medial (VM) and lateral vasti (VL), rectus femoris (RF), and medial and lateral hamstrings (Bortec Biomedical, 2000 Hz) were collected using standardized protocols [7]. Maximum voluntary isometric contraction exercises were used for EMG normalization and strength testing [7].

Principal component analysis extracted key features of variability (PCs) in gait biomechanics [7]. Participants were grouped into i) healthy/overweight: BMI <= 30 (N = 35) and ii) class II obesity: BMI >=35 (N = 36). Two-way mixed model ANOVAs examined group and time interactions of all gait biomechanics, and main effects ($\alpha = 0.05$).

RESULTS AND DISCUSSION

The class II obesity group (25 females) was significantly younger (mean diff.: 6 yrs.) than the healthy and overweight group (17 females) ($p<0.05$). Gait speed and strength were not different between groups at either time point ($p>0.05$).

There were no statistically significant interactions or group effects on 3D knee angles or moments during gait, but significant time effects, as previously reported [2]. While differences have been reported with obesity in individuals with moderate OA [5], the lack of differences in TKA patients may reflect the level of severity in gait compensations in the group as a whole, regardless of BMI.

There were no statistically significant interaction effects on sEMG patterns, but group differences for overall activation magnitudes (PC1) of VM and RF, with class II obesity associated with higher activation magnitudes of both throughout stance ($p=0.012$, $p=0.016$). In addition, the class II obesity group walked with a phase shift in MG resulting in later peak activity in late stance (PC2) ($p=0.028$). Only two muscle differences were found, this was not surprising given no biomechanical or strength differences. The shift in MG activity supports increased synergetic gastrocnemii activity during late stance propulsion in the class II group. The potential for crosstalk and phase shifts are associated with greater adiposity but likely do not explain the differences found, as they were muscle specific, not uniform.

CONCLUSIONS

Despite a few muscle activation differences, our current results suggest those with class II obesity do not have significantly different knee joint biomechanics during gait before or after surgery compared to those of lower body mass, and do not support a hypothesis that those of class II obesity can expect a poorer functional outcome to TKA surgery than those of lower body masses. Biomechanics in end stage knee OA, and the functional response to TKA surgery are highly variable, and the current results suggest that more than BMI alone is needed to understand knee joint function variability among those presenting for TKA.

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