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Impact of Footwear on Mechanisms of Knee Osteoarthritis Progression

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Impact of Footwear on Mechanisms of Knee Osteoarthritis Progression

A Thesis Presented

By

ETHAN STEINER

Submitted to the Graduate School of the
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of the requirement for the degree of

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Impact of Footwear on Mechanisms of Knee Osteoarthritis Progression

A Thesis Presented

By

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ABSTRACT

IMPACT OF FOOTWEAR ON MECHANISMS OF KNEE OSTEOARTHRITIS

PROGRESSION

MAY 2019

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Knee osteoarthritis (OA) is a debilitating disease affecting the entire knee joint by inducing pathological changes to the cartilage and menisci. Currently, the etiology of OA is not completely understood. However, altered gait mechanics, specifically increased joint loading, of OA patients have a clear association with both symptomatic and structural OA progression. Non-surgical intervention tools, such as variable stiffness shoes (VSS), have been developed as a way to decrease loading within the knee joint. However, with external moments being surrogate measures for knee loading, it is unclear if changes in knee moments with the footwear are sufficient to result in a clinical benefit. Therefore, this project's purpose was to investigate whether a VSS intervention can alter knee joint loading and menisci function in a knee OA population. We used gait analysis, musculoskeletal modeling, and finite element (FE) analysis to determine the effect of VSS on gait mechanics, knee joint contact force, and menisci stress and strain, compared to a control shoe. We found knee moments did not decrease with the VSS intervention. Furthermore, participants who did experience a decrease in knee adduction moment did not always experience a decrease in medial compartment contact force. However, results from our FE modeling of the tibiofemoral joint indicate significant changes in knee joint contact force can influence stress placed on the menisci. Results from this study suggest knee contact forces and tissue stress, not only external moments, should be considered when investigating if VSS can positively impact an OA population.

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CHAPTER 1

INTRODUCTION

Knee osteoarthritis (OA) is a painful debilitating disease with approximately 33% of older adults over the age of 60 having radiographic evidence of knee OA. Additionally, an estimated 45% of individuals develop symptomatic knee OA within their lifetime (Lawrence et al., 2008; Neogi, 2013). OA can occur in any of the three compartments of the knee; however, the medial compartment of the tibiofemoral joint is most commonly affected (Thomas, Resnick, Alazraki, Daniel, & Greenfield, 1975). Thus, the term “knee OA” in this document will refer to medial compartment tibiofemoral osteoarthritis. The most common symptoms associated with knee OA are pain, joint inflammation, joint stiffness, and decreased mobility, all of which have an impact on joint health and an individual’s overall physical function. There is currently no cure for knee OA, and the end stage treatment option for knee OA is total knee arthroplasty (TKA). As surgery can pose significant risks and arthroplasty implants have a limited lifespan, surgery is only considered a treatment option after all conservative treatments have failed. The number of TKAs performed annually has doubled in the last decade and there is expected to be an estimated increase of 673% in surgeries performed from 2005 to 2030 (Kurtz, Ong, Lau, Mowat, & Halpern, 2007; Weinstein et al., 2013). With the continuing increase in incidence of TKA, which places a large economic burden on the United States health care system, there has been a concentration in development of non-surgical treatment options for knee OA. To enhance the efficacy of these non-surgical options, there is a need to understand the mechanisms of these treatments and how they relate to the factors leading to the initiation and progression of knee OA.

Knee OA is a complex disease with many risk factors such as aging, obesity, joint trauma, joint alignment, genetics, and cell morphology, suggesting several pathways for the development and progression of OA (Andriacchi, Thomas P., 2012; Andriacchi, Thomas P., Favre, Erhart-Hledik, & Chu, 2015; Felson et al., 2000; Felson, 2013). While OA's hallmark is the degradation of cartilage, knee OA affects the entire joint by inducing concomitant pathological changes involving degeneration of the articular cartilage, ligaments, and menisci, along with osteophyte formation, thickening of subchondral bone, and synovial fluid inflammation (Hunter, D. J., Zhang, Niu, Tu, Amin, Clancy, Guermazi, Grigorian, Gale, & Felson, 2006a; Loeser, Goldring, Scanzello, & Goldring, 2012). In healthy knees, cartilage adapts to mechanical loading by maintaining and thickening cartilage in highly loaded contact areas. However, in osteoarthritic knees, altered mechanical loading has been shown to degrade the overall cartilage matrix (Figure 1.1) (Andriacchi, Thomas P. et al., 2004; Astephen, Deluzio, Caldwell, & Dunbar, 2008). This cartilage degradation is exacerbated by the concomitant deterioration of the menisci and ligaments within the knee joint (Abraham, Pauly, & Donahue, 2014; Englund, Guermazi, & Lohmander, 2009; Lohmander, Englund, Dahl, & Roos, 2007). Deterioration of the other tissues in the joint amplifies stress applied to the cartilage, causing a vicious cycle of cartilage and whole joint degeneration (Andriacchi, T. P., Koo, & Scanlan, 2009). The vicious cycle ultimately results in a loss in joint function and need for a TKA (Andriacchi, T. P. et al., 2009; Andriacchi, Thomas P. et al., 2004). While a multitude of factors contribute to the formation of this cycle, conservative intervention tools are often focused on gait mechanics because of the significant role gait mechanics plays in OA initiation and progression (Andriacchi, T. P.

et al., 2009; Andriacchi, Thomas P. & Mündermann, 2006; Chu & Andriacchi, 2015; Felson, 2013).

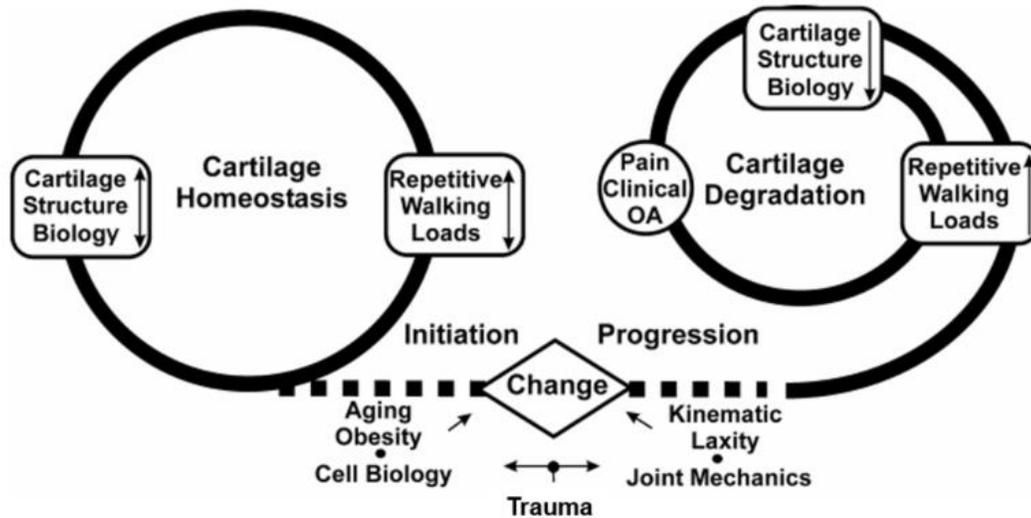


Figure 1.1: Cartilage homeostasis is maintained by repetitive loading and tissue remodeling, but change in a variety of variables can lead to the initiation of a vicious cycle of cartilage degradation (Andriacchi, T. P. et al., 2009).

Numerous studies have found a strong evidence that gait kinematics and kinetics have a pronounced affect overall on OA initiation and progression (Bennell, Bowles, Wang et al., 2011; Chehab, Favre, Erhart-Hledik, & Andriacchi, 2014; Erhart-Hledik, Favre, & Andriacchi, 2015; Miyazaki et al., 2002). For healthy young adults, cartilage adapts to the femoral tibial contact location during the repetitive high loads of gait, resulting in greater cartilage thickness in highly loaded areas (Andriacchi, Thomas P. & Favre, 2014; Erhart-Hledik et al., 2015; Koo & Andriacchi, 2007). However, changes in knee kinematics due to age and musculoskeletal injury can cause a shift in tibiofemoral contact to new specific regions of the cartilage which have not experienced high degrees of loading previously (Andriacchi, Thomas P. et al., 2004). As cartilage has adapted to

areas of typical loading, this regional loading shift results in high loading of thinner cartilage within the joint. As high loads are now occurring on already thinned cartilage, it is believed the cartilage may not have the capacity to adapt to the new loading pattern, initiating the degenerative changes of OA (Andriacchi, Thomas P. & Favre, 2014). Specifically, a link has been established between changes in sagittal plane knee kinematics during walking at heel strike, which marks a period of high joint loading, and changes in cartilage thickness (Andriacchi, Thomas P. & Favre, 2014). Kinematic changes, such as increased knee flexion and increased anterior femoral displacement at heel strike in walking, have been associated with patterns of cartilage thinning in older adults and young adults following anterior cruciate ligament (ACL) tears (Bytyqi et al., 2014; Favre, Erhart-Hledik, & Andriacchi, 2014). In addition, for individuals with ACL and meniscus injuries, changes in tibial rotation with respect to the femur during the stance phase of gait have also been associated with patterns of cartilage thinning (Andriacchi & Favre, 2014; Netravali, Giori, & Andriacchi, 2010). While the shifting of loading region is thought to impact OA initiation, several studies have found a relationship between the magnitude of ambulatory knee loads, such as the external knee joint flexion and adduction moments, and OA progression (Andriacchi, T. P. et al., 2009; Andriacchi, Thomas P. & Mündermann, 2006; Boyer, Katherine A., 2018). Both knee flexion and adduction moments are surrogate measures for contact forces occurring within the joint, with knee flexion moment relating to total knee loading and adduction moment relating to the distribution of loading between the medial and lateral compartment of the knee (Schipplein & Andriacchi, 1991). Compared to healthy controls, knee OA patients have greater knee adduction moments during gait (Baliunas et al.,

2002). Additionally, OA patients with greater knee flexion and adduction moments at baseline had greater medial compartment disease progression at follow-up 5-6 years later (Chang et al., 2015; Chehab et al., 2014; Miyazaki et al., 2002). Along with impacting cartilage health, high knee adduction moment has also been significantly related to degenerative meniscus pathology (Vanwanseele et al., 2010). Because of this clear relationship between increased knee adduction and flexion moments and OA progression, mechanical interventions focusing on altering joint loading have been developed. These interventions have found varied success in slowing OA progression by modifying joint mechanics, highlighting a need to further understand the factors contributing to variation in the magnitude of joint loading changes.

While there is substantial evidence that knee joint kinetics play a role in knee OA progression, the relationship between joint kinetics and OA symptoms is not as clear. It is unclear if OA symptoms, such as pain, influence joint kinetics or if joint kinetics are the root cause of the symptoms. Rather it may be that both scenarios are occurring at the same time resulting in a circular relationship between joint kinetics and OA symptoms. Understanding the relationship between OA symptoms and joint kinetics is necessary for developing rehabilitative or other conservative intervention options to target both OA symptoms and disease progression. The consensus of the field is that high knee joint loads lead to greater pain, and therefore the use of interventions that would reduce joint loading should have a positive impact on OA symptom severity. Prior studies have shown early stage OA patients frequently develop a compensatory gait strategy to reduce knee flexion moment as a pain adaptation, and this adaptation is similar to that adopted by healthy individuals undergoing experimental knee pain through saline injections

(Boyer, Katherine A., 2018; Henriksen, Graven-Nielsen, Aaboe, Andriacchi, & Bliddal, 2010; Huang et al., 2008). It is believed that the musculoskeletal system develops this protective gait strategy to reduce risk of tissue damage and hinder further pain development. However, there are some conflicting reports on whether this protective strategy may also impact the association between knee adduction moments and patient's symptomatic pain severity (Boyer, Katherine A., 2018; Henriksen, Aaboe, & Bliddal, 2012; Maly, Costigan, & Olney, 2008). Even with the convoluted relationship between knee adduction moments and reported pain, evidence has indicated knee joint kinetics influence both radiographic and symptomatic OA progression, which has resulted in significant interest in load modifying non-surgical interventions designed to mimic a protective musculoskeletal response as treatment options for OA.

Different forms of non-surgical treatment interventions have been implemented in an attempt to relieve pain and slow disease progression potentially brought on by the altered gait mechanics associated with knee OA. Initial investigation into pharmaceutical interventions found improvement in patients perceived pain; however, the alleviation of pain has shown to result in increased joint moments which may further patient's OA progression (Henriksen et al., 2006a). Load modifying interventions, such as footwear modifications (including lateral wedge insoles or variable stiffness shoes), are an attractive substitute to pharmaceuticals as these interventions produce a protective gait response of reduced surrogate joint loading and result in decreased reported pain (Erhart, Mündermann, Elspas, Giori, & Andriacchi, 2008). Lateral wedge insoles are angled inserts used in shoes that change lower limb static alignment to reduce frontal plane knee joint moments. Many studies have investigated the effects of laterally wedged insoles on

knee joint mechanics in both healthy controls and OA patients, and have commonly found reductions in knee adduction moments in both populations (Arnold, Wong, Jones, Hill, & Thewlis, 2016; Hinman, Payne, Metcalf, Wrigley, & Bennell, 2008; Toda & Tsukimura, 2004).

Similar to lateral wedge insoles, variable stiffness shoes (VSS) are another footwear intervention that have been found to be similarly effective at lowering joint moments (Erhart et al., 2008). VSS are normal appearing athletic shoes with a midsole that is divided into two sides, with the lateral side of the midsole having a 1.5 times greater material stiffness than the medial side. Current literature has found large variation in individuals' pain and mechanical loading response to both VSS and lateral wedges, but overall studies have shown between 68 to 82% of participants experience decreased peak knee adduction moments with the VSS as compared to control shoes (Erhart et al., 2008; Erhart, Mündermann, Elspas, Giori, & Andriacchi, 2010). The increased lateral stiffness of the VSS leads to a medial shift in walking ground reaction force (GRF) line of action and foot center of pressure (COP), which effectively lowers knee adduction moments by reducing frontal plane lever arm at the knee joint (Boyer, K. A., Federolf, Lin, Nigg, & Andriacchi, 2012; Jenkyn, Erhart, & Andriacchi, 2011). Literature to date has focused primarily on the knee adduction moment when wearing VSS; however, a few studies have considered the shoes' impact on other joint's frontal plane gait mechanics in healthy and OA patients. These studies have reported that VSS compared to control shoes result in decreased and increased hip adduction and ankle eversion moments, respectively. (Erhart et al., 2010; Fisher, Dyrby, Mündermann, Morag, & Andriacchi, 2007). With the focus of prior research on the influence of VSS

on frontal plane joint mechanics, little has been reported on the impact of VSS on sagittal and transverse plane gait mechanics. However, the overall shifting of the GRF line of action and COP may influence both sagittal and transverse, as well as the intended frontal plane gait mechanics when wearing VSS (Boyer, K. A. et al., 2012; Jenkyn et al., 2011). As previous work has demonstrated an association between knee OA progression and both knee flexion moment and tibial rotation (Andriacchi, Thomas P. et al., 2004), there is a need to understand how these mechanisms for OA are altered by VSS. Further investigation of all 3 lower limb joint mechanics in all 3 planes of movement will provide a more complete understanding of the impact of VSS on OA patient's gait.

A current limitation to footwear interventions is the highly variable symptomatic response participants have to the footwear. While some studies in the literature have found both lateral wedges and VSS reduce pain symptoms (Erhart-Hledik, Elspas, Giori, & Andriacchi, 2012; Erhart et al., 2010; Hinman et al., 2008; Toda & Tsukimura, 2004), a recent meta-analysis of the literature found that when compared to control shoes, lateral wedges cause a varied response resulting in no significant or clinically important changes in knee pain (Parkes et al., 2013). While fewer studies have been performed with VSS, many of them have also reported high variations in participant's change in pain and gait mechanics in response to the shoes (Bennell, Kean, Wrigley, & Hinman, 2013; Boyer, Katherine A., 2018; Erhart et al., 2008). It is unclear why there is such high variability in symptom responses to footwear interventions, but a possible explanation for the varied response in pain may be attributed to the measurement of knee loading. While knee flexion and adduction moments have been correlated with knee OA progression, they are simply surrogate measures for knee joint loading (Andriacchi, Thomas P. et al., 2004;

Schipplein & Andriacchi, 1991; Walter, D'Lima, Colwell, & Fregly, 2010). The reduction in knee adduction moment due to footwear interventions may not always be reciprocated in knee contact forces, and if that is the case, then a reduction in pain or slowing of degeneration would not be expected.

Currently, an instrumented knee replacement is needed to directly measure knee joint loading in vivo. However, computer modeling and simulation of the musculoskeletal system has become a useful non-invasive tool to estimate the forces and tissue stress occurring within the joint during walking (Adouni, Shirazi-Adl, & Shirazi, 2012; Delp et al., 2007; Lerner, DeMers, Delp, & Browning, 2015; Smith, Brandon, & Thelen, 2019; Steele, DeMers, Schwartz, & Delp, 2012). Using a computer modeling approach allows for reliable estimations of individual muscle force production, which can then be used to predict knee contact forces and knee joint tissue stress (Adouni & Shirazi-Adl, 2014; Knarr & Higginson, 2015; Lerner et al., 2015; Richards & Higginson, 2010). Studies have used musculoskeletal modeling procedures to investigate the differences in medial compartment and total knee contact forces between OA patients and healthy controls. These studies have found knee contact forces increase with OA severity; however, the knee adduction moment is not strictly the root cause for these differences (Kumar, Manal, & Rudolph, 2013; Meireles, S. et al., 2016; Walter et al., 2010). As the knee joint moments do not always directly relate to in vivo joint loading, it is difficult to determine if reductions in external knee joint moments due to VSS translate to decreases in joint contact forces and effectively lowers risk of OA progression. This may further explain why there may be such a varied response in change in pain due to footwear interventions, as it is unclear if there are changes to contact loads within the joint, which

are impacting individual's pain response. Implementation of computer musculoskeletal modeling and simulations would provide a powerful tool to estimate both medial compartment and total knee joint contact forces in OA patients while wearing a VSS and control shoes.

To further determine how changes in knee joint contact forces due to VSS are a mechanism for changes in OA rate of progression, tissue mechanics must be considered. Finite element (FE) analysis has become a popular tool in knee biomechanics to understand the link between gait mechanics and knee OA progression by analyzing specific tissue behavior under varying loading conditions (Adouni & Shirazi-Adl, 2014; Donahue, Hull, Rashid, & Jacobs, 2002; Kiapour et al., 2014; Mononen, Tanska, Isaksson, & Korhonen, 2016; Netravali, Koo, Giori, & Andriacchi, 2011; Zielinska & Donahue, 2006). When imposing musculoskeletal modeling gait mechanics as constraints into FE models, the OA literature has focused primarily on cartilage contact mechanics. As a result, there have been fewer advancements in understanding the role the menisci have in preservation of healthy knee function (Donahue, Hull, Rashid, & Jacobs, 2003; Netravali et al., 2011; Pena, Calvo, Martinez, & Doblare, 2006; Zielinska & Donahue, 2006). Simulated increases in knee adduction moment with a cadaver have been shown to result in increased meniscal strain (Netravali et al., 2011). In addition, prior work showed simulated removal of the menisci resulted in increased strain patterns on the tibial cartilage during walking (Lee et al., 2006; Pena, Calvo, Martinez, Palanca, & Doblare, 2005; Shirazi & Shirazi-Adl, 2009; Tanska, Mononen, & Korhonen, 2015). However, there is no current literature on the impact of altered gait mechanics due to VSS on knee joint tissue strain. Decreased knee joint contact forces due to VSS may

decrease joint tissue strain leading to slowed OA progression, or the alteration in gait kinematics due to the VSS may cause loading in new contact areas furthering OA progression. The menisci specifically may be significantly impacted by the introduction of VSS due to the tissue's critical role in stabilizing the knee joint and resisting compressive and shear stress and strain patterns imposed by walking joint contact forces (Englund, Roemer, Hayashi, Crema, & Guermazi, 2012; McNulty & Guilak, 2015). Further investigation into the relationship of altered gait mechanics due to VSS and the menisci may provide insight on how the footwear can alter OA progression. Ultimately, understanding the relationship between VSS and the mechanisms for OA progression may lead to improved application of the intervention to a clinical medial compartment knee OA population.

Therefore, this project's overall objective is to investigate whether a VSS intervention will alter knee joint loading and menisci function in a symptomatic medial compartment knee OA population. **Our central hypothesis is that VSS, compared to a neutral control shoes, will decrease medial compartment loading of the knee joint, resulting in decreases in medial menisci stress and strain (Figure 1.2).** We propose to use gait analysis, musculoskeletal modeling, and FE analysis to determine the effect of VSS on gait mechanics, knee joint loading, and menisci stress and strain, compared to a control shoe in medial compartment knee OA patients.

Aim 1 Quantify the impact of VSS on 3-D lower extremity joint mechanics in OA patients

H 1.1. VSS, compared to the control shoe, will decrease knee adduction moment, not change knee flexion moment, and increase knee external rotation moment during walking.

H 1.2. VSS, compared to the control shoe, will increase ankle eversion and decrease hip adduction moments during walking.

Aim 2) Estimate the influence of VSS shoes on medial compartment tibiofemoral joint contact forces

H 2.1. VSS, compared to the control shoe, will decrease the medial compartment joint contact forces during walking.

Exploratory Aim) Develop and validate a tibiofemoral knee joint finite element model to estimate meniscal stress and strain

Outcomes from the proposed project will provide a foundation for understanding the effect of changing gait mechanics on knee joint and menisci health and function in symptomatic knee OA populations. Knee loading and menisci function have been identified as possible influences for both pain and disease progression in OA patients. Quantifying the impact of altered gait mechanics on the menisci, as a result of wearing VSS, may provide insight into the underlying mechanism associated with the clinical outcomes of pain and progression.

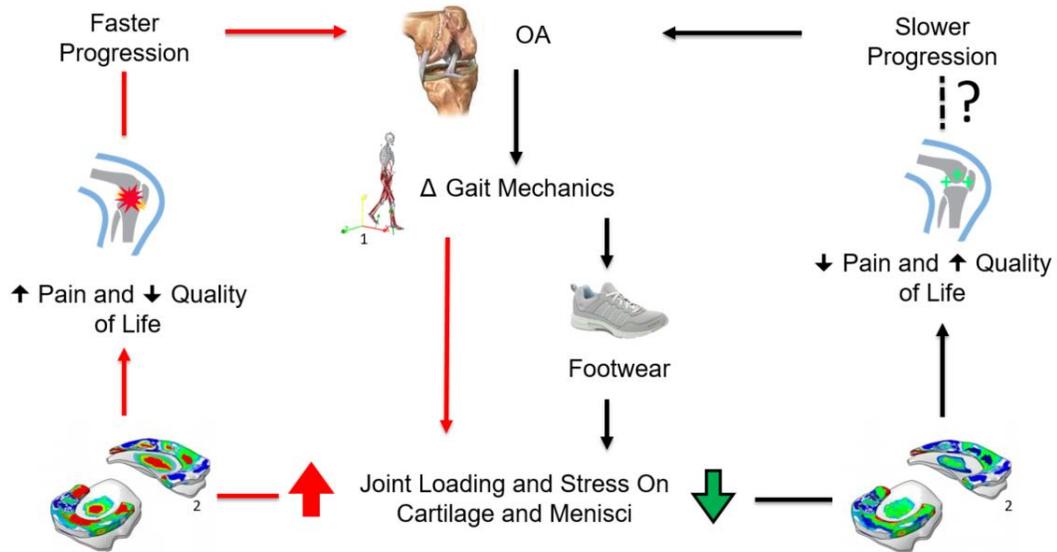


Figure 1.2: Visual framework for how a VSS intervention may alter knee joint loading and menisci function in a knee OA population. Alteration in gait mechanics due to the footwear may lower joint contact forces, which would in turn reduce stress imposed on the menisci. Decreased stress on tissue in the joint may result in a decrease in symptomatic pain and slower OA progression. Pictures adapted from (Delp et al., 2007; Kłodowski et al., 2016a).

CHAPTER 2

LITERATURE REVIEW

Osteoarthritis (OA)

Knee OA is a complex disease characterized by the degradation of the articular cartilage within the joint. Risk factors for OA include aging, obesity, joint trauma, joint alignment, genetics, gender, physical activity, muscle weakness, and cell morphology (Blagojevic, Jinks, Jeffery, & Jordan, 2010; Felson et al., 1997; Felson et al., 2000). In knee OA, the hallmark cartilage degradation is accompanied by deterioration of all the tissues within the joint including the ligaments, menisci, synovial fluid, and subchondral bone (Englund et al., 2009; Loeser et al., 2012). Pathological changes to one tissue within the knee joint can have a concomitant effect of degrading the other tissues within the joint (Andriacchi, Thomas P. et al., 2004; Loeser et al., 2012). When a joint is deemed too damaged and patient's pain is detrimental to their lifestyle, a total knee arthroplasty (TKA) is performed to replace the entire knee joint. With a continuing increase in incidence and economic burden of TKA, there has been a focus to develop conservative treatment options that target the mechanisms for initiation and progression of OA (Boyer, Katherine A., 2018; Weinstein et al., 2013).

Currently, the etiology behind OA is still unclear. The degradation of the tissues in the joint are evoked from a multitude of risk factors ranging from the cell to the whole joint level (Andriacchi, Thomas P. et al., 2015; Chu & Andriacchi, 2015). Because of the diversity in the risk factors for knee OA, vast literature has been established investigating knee OA using interdisciplinary methods that consider the biological, mechanical, and structural components that characterize the disease (Andriacchi et al., 2015). This review

will outline the current state of literature in regards to the prevalence and burden of OA, the mechanisms behind the development and progression of OA, and provide background on how footwear intervention, a conservative treatment option, may impact these mechanisms. Additionally, the review will discuss the potential of using musculoskeletal modeling and finite element analysis (FEA) to investigate how both OA and changing gait mechanics can impact the knee at the whole joint and tissue level.

Prevalence and Burden of OA

OA is reported as the most common form of arthritis impacting approximately 14% of adults over the age of 25 (Neogi, 2013). The knee joint is the most prevalent joint to develop OA, with knee OA impacting roughly 33 % of adults over the age of 60 (Lawrence et al., 2008). Furthermore, risk of OA increases with age as 45% of individuals develop symptomatic OA at some point within their lifetime (Neogi, 2013). OA can be classified and diagnosed as radiographic and symptomatic. Radiographic OA is diagnosed as a loss in knee joint space and formation of osteophytes, while symptomatic OA is the formation of symptoms associated with OA, specifically pain. Knee OA can develop within medial or lateral tibiofemoral or the patellofemoral compartment of the joint, but medial compartment OA is most common (Thomas et al., 1975).

As there is no cure to reverse the progression of OA, TKA has become a common surgical procedure performed by orthopedists. Currently, 4.5 million adults above the age of 50 years old in the United States have had at least one TKA and this number is projected to increase (Kremers et al., 2015). Kurtz and colleagues have previously

estimated the number of TKA surgeries performed annually will increase by 673% between the years 2005 to 2030 (Kurtz et al., 2007). The significant increase in TKA is expected to place a significant burden on the U.S health care system (Weinstein et al., 2013). Additionally, an increase in overall TKA performed may lead to an increase in costly and burdensome revisional procedures as the first implant may loosen or wears out (Weinstein et al., 2013).

Tissue Properties

Cartilage

Articular cartilage is a thin layer of soft tissue that lines contact surfaces of the knee joint, and allows for load transfer and frictionless joint movement. Cartilage achieves these functions through its complex structure made up of depth-dependent collagen fibrils and proteoglycans (Robinson et al., 2016). Chondrocytes are the cells of the cartilage that regulate the proteoglycan and collagen extracellular matrix and maintain an equilibrium between the breakdown of old and production of new cartilage. Chondrocytes do this through the regulation of matrix-degrading enzymes (Andriacchi, Thomas P. et al., 2004; Loeser et al., 2012). Healthy cartilage behaves as anisotropic hyperelastic material that is incompressible during cyclic ambulatory physiological mechanical loading. However, cartilage also acts as a time-dependent viscoelastic material resulting in deformation due to fluid redistribution during prolonged loading (Robinson et al., 2016; Setton, Elliott, & Mow, 1999). Healthy cartilage responds and adapts to the mechanical joint loading, which activates chondrocytes turnover of cartilage and regulates the matrix-degrading enzymes. The new formation cartilage ensures

smooth gliding of the knee joint during movement and proper joint function (Andriacchi et al., 2004; Andriacchi, 2012).

The mechanical loading in the knee is a combination of active force generation from muscle contractions and reaction forces to external loads carried by passive structures (Halloran et al., 2012). The cyclic loading experienced during daily ambulatory movement are important for maintaining healthy homeostasis. In OA however, the chondrocytes become activated and produce increased amounts of degrading enzymes resulting in damage and inflammation of the extracellular matrix (Loeser et al., 2012). This damage is characterized as fibrillation of the cartilage, with the development of cracks, fissures within the matrix, or complete loss of chondrocytes. The breakdown and change in the extracellular matrix impacts the tissue's mechanical properties and elicits comorbid pathological changes impacting other tissues within the joint (Englund et al., 2012; Loeser et al., 2012). There is strong evidence that these biochemical changes, when combined with altered joint loads, lead to accelerated alterations in structure, composition, and mechanical properties of the cartilage and other joint tissues (Halloran et al., 2012; Setton et al., 1999).

Menisci

The menisci are fibrocartilaginous tissues that, like cartilage, are critical in the distribution of loads across the knee joint. Menisci's unique and complex structure allow for loads to be transmitted to large areas of the articular cartilage and for stabilization of the knee joint during dynamic movements (Englund et al., 2009; Englund et al., 2012; Fithian, Kelly, & Mow, 1990; McNulty & Guilak, 2015). The menisci are wedge shaped

discs made of up of a similar hydrated extracellular matrix, but with a larger percentage of collagen fibrils as compared to articular cartilage (Messner & Gao, 1998). The collagen fibers are tightly woven in a circumferential orientated pattern, which allows for the menisci to resist tension, compression, and shear stress (Englund et al., 2012; Fithian et al., 1990). In order to maintain optimum load distribution over dynamic movement of the knee joint, the menisci attach to the tibia via ligament like structures called horns. The meniscal horns and fluid like collagen matrix of the menisci allow for excursion and deformation of the menisci during knee flexion and extension of the joint (Fithian et al., 1990; McDermott, Masouros, & Amis, 2008). However, too much meniscal excursion can be a cause for tears to the menisci and result in degeneration and breakdown of both the cartilage and the menisci within the knee joint (Englund et al., 2012; Sharma et al., 2008)

With OA, the menisci experience similar pathological degeneration to that of cartilage, which includes matrix disruption, fibrillation, and cell degradation (Loeser et al., 2012). The literature has shown strong correlations between the degeneration of both the cartilage and menisci from within the same knee joint (Abraham et al., 2014; Hunter, D. J., Zhang, Niu, Tu, Amin, Clancy, Guermazi, Grigorian, Gale, & Felson, 2006b; Sharma et al., 2008). Furthermore, meniscal degeneration has been reported as a possible source for the severe pain experienced by OA patients (Englund et al., 2012; Loeser et al., 2012). Because of this pain, meniscectomies have been performed to surgically remove the menisci and alleviate short term pain; however, meniscectomies have shown to increase stress and degradation of the cartilage in the long term (Lohmander et al., 2007; Netravali, Giori, & Andriacchi, 2010; Pena et al., 2005; Shirazi & Shirazi-Adl,

2009). One study in particular showed removing 60% of the medial meniscus resulted in a 65% and 55% increase in contact pressures of the medial meniscus and medial tibial cartilage, respectively (Zielinska & Donahue, 2006). With the observed link between menisci function and cartilage stress, it is believed the menisci play an integral role in OA initiation and progression.

Gait Mechanics of OA

As the major hallmark of OA is the degradation and breakdown of articular cartilage, it is important to explore the impact of the chronic mechanical loading of the knee joint that occurs during ambulation, which may play an important role in joint degradation. Changes to mechanical loading patterns are believed to have a strong impact on the etiology of OA and have been one of the primary focuses of the OA literature (Andriacchi, Thomas P. et al., 2004; Andriacchi, Thomas P. & Mündermann, 2006; Andriacchi, Thomas P. & Favre, 2014). Gait analysis has been the primary tool used for this research as it allows for assessment of the functional mechanical changes occurring to the joint due to OA (Andriacchi, Thomas P. & Mündermann, 2006; Baliunas et al., 2002; Mündermann, Dyrby, & Andriacchi, 2005). The literature has broken down OA gait mechanics research into 2 separate stages of OA, initiation and progression (Andriacchi, Thomas P. et al., 2004; Andriacchi, Thomas P. & Mündermann, 2006).

Initiation

Before the initiation of OA, the mechanical loading occurring during everyday activity produces a positive healthy cartilage remodeling response (Andriacchi, Thomas

P. et al., 2004; Felson, 2013). Healthy cartilage adapts to mechanical loading and develops greater cartilage thickness at locations within the knee joint that experience the greatest ambulatory loading (Andriacchi, T. P. et al., 2009; Koo & Andriacchi, 2007; Koo, Rylander, & Andriacchi, 2011). Typically the highest loads occur during the gait cycle at heel strike, when the knee is near full extension. The tibiofemoral contact locations when the knee is near full extension have been shown to have greater cartilage thickness, suggesting an association of high loading and cartilage thickness (Koo et al., 2011). Shifts in these tibiofemoral contact locations are believed to be a primary contributor to the initiation of OA (Andriacchi, Thomas P. et al., 2004; Andriacchi, Thomas P. & Mündermann, 2006).

Changes and abnormal knee joint kinematics with joint trauma or with OA are believed to result in a shift in tibiofemoral contact locations within the knee joint. The shift in tibiofemoral contact location due to these abnormal knee joint kinematics results in high loading occurring at cartilage locations that have not been heavily loaded previously (Andriacchi, Thomas P. & Mündermann, 2006). As cartilage adapts in heavily loaded contact areas, underutilized regions of the cartilage can display fibrillation at a relatively young age (Andriacchi, Thomas P. et al., 2004). Therefore, the shifting of high load transmissions to areas that are already degraded is believed to initiate OA (Andriacchi, Thomas P. et al., 2004; Andriacchi, Thomas P. & Favre, 2014). The literature hypothesizes that cartilage in these new contact areas may not be able to adapt to the sudden increase in mechanical loading (Andriacchi, Thomas P. et al., 2004).

Joint Trauma

Traumatic injuries to the tissue of the knee joint have shown a significant impact on cartilage health and the initiation of OA likely due to the resulting kinematic changes in the joint (Andriacchi, Thomas P. et al., 2004; Felson, 2013; Lohmander et al., 2007). Tearing of the anterior cruciate ligament (ACL) is a common sports injury for young adults. There is substantial evidence that links ACL tears to the development of premature knee OA in young adults (Felson, 2013; Lohmander et al., 2007). The ACL's primary roles are to resist anterior-posterior translation and internal-external rotation of the knee joint. Research has shown patients with an ACL tear or reconstruction display distinct changes to both the anterior-posterior displacement and internal-external rotation compared to their contralateral healthy knee (Andriacchi, T. P. et al., 2009; Andriacchi, Thomas P. et al., 2004). Furthermore, these studies have shown that tibial cartilage thinning occurs in the region associated with the patient's specific kinematic changes (Andriacchi, T. P. et al., 2009). The specific kinematic changes occurring in ACL deficient or reconstructed knees supports the idea that shifting tibiofemoral contact location plays a significant role in OA initiation.

Similar to ACL injuries, evidence suggests major tears to a meniscus in young athletes lead to higher rates of OA development later in life (Englund et al., 2012). However, meniscus tears or lesions are also shown to occur incidentally in 30-60% of adults over the age of 50 (Englund et al., 2009). The development of a meniscus lesion as an older adult was estimated to result in a 10-fold increase in the risk of development of OA post detection of the tear (Englund et al., 2009). The literature has also shown a clear association between medial and lateral meniscal damage and quantitative thinning

cartilage using MRI (Englund et al., 2009; Englund et al., 2012; Lohmander et al., 2007; Sharma et al., 2008). These meniscal tears have been documented to lead to cartilage degeneration in the vicinity where the menisci damage occurred, inducing a whole joint effect of inflammation and pain (Englund et al., 2012). Both cadaver and modeling studies have shown meniscal tears increase contact pressure and stress induced on the tibial cartilage, which likely explains the reported association between cartilage thinning and meniscal lesions (Bedi et al., 2010; Marzo & Gurske-DePerio, 2009; Mononen, Jurvelin, & Korhonen, 2013; Shirazi & Shirazi-Adl, 2009). Abrupt injuries and removal of the menisci have also been shown to result in changes to knee joint kinematics such as greater external rotation, lateral translation, and anterior translation during the stance phase of gait (Marsh, Martin, Harner, & Tashman, 2014; Netravali et al., 2010). Similar to ACL injuries, abnormal knee joint kinematics due to meniscal tears shift tibiofemoral contact locations, and in combination with increase tissue stress, may ultimately lead to the development of OA.

Degenerative meniscus tears can also be a major source for pain experienced by OA patients as catching and locking of the torn meniscus can occur during dynamic movement (Englund et al., 2012). As degeneration of the meniscus leads compromised meniscal function and increased stress placed on the knee joint cartilage, studies have shown the development of bone marrow lesions and synovial fluid inflammation, both of which have been associated with knee pain fluctuations (Englund et al., 2009; Englund et al., 2012). Increased vascular penetration and nerve growth has also been observed in menisci from osteoarthritic knees, and may be another contributor to pain experienced by OA patients (Ashraf et al., 2010). Thus, because of the association between menisci

function and both OA symptomatic and structural progression, understanding how conservative interventions may impact menisci health is important in helping improve efficacy of the interventions.

Progression

OA progression is believed to begin when the cartilage degradation goes beyond the point where remodeling of new cartilage can occur (Andriacchi, Thomas P. et al., 2004). While initiation is thought to be brought on by abnormal knee joint kinematics, kinetics have shown to be the driving factor in furthering progression of OA (Andriacchi, Thomas P. et al., 2004). For healthy cartilage, high loads lead to greater cartilage remodeling (Koo et al., 2011). However, the literature has shown when greater compressive and shear mechanical loads are placed on cartilage that have started to show signs OA, there is a rapid increase in disease progression (Andriacchi, T. P. et al., 2009; Andriacchi, Thomas P. et al., 2004).

The literature has primarily used peak external knee moments as surrogate measures for the mechanical contact loading that occurs within the knee joint (Schipplein & Andriacchi, 1991). Studies have found external knee moments generally predict and correlate well with in-vivo joint loads (Erhart et al., 2010; Kutzner, Trepczynski, Heller, & Bergmann, 2013), but others have found these surrogate measures do not account for all the factors contributing to joint contact forces occurring within the joint (Schipplein & Andriacchi, 1991; Walter et al., 2010). A more detailed investigation of in vivo contact forces can be done using musculoskeletal modeling, which will be discussed later (Meireles, S. et al., 2016; Richards & Higginson, 2010; Saxby et al., 2016; Winby, Lloyd,

Besier, & Kirk, 2009). However, the simple measurement of external knee moments has been shown to have a strong association with cartilage degradation and overall OA progression. (Andriacchi, Thomas P. & Favre, 2014).

The most studied external moments associated with knee joint loading and OA progression are peak knee flexion and first peak adduction moments (Andriacchi, Thomas P. et al., 2004; Baliunas et al., 2002). Peak knee flexion moment is a surrogate measure for total knee loading, while the first peak adduction moment is a surrogate measure for the distribution of load between medial and lateral compartment of the knee, with both peaks occurring during weight acceptance of stance phase (Schipplein & Andriacchi, 1991). There have been mixed findings on knee flexion moments relationship to OA (Baliunas et al., 2002; Erhart-Hledik et al., 2015; Henriksen et al., 2010; Kaufman, Hughes, Morrey, Morrey, & An, 2001), but overall the literature has found decreases in knee flexion moment with early stage OA, which is thought to be a compensatory gait strategy (Henriksen et al., 2010; Kaufman et al., 2001). This compensatory gait strategy is assumed to reduce stress placed on the cartilage and has been related to an adaption associated with the onset of pain symptoms (Henriksen et al., 2010). The relationship between knee flexion moment and symptomatic OA will be discussed in greater detail in the pain section below. While joint kinetics are thought to play a primary role in OA progression, alterations in joint kinematics may interact with altered loading and contribute to progression. The literature has found OA patients display abnormal knee joint kinematics such as increased knee flexion and anterior displacement of the femur at heel strike compared to healthy younger and older adults (Childs, Sparto, Fitzgerald, Bizzini, & Irrgang, 2004; Favre, Erhart-Hledik, &

Andriacchi, 2014). Furthermore, OA patients reduce overall knee joint range of motion as severity increases (Aststephen et al., 2008; Childs et al., 2004; Kaufman et al., 2001).

Knee adduction moments have been the gait mechanics measurement with the most clear association with OA, as numerous studies have found OA patients walk with greater knee adduction moments compared to their healthy counterparts (Andriacchi, Thomas P. et al., 2004; Baliunas et al., 2002; Henriksen, Creaby, Lund, Juhl, & Christensen, 2014; Kaufman et al., 2001). Studies have also found peak knee adduction moment increases as OA severity increases (Thorp et al., 2006). Greater peak knee adduction moments may lead to progressing OA severity, as knee adduction moments have been correlated with reduced cartilage thickness in OA patients (Erhart-Hledik et al., 2015). The literature has found a causal relationship with high peak knee adduction moments at baseline resulting in greater structural progression of OA at a 1-6 year follow-up periods by measuring radiographic joint space narrowing, medial compartment cartilage volume, and cartilage thickness (Bennell et al., 2011; Brisson et al., 2017; Chang et al., 2015; Chehab et al., 2014; Miyazaki et al., 2002). Furthermore, one study reported OA patients with high knee adduction moments display greater medial meniscus extrusion and lower medial meniscus height (Vanwanseele et al., 2010). These results suggest high knee adduction moment in OA patients can lead to greater degradation of both the cartilage and menisci.

Due to the observed strong connection between knee adduction moment and OA progression, there has been a focus to target this measure using a wide range of interventions. One intervention is done surgically by performing a high tibial osteotomy, which inserts a bone graft into the tibia to change knee joint alignment (Andriacchi,

Thomas P. & Mündermann, 2006). Overall, the procedure is successful but studies of high tibial osteotomy have shown patients with greater changes in knee adduction moment pre to post surgery see substantially better clinical outcomes (Andriacchi, Thomas P. & Mündermann, 2006). The success of these procedures supports the relationship between knee adduction moment and OA progression and potential for the knee adduction moment to be a target for interventions. However, due to the extensiveness of the surgical procedure, there has been a shift to more conservative intervention measures such as joint bracing or footwear.

Pain

The hallmark symptom of OA is joint pain (Felson et al., 2000; Loeser et al., 2012; Neogi, 2013). Symptomatic pain is the primary reason OA patients seek treatment; however, it is unknown if pain has any significance on the initiation or progression of structural OA (Boyer, Katherine A., 2018; Maly et al., 2008; Peat, McCarney, & Croft, 2001). Pain in OA is highly variable between patients, with some patients having pain that matches their structural progression, but others having pain severity opposite to their structural health (Henriksen et al., 2012; Hunter, David J., Guermazi, Roemer, Zhang, & Neogi, 2013; Szebenyi et al., 2006). Exercise is the most recommended and favorable treatment for managing pain symptoms, but other treatment options such as pharmaceuticals and footwear have been developed with end-goals to reduce pain symptoms (Boyer, Katherine A., 2018; McAlindon et al., 2014; Sarzi-Puttini et al., 2005). These treatment options work in separate ways as pharmaceuticals attempt to reduce joint inflammation and block pain pathways, while footwear attempts to mechanically offload

the joint resulting in less stress placed upon the tissues (Boyer, Katherine A., 2018; McAlindon et al., 2014; Sarzi-Puttini et al., 2005).

To understand the potential response to footwear interventions, it is important to consider the mechanics and control of movement that may occur with joint pain. Theoretical models for motor response to pain in voluntary movement suggest our human motor system has its own active pain response to attempt to alleviate pain symptoms (Boyer, Katherine A., 2018; Hunter, David J., McDougall, & Keefe, 2008; Lund, Donga, Widmer, & Stohler, 1991). The motor system pain response is believed to inhibit muscles that produce a painful movement, while exciting the antagonist muscles to the painful movement (Hunter, David J. et al., 2008; Lund et al., 1991). This selective activation of muscles is thought to reduce loads occurring within the joint which would effectively reduce symptomatic pain as well as help maintain joint health (Boyer, Katherine A., 2018). In early stage OA patients, this motor systems pain response is believed to induce a compensatory gait strategy seen in early stage OA patients, which includes smaller knee flexion angles and reduced peak knee flexion moments (Andriacchi, Thomas P. & Favre, 2014; Boyer, Katherine A., 2018; Henriksen et al., 2010; Henriksen et al., 2012; Maly et al., 2008). Multiple studies have shown knee flexion moment decreases as OA severity increases and knee flexion moment in OA patients is significantly smaller compared to healthy counterparts (Andriacchi, Thomas P. & Favre, 2014; Boyer, Katherine A., 2018; Henriksen et al., 2012). Similar findings of decreased knee flexion moment have also been observed in experimental protocol studies that induce knee pain using hydrotonic saline injections (Henriksen et al., 2010). These common findings support the theoretical motor system pain model of lowering joint loads

and stress on the joint tissues to alleviate pain and preserve joint health. Overall the reductions in loads on the joint are thought to help slow progression of OA (Andriacchi, Thomas P. et al., 2004; Boyer, Katherine A., 2018).

Experimental studies that alleviate knee pain through pharmaceuticals have been shown to result in overall changes to ambulatory function and joint loading (Boyer, Katherine A., Angst, Asay, Giori, & Andriacchi, 2012; Boyer, Katherine A., 2018; Henriksen et al., 2006b; Shrader, Draganich, Pottenger, & Piotrowski, 2004). These studies have shown pharmaceuticals result in an increased walking speed and increased knee extension at heel strike, but also result in greater knee adduction and flexion moments (Boyer, Katherine A., 2018). Specifically, there is a reported 0.21% to 0.48% increase in knee flexion moment, but the results for increase in knee adduction moments have been smaller and highly variable (Boyer, Katherine A. et al., 2012; Henriksen et al., 2006b; Shrader et al., 2004). While overall pharmaceuticals have shown to benefit pain symptoms and overall joint function, the resulting increased joint loads may be detrimental to joint health and increase risk in both structural and symptomatic progression of OA. Because of the possible risk pain alleviation through pharmaceuticals has on OA progression, footwear interventions may be a more attractive pain management option as they attempt to mimic the motor system's natural pain response.

Footwear

Various specialized footwear interventions have been prescribed to reduce pain symptoms and progression of knee OA. All OA inspired specialized footwear are designed to reduce the load placed on the knee joint during ambulatory activities by

changing joint alignment and redistributing loading location within the joint (Boyer, K. A. et al., 2012; Jenkyn et al., 2011; Kerrigan et al., 2002). One footwear intervention designed to treat knee OA is the lateral wedge insole. The insoles are placed inside the OA patient's shoe and are angled between 5 ° and 15° so that the lateral edge is thicker than the medial edge. The elevated lateral edge of the insole shifts the alignment of the ankle joint and moves the center of pressure (COP) when the foot is in contact with the ground, both of which result in a shortening of the ground reaction force (GRF) lever arm (Toda & Tsukimura, 2004). Another footwear intervention is called the variable stiffness shoes (VSS), which acts similar to lateral wedge insoles. VSS are normal appearing athletic shoes with a midsole that is divided into two sides, with the lateral side of the midsole having a 1.5 times greater material stiffness than the medial side. The stiffer lateral midsole results in a medial shift in COP, which lowers the knee adduction moment arm during walking.

Less research has focused on the VSS as they are a newer product, but the literature has found similar results for both VSS and lateral wedge insole footwear interventions. Overall there have been mixed results on footwear's ability to impact mechanisms and symptoms of OA, largely due to highly variable responses each individual has to footwear (Arnold et al., 2016; Parkes et al., 2013). This varied response is particularly significant for symptoms such as pain, which already has large variation between OA patients (Bennell et al., 2011; Parkes et al., 2013). There are more consistent results for footwear intervention's ability to lower knee joint loading compared to pain, with several studies stating footwear can slightly lower external knee adduction moments during walking (Arnold et al., 2016; Bennell et al., 2013; Erhart-Hledik et al.,

2012; Erhart et al., 2008; Erhart et al., 2010; Fisher et al., 2007; Toda & Tsukimura, 2004). Currently, most of the literature for footwear interventions have focused on knee adduction moment, so less is known on the direct impact of footwear on medial contact force. Furthermore, as knee adduction is only a surrogate measure for knee loading, one study had a participant with an instrumented knee replacement walk in VSS and control shoes (Erhart, Dyrby, D'Lima, Colwell, & Andriacchi, 2010). This study found that the VSS significantly reduced both knee adduction moment and medial contact force (Erhart et al., 2010). While the footwear interventions can institute relatively small changes in knee adduction moment, there is no current evidence that suggests any effect of footwear on attenuating structural progression of OA (Bennell et al., 2011). One review states that highly varied response to footwear may be the cause of the observed small changes in loading, and that patients with greater ankle eversion are predisposed to have greater reduction in knee adduction moment due to footwear (Arnold et al., 2016). This may suggest footwear interventions that are developed to specifically target OA patients with gait mechanics will lead to maximum effectiveness of the shoes.

Computational Modeling

Quantifying the joint contact loads and tissue stress OA patients experience while walking and performing daily activity is crucial in order to formulate an understanding on how OA progresses. However, this data is impossible to obtain in vivo without instituting invasive measurement techniques. Currently, joint contact loads can only be measured in vivo in TKA patients who have a knee replacement instrumented with force gauges (Erhart et al., 2010; Fregly et al., 2012; Kutzner et al., 2013). While this

technology helps in quantifying the standard knee loads the human body experiences when walking, which is roughly three times body weight, the population with instrumented knee replacement is very small, making collection of this data quite difficult (Kutzner et al., 2013). Furthermore, as the knee replacement removes all joint tissues, it is not possible to measure joint tissue stress in vivo. Tissue stress has been measured using in vitro techniques such as harvesting a cadaver knee joint and instituting gait like loading using a muscle mounted loading rig (Lee et al., 2006; Netravali et al., 2011). The loading of the tissue in vitro gives an accurate representation of tissue stress and contact pressure endured during walking, however inducing these loading constraints can be difficult as well as time and cost intensive (Lee et al., 2006; Netravali et al., 2011).

Due to the challenges of quantifying in vivo contact forces and in vitro joint stress, the majority of OA research has used external knee moments as a surrogate measure for knee joint loading. While studies have found external knee moments correlate well with in vivo joint loads in some instances (Erhart et al., 2010; Kutzner et al., 2013), these surrogate measures do not account for all the factors impacting joint contact forces occurring within the joint and provide no information on the tissue mechanics (Ali et al., 2017; Halloran et al., 2012; Halonen et al., 2017; Walter et al., 2010). With the advances in technology in recent years, computational modeling has become an attractive solution to overcoming the multiple issues concerning in vivo/vitro measurement and external joint moments (Halloran et al., 2012; Pandya & Andriacchi, 2010; Walter et al., 2010). A standard comprehensive modeling workflow has been developed for translating experimental motion capture data collection into estimation of forces and tissue stress occurring within the knee joint (Adouni et al., 2012; Ali et al.,

2017; Halloran et al., 2012; Halonen et al., 2017). This workflow starts with the development of a 3D musculoskeletal model of the lower limbs where individual muscle and joint contact forces can be estimated. The workflow is completed with the institution of these contact forces into a finite element analysis (FEA) model that allows for estimation of specific tissue mechanics. Overall, this modeling workflow allows for a more in depth investigation into how gait mechanics can influence knee joint health and function.

Musculoskeletal Modeling

Musculoskeletal Modeling is a computational method that allows researchers to investigate and estimate muscle forces during movement (Delp et al., 2007; Pandy & Andriacchi, 2010). Muscle forces can be estimated either using either static or dynamic optimization procedures (Pandy & Andriacchi, 2010; Thelen, Anderson, & Delp, 2003). These optimizations work by using a cost function in order to solve for the redundant number of muscles within the body (Pandy & Andriacchi, 2010). The optimization cost function used frequently is to minimize muscle activation, but other functions such as minimizing joint contact loads and error from experimental electromyography (EMG) have been used as well (DeMers, Pal, & Delp, 2014a; Lloyd & Besier, 2003; Thelen et al., 2003). Static optimization solves for muscle force independently at each time point throughout a movement, while dynamic forward optimization integrates the equation of motion forward in time using neural activation parameters, which allows for institution of such cost functions as matching collected EMG (Serrancoli, Kinney, Fregly, & Font-Llagunes, 2016; Steele et al., 2012; Walter et al., 2014; Walter & Pandy, 2017). There

are a vast number of studies that have investigated muscle forces using both optimization procedures. It has been demonstrated that both practices have shown to produce very similar results in muscle force production during walking (Pandy & Andriacchi, 2010). Since static optimization requires much less computation time compared to forward dynamics, (e.g., 5 minutes versus multiple hours), it has become a widely accepted tool for estimating muscle forces in submaximal activities.

Various simulation software packages have been developed, two of which are SIMM and Open-Sim, to provide both static and forward dynamic optimization based gait simulations. These simulations allow researchers to use previously constructed lower limb 3D models to estimate muscle forces (Delp et al., 1990; Delp et al., 2007). This software has been used in conjunction with MATLAB to allow for the estimation of joint contact forces by summing joint reaction forces, muscle forces, and external forces (Winby et al., 2009). Static and forward dynamic optimizations have been used to estimate contact forces throughout the literature, with varying accuracy depending on the input parameters used (Haight, Lerner, Board, & Browning, 2014; Knarr & Higginson, 2015; Lerner, Board, & Browning, 2014; Richards & Higginson, 2010; Serrancoli et al., 2016; Steele et al., 2012). Several parameters have been shown to improve the accuracy of both of the optimization procedures. For forward dynamics, usage of experimental EMG as input into the modeling workflow has been shown to generally improve joint contact estimation (Serrancoli et al., 2016; Walter et al., 2014; Walter & Pandy, 2017). For static optimization, the inclusion of muscle weighting parameters that hinder gastrocnemius and hamstring muscle activation has shown to improve accuracy for both joint contact force and experimental EMG activation (Steele et al., 2012). Further

accuracy improvement for both optimizations can be obtained by instituting subject-specific scaling parameters, such as geometry and muscle strength (Henak, Anderson, & Weiss, 2013; Knarr & Higginson, 2015; Moissenet, Modenese, & Dumas, 2017). While using subject-specific geometry is an attractive option, as each participant can have highly varied bone geometry, muscle paths, and muscle architecture, it is very time extensive and not always available (Pandy & Andriacchi, 2010). Scaling for subject specific muscle strength can improve accuracy and when available requires significantly less time to implement than geometry (Knarr & Higginson, 2015).

Another important modeling parameter emphasized in the literature is the degrees of freedom of the knee. Originally, the knee joint model was designed as a planar one degree of freedom joint that allowed for flexion/extension and some anterior translation based upon the knee flexion angle (Delp et al., 1990; Delp et al., 2007). This model of the knee joint has been used extensively over many years modeling simulations, but recently six degree of freedom models have been used since they can represent the accurate knee movement occurring while walking (Guess, Thiagarajan, Kia, & Mishra, 2010; Halonen et al., 2017; Lenhart, Kaiser, Smith, & Thelen, 2015; Smith et al., 2019). The six degree of freedom models include all the ligaments of the knee, allowing for realistic changes in knee joint contact location.

Models for estimation of knee joint contact forces are frequently first developed using data from instrumented knee replacement participants as estimated forces can be easily validated against forces measured in vivo from the force gauges (Fregly et al., 2012). These models have then been used to estimate contact loading in a number of populations during numerous ambulatory activities (Lenhart et al., 2015; Lerner et al.,

2014; Saxby et al., 2016; Walter & Pandy, 2017). Specifically for OA, studies have found greater medial compartment and total contact force in OA patients during walking compared to healthy controls (Meireles, S. et al., 2016; Meireles, Susana et al., 2017; Richards & Higginson, 2010). Additionally, studies have reported contact force increases with OA severity and that a compensatory gait strategy is established to change in-vivo joint loading (Meireles, S. et al., 2016; Richards & Higginson, 2010). The compensatory gait strategy has been found to either lower overall contact forces in early stage OA patients or lower time spent at high loading in severe OA patients.

Finite Element Analysis (FEA)

Along with musculoskeletal modeling, FEA has become a widely used tool within the field of knee biomechanics. FEA uses differential equations of equilibrium to approximately solve the behavior of mesh from a geometry under given loading and boundary conditions (Erdemir, Guess, Halloran, Tadepalli, & Morrison, 2012; Halloran et al., 2012). With FEA tissue mechanics can be estimated under varying compartmental loading conditions, allowing for the development of a more comprehensive understanding of joint tissue health and function. Because FEA can quantitatively predict mechanical and physiological behavior of all the tissue within the knee joint, extensive research has been invested in constructing realistic models that accurately predict such behavior (Halloran et al., 2012; Peters, Akhtar, Comerford, & Bates, 2018). FEA models have been developed at the whole joint, tissue, and cell level to understand how mechanical loading can influence all aspects of the knee joint (Halloran et al., 2012). When observing the direct influence of gait mechanics, FEA of the whole knee joint has

been used primarily, as estimated joint contact mechanics can be applied directly to the femur and tibia (Halonen et al., 2017; Kłodowski et al., 2016a). To construct a whole knee joint FEA model, magnetic resonance images (MRIs) of a participant's knee are used to generate solid 3D geometries of each tissue of the knee, which then are assigned specific material properties. The geometries are then assembled and a mesh is generated, subdividing the geometries into a collection of finite polyhedrons elements. These finite elements are typically tetrahedral and hexahedral elements. Musculoskeletal modeling outputs of gait kinematics and joint loading are then input into the FEA model as constraints and boundary conditions to solve for the stresses and strains distribution within each element.

One of the first decisions when developing a model to investigate the relationship between gait mechanics and tissue stress has been whether or not to include the patella in the model. As the knee joint is constructed of a patellofemoral and tibiofemoral joint, the research question of interest must be considered when deciding to remove or keep the patella. As OA occurs most frequently in the medial compartment of the tibiofemoral joint (Thomas et al., 1975), some studies have removed the patella to save on computational time. Removal of the patella has found to have no distinct result on the contact mechanics of the tibiofemoral joint (Donahue et al., 2002; Donahue et al., 2003; Netravali et al., 2011). Other studies have included the patella to investigate patellofemoral pain using FEA (Ali et al., 2016; Besier et al., 2015).

The literature has found the material properties that are assigned to each tissue of the knee joint are crucial in predicting realistic tissue behavior under the gait loading conditions (Klets et al., 2016; Peters et al., 2018). The tissue properties selected for each

model are dependent on the question being asked and the allowance for computational time. There has been vast advancement in the material models and properties used for the knee tissues in FEA models over the past decade due to the improvement of in vitro mechanical testing (Peters et al., 2018). More complicated tissue properties can provide a more realistic estimation of tissue contact behavior. However, they can be very computationally extensive and have difficulties converging on a solution (Klets et al., 2016). Generally in the literature, it is accepted to model the bones of the knee joint as rigid non-deformable objects (Peters et al., 2018). This is due to the relatively higher elastic modulus of bone compared to that of the soft tissues such as cartilage, menisci, and ligaments. For example, the ratio of elastic modulus of bone to articular cartilage is on the order of 1,000. The complicated material properties incorporated into FEA models mimic the tissue properties of cartilage discussed above and are usually depth-dependent fibril-reinforced viscoelastic cartilage models (Halonen et al., 2017; Klets et al., 2016; Robinson et al., 2016). The menisci are generally less complicated and modelled as directionally linear elastic models, as they are frequently not the tissue of interest and less is known about their exact tissue properties (Peters et al., 2018). Some studies have used complicated viscoelastic tissue properties when inputting gait mechanics as boundary conditions, but due to the quick high loading of the gait cycle not inducing large deformation and fluid change in cartilage, simpler linear elastic properties have been employed (Klets et al., 2016).

For OA, there is currently little information on FEA modeling studies performed using tissue models of osteoarthritic cartilage, which is most likely due to the high complexity of modeling the breakdown of cartilage's extracellular matrix (Halonen et al.,

2017; Robinson et al., 2016). However, FEA has used healthy cartilage models to investigate various changes in gait mechanics exhibited by both OA and healthy participants (Adouni & Shirazi-Adl, 2014; Halonen et al., 2017; Shirazi & Shirazi-Adl, 2009). The majority of the FEA literature has focused primarily on how gait impacts healthy cartilage mechanics, but some studies have looked at the role both the ACL and menisci play in cartilage mechanics. Prior work has shown the removal of the menisci or ACL drastically increases stress placed on the cartilage, suggesting risk of OA progression (Netravali, Giori, & Andriacchi, 2010; Pena et al., 2005; Shirazi & Shirazi-Adl, 2009; Zielinska & Donahue, 2006). Additionally, one study has shown gait adaptations and lateral wedge insoles designed to lower knee joint loading have a small effect on lowering cartilage tissue stress (Halonen et al., 2017). Less research has been done to investigate the menisci under different loading patterns. However, it has been shown that increases in knee adduction moment increase meniscal strain (Netravali et al., 2011). Also, it has been identified that meniscal tears result in increased stress placed both on the menisci and cartilage at the tear location (Mononen et al., 2013). These increases in tissue stress support the relationship between damaged menisci and OA development.

Summary

Knee OA is a debilitating disease affecting the entire knee by inducing pathological changes involving degradation of cartilage, deterioration of the menisci, osteophyte formation, and synovial fluid inflammation. The etiology of OA is not completely understood; however, several mechanisms for initiation and progression of OA have been

found. The menisci play an integral in maintaining cartilage health and deterioration in menisci structure and function is closely linked to the development of OA. In addition to menisci function, altered gait mechanics of OA patients have a clear association with both symptomatic and structural disease severity. Changes in knee joint loading, both in location and magnitude, have shown to lead to the initiation and progression of OA. Currently, non-surgical intervention tools, such as footwear, have been developed as a way to decrease loading within the knee joint. However, due to the external moments being surrogate measures for knee loading, it is unclear if changes in joint loading with footwear are sufficient to result in a clinical benefit. To resolve this issue, musculoskeletal and FEA modeling have become attractive tools to estimate contact forces and tissue stresses occurring within the joint.

CHAPTER 3

METHODS

Participants

Participants recruited had to fit the following criteria: 1) be between the ages of 50 -79 years old; 2) have a body mass index less than 35 kg/m^2 ; 3) have mild/moderate to severe diagnosed medial compartment knee OA; 4) and could walk unaided for more than 20 minutes at a time. Participants were excluded if they had a current acute injury to the lower extremities, moderate to severe low back pain, a history of significant heart problems or neurological disorders, have undergone a hip or knee replacement, or have undergone a complete meniscectomy or other traumatic surgical knee procedures within the past year.

Footwear

Data of participant's walking mechanics was collected while they wore two different pairs of footwear during the motion capture component of data collection (Figure 3.1), which is discussed in greater detail below. One pair of shoes was a variable stiffness shoe (VSS) constructed so the lateral midsole would have roughly 1.5 times greater material stiffness than the medial side (Abeo Smart 3300). However, after material testing the footwear appeared to be only 1.1 times stiffer on the lateral side (Table 3.1). The other pair of shoes was a standard neutral control shoe with constant midsole properties (New Balance MW411v2). The material properties for both shoes were determined via standard footwear mechanical impact and flex testers (Exeter Research, NH, USA) (Table 3.1; Figure 3.1) (ASTM International, 2013).

	<i>Acceleration (g)</i>	<i>Force (N)</i>	<i>Max Displacement (%)</i>	<i>Longitudinal Stiffness (Nm /deg)</i>	<i>Flex Torque (Nm)</i>
<i>New Balance Control Shoe</i>	19.4	1610	49	0.284	11.24
<i>Abeo Variable Stiffness Shoe</i>	Medial: 19.8 Lateral: 21.7	Medial: 1650 Lateral: 1810	Medial: 50 Lateral: 46	0.403	10.51

Table 3.1: Footwear impact and flex testing results. Variable stiffness shoe was impact tested on the medial and lateral side to determine difference in medial and lateral material properties. The projectile with a mass of 8.5 kg was dropped from a height of 30 mm during impact testing. Results from 10 impacts were averaged. Longitudinal stiffness was assessed on a flex tester for 2 sets of 50 flexes.



Figure 3.1: (Left) Neutral control (New Balance MW411v2) and variable stiffness shoe (Abeo Smart 3300) conditions used for this study. (Right) Impact testing of VSS. Shoe was positioned under the impact tester while a projectile with a mass of 8.5 kg was dropped from a height of 30mm. Load cell within the projectile measured projectile acceleration, force, and displacement.

Experimental Protocol

Participants partook in one laboratory testing session lasting approximately 4 hours all within the Integrated Applied Life Sciences (IALS) building at the University of Massachusetts Amherst (Figure 3.2). Prior to attending the lab session, individuals interested in participating underwent a phone screening determine if they are eligible to participate. If the prospective participant qualified and was interested in partaking in the study, they were asked to first arrive at the Human Magnetic Resonance Center (hMRC) located in the IALS building. Upon arrival each individual first completed an informed consent form approved by the University of Massachusetts Institutional Review Board (IRB). In addition to completing the IRB, the prospective participant completed a Magnetic Resonance (MR) Safety Questionnaire to determine if they are MR compatible. If the individual consented to participating and was MR compatible, data was be collected on their age, height, weight, and osteoarthritic symptomatic leg. Each participant was then asked to fill out a Physical Activity Readiness Questionnaire (PAR-Q), to assess their ability to perform physical activity. Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire was also administered to evaluate short and long-term OA symptoms and joint function (Nilsson, Lohmander, Klässbo, & Roos, 2003). These questionnaires assess knee joint symptoms and function by providing questions on 5 separate categories: pain, other symptoms, function in activities of daily living, function in sport and recreation, and joint related quality of life. Each category is scored separately on a scale from 0 to 100, with a low score representing extreme joint problems and 100 representing no joint problems.

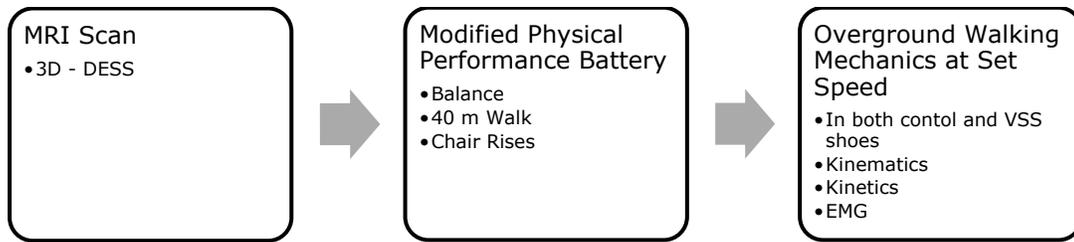


Figure 3.2: Study protocol workflow

Magnetic Resonance Imaging (MRI)

Upon completion of all forms and questionnaires, participants underwent a MRI protocol in line with the Osteoarthritis Initiative Imaging Guidelines to obtain information on participant’s knee joint health and 3D knee joint geometry (Peterfy, Schneider, & Nevitt, 2008). The participant was prepared for the MRI sequence in a 3 Tesla Siemens Skyra System MRI Scanner by the MR technician at the hMRC. The MRI protocol took approximately one hour to complete, during which the participant lies still within the MR machine. Using a 15 channel Tx/Rx knee coil, images of the knee were obtained using a fat-suppressed 3D dual-echo in steady state (3D-DESS) sequence with a slice thickness of 0.7mm. The 3D-DESS images allowed for 3D knee geometry segmentation.

Modified Physical Performance Battery (MPPB)

Following the MRI, participants were taken to the Human Testing Center on the 3rd floor of the IALS building to finish the rest of the data collection. First, participants completed a performance battery test in the Human Motion Lab to quantify physical performance. The test consisted of walking 40 meters as quickly as possible, performing as many chair rises as possible in 30 seconds, and performing a series of 30 second

standing balance tests. Results from each test of the performance battery were scored on a 0 to 1 scale and used to characterize physical function of the participants. The 40m walk was completed as 4 x 10m straight walks and participant's time to complete the walk was recorded. To calculate the 40 meter walk score, the equation ($Score = \frac{20}{Time\ to\ walk\ 40\ meters\ (s)}$) was used. The balance test included side-by-side, semi-tandem, tandem, and single leg standing postures. Participants held each position as long as they could or until the 30 second time limit was met. The total balance score was the sum hold time for all positions divided by 90 ($Score = \frac{Total\ balance\ time}{90}$). For the chair rises, participants completed the task with their arms crossed their chest and they were asked to fully stand up and sit back down ensuring to make full contact with the chair between stands. The number of completed stands was be recorded and divided by 30 to calculate a score for the chair stand test ($Score = \frac{Number\ of\ chair\ stands}{30}$). The score for each of the 3 tests was averaged together to obtain an overall score of physical function for each participant on a 0 to 1 scale, with 1 being considered high function and 0 being low function.

Motion Capture and Electromyography

Kinematic, kinetic, and electromyography (EMG) data were collected for the osteoarthritic side, while just kinematic and kinetic data were collected for contralateral side, using motion capture technology and wireless EMG electrodes (Delsys Trigno, Natick, MA). Participants first had EMG electrodes were placed on the vastus lateralis (VL), vastus medialis (ML), rectus femoris (RF), biceps femoris (BF), semitendinosus (ST), medial and lateral gastrocnemius (MG, LG), and tibialis anterior (TA) of the

osteoarthritic leg to record EMG data during the walking trials. The location for electrode placement was determined by palpating participants' muscles and finding their muscle belly. Prior to electrode placement, the skin was prepared by shaving the area and wiping the area with isopropyl alcohol. All EMG placement and skin preparation was based of the SENIAM recommendations. EMG data was sampled at 2000 Hz and collected using Qualysis Track Manager (QTM) (Qualysis, Inc., Gothenburg Sweden). Prior to data collection, participants were asked to perform leg movements and tasks that isolated strong activation of each muscle. During this time, the EMG signal was visually inspected in QTM to ensure the electrodes were placed correctly, ensuring appropriate signal to noise ratio.

Next, participants were fitted bilaterally with 69 retro-reflective markers that were tracked by nine infrared motion capture cameras (Oqus 7 series, Qualysis, Inc., Gothenburg, Sweden). Marker trajectories were recorded at 200 Hz. A total of 27 markers were placed on each lower limb with 9 markers being placed as clusters on the thighs and six 6 being placed as clusters on the shanks. The remaining 12 markers for each lower limb were placed at the following landmark locations: medial and lateral femoral epicondyles, medial and lateral tibial plateau, medial and lateral malleoli, first and fifth metatarsal heads, hallux, and medial, central and lateral heel. Markers were then placed on the pelvis at the left and right anterior superior iliac spine, posterior superior iliac spines, iliac crests, and greater trochanter. The remaining markers were placed at both wrists, elbows, shoulders, and at the sternum.

Once EMG and markers were placed, participants were asked to walk overground through the motion capture space at a set walking speeds of speed of 1.2m/s in the 2

different shoe conditions (VSS and neutral control shoe). Participant's first walked in the neutral control shoe then the VSS. Participants walked over 3 force plates (AMTI, Watertown, MA, USA) located in the middle of the capture space, which collected GRFs at 1000 Hz. A static standing calibration trial was recorded using the motion capture cameras prior to collecting the overground walking trials. Participants completed 5 successful walking trials in both shoe conditions for a total of 10 successful trials. A walking trial was deemed successful if the participants walked with a speed within 5% of 1.2m/s and made full contact with the all 3 force plates.

AIM 1 and 2 Data Processing

Kinematic and Kinetic Data

The kinematic and kinetic data collected was used to calculate measures for Aim 1 of this study. The point cluster technique (PCT) was used to calculate segment motion for each participant from the markers placed on the skin via. PCT considers the soft tissue artifact associated with the non-rigid movement of markers that are placed on the skin, which allows for reduced errors in calculating segment motion (Andriacchi, T. P., Alexander, Toney, Dyrby, & Sum, 1998). With the PCT marker set, the cluster of reflective markers placed on the thigh and shank estimate the movement of the underlying femur and tibia by creating coordinate systems for each cluster. The cluster coordinate systems are determined by calculating the principal axes of the PCT marker clusters assuming a unit weight for each marker. The definition of principal axes and weighting of markers allow for correction in the coordinate system due to non-rigid movement (Andriacchi, T. P. et al., 1998). Visual 3D and a custom MATLAB script

were used to process PCT kinematic and kinetic data to calculate 3D lower limb joint angles and moments. Kinematic and kinetic data was filtered using a low pass Butterworth filter with cutoff point of 8 and 15 Hz, respectively. Discrete time points for heel strike and toe off of the symptomatic leg were determined when vertical GRFs surpassed 20N. Joint moments were normalized to the percent body weight multiplied by height. Joint angles and moments were interpolated to 101 data points representing the length of the stance phase of the gait cycle.

Musculoskeletal Model

A three-dimensional musculoskeletal model was used to estimate 10 participant's joint contact forces while walking for Aim 2 of this study. The model included 12 body segments consisting of the following: torso, pelvis, right and left femur, tibia, talus, calcaneus, toes. The model had 23 degrees of freedom, and 92 musculotendon actuators, representing 76 muscles in the lower extremity and torso (Delp et al., 2007; Saxby et al., 2016). The torso was articulated with pelvis via a ball and socket modeled lumbar joint. Each hip joint was also modeled as a ball and socket joint. The knee joints were modeled as a single-degree-of-freedom hinge joint with translation of the femur being proportional to knee flexion angle. Two contact points were added to the knee joint defining medial and lateral compartment contact locations, which allowed for estimations of knee joint contact forces described later (Saxby et al., 2016). The ankle and subtalar joints were modeled as a hinge joints, while the metatarsophangeal was constrained to no movement.

Joint Contact Forces

Knee contact forces were estimated using the musculoskeletal modeling simulation software OpenSim and a custom MATLAB script (Delp et al., 2007; Steele et al., 2012). A workflow within OpenSim was established to estimate muscle forces using static optimization (Figure 3.3). First, the musculoskeletal model discussed above was assigned model markers which allowed for the model to be scaled to match the anthropometrics of each participant based on their experimental marker location from the standing static calibration trial.

The scaled model for each participant was then used to track and estimate lower limb joint angles from the experimental walking trials in both shoe conditions using the Inverse Kinematics Tool (Delp et al., 2007). The Inverse Kinematics tool uses a weighted least-squares equation to minimize the distance between the experimental markers and the corresponding model markers. Joint moments were then calculated via the Inverse Dynamics tool, and were later used to estimate joint contact forces.

A Reduced Residual Algorithm (RRA) was run for each subjects' model to reduce dynamic inconsistencies between the models' motion and the measured GRF. RRA uses a tracking controller to follow a model's kinematics produced by the Inverse Kinematics tool. The controller replaces all muscles within the model with force actuators, which allows for determination of the model's segment mass distribution and joint kinematics that are consistent with the measured GRFs. Following completion of RRA, a new subject model file with adjusted torso center of mass location and kinematics was created.

Static optimization analysis was then used with inputs of kinematics from RRA and measured GRFs to estimate muscle force production. Static optimization solves for

each joints' moment at a given time step during the gait cycle, while simultaneously using an objective function to estimate each individual muscle's force needed to produce the joint's moment at that time step. The objective function of $J = \min \sum_{i=1}^N w_i a_i^2$ was used, where N is the number of muscles in the model, a_i^2 is the square of muscle activation, and w is a muscle specific weighting term. This objective function solved to minimize each muscles' activation during each time step for the simulation; however, the muscle weighting term penalized activation of a muscle if ($w_i > 1$) and encouraged a muscle's activation if ($w_i < 1$). The weights were set as follows: medial gastrocnemii ($w_i = 4$), lateral gastrocnemii ($w_i = 7$), hamstring ($w_i = 2$), rectus femoris ($w_i = 3$), soleus ($w_i = 0.9$), gluteus minimus ($w_i = 0.9$), gluteus medius ($w_i = 0.9$), and all other muscles in the model set to a weight of 1. Muscle weightings were instituted using a plug-in for OpenSim (Steele, Tresch, & Perreault, 2015). These weighting were used as they have been shown to help generate resulting joint contact forces that best match validated physiological magnitudes (DeMers, Pal, & Delp, 2014b; Smith et al., 2019; Steele et al., 2012). Following static optimization, MuscleAnalysis under OpenSim's analyses tool was run to determine the moment arms for each muscle crossing the knee joint for the stance phase of the symptomatic leg (semitendinosus, semimembranosus, biceps femoris long head, biceps femoris short head, sartorius, tensor fasciae latae, gracilis, rectus femoris, vastus medialis, lateralis, intermedius, medial gastrocnemius, and lateral gastrocnemius).

Medial and lateral compartment loading were then estimated using the muscle forces from static optimization, the external moments from Inverse Dynamics, and moment arms from MuscleAnalysis. The external frontal plane knee moments was

applied separately to each of the femoral/tibial contact points, which was balanced by both the load at the contact points and the moments each muscle produced crossing the knee joint, (Figure 3.4) (Winby et al., 2009). A static equilibrium problem was then solved for each time step of the stance phase to obtain estimates of medial and lateral contact loading for each trial. Medial and lateral contact force were added together to estimate total contact force. Total, medial, and lateral contact force were normalized to each participant's BW and interpolated to 101 data points representing the length of the stance phase of the cycle.

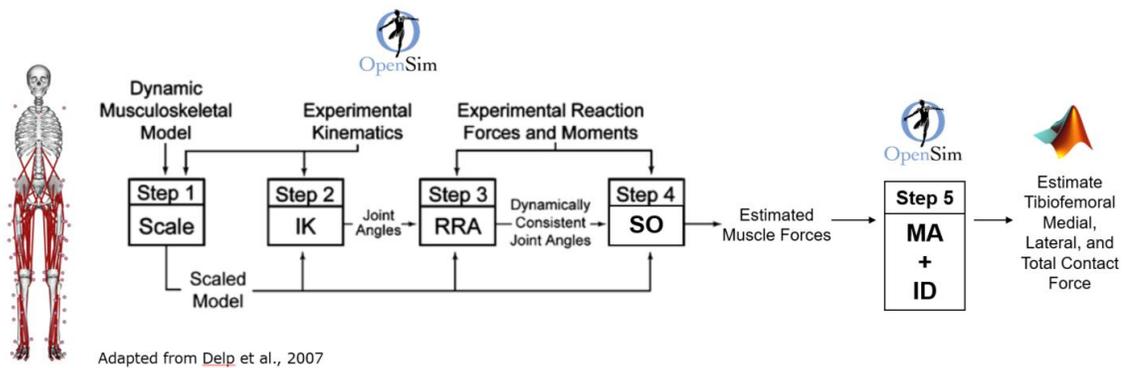
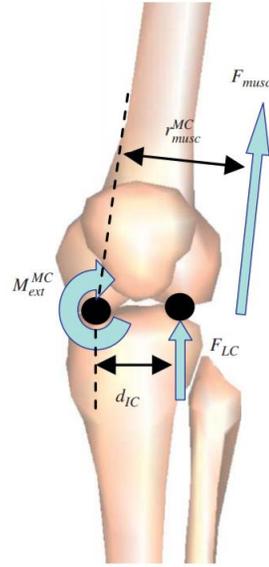


Figure 3.3: Musculoskeletal modeling workflow to estimate knee joint contact loading



$$M_{Med} = d * F_{Lat} - M_{mus,Med} + M_{ext} = 0$$

$$M_{Lat} = d * F_{Med} - M_{mus,Lat} + M_{ext} = 0$$

Figure 3.4: Free body diagram for estimating lateral contact force, and equations for estimating medial and lateral compartment contact force (Winby et al., 2009). M_{Med} and M_{Lat} are equal to the internal moment at the medial and lateral condyles, respectively. F_{Med} and F_{Lat} are the contact force at each condyle, and d is the distance between the condyles. $M_{mus,Med}$ and $M_{mus,Lat}$ are the moments created by the muscle forces (i.e. summed muscle moment magnitude), which in the diagram is equal to $F_{mus} \times r_{mus}^{MC}$. Finally, M_{ext} is equal to the external adduction moment, also shown as M_{ext}^{MC} in the diagram.

Model Validation

Muscle activation results from static optimization were qualitatively compared to experimentally collected EMG. Furthermore, estimated joint contact forces were compared to results in from the literature and ensured to lie within the physiological range of 2.0 to 4.0 BW.

Outcomes and Statistics

The statistical methods used for both Aim 1 and 2 were the same. All statistical tests used an alpha criterion level of ($\alpha = 0.05$). Paired t-test were used to test for differences in measures of interest between the variable stiffness and control shoes. The primary measures (H1.1) of interest for Aim 1 included three dimensional knee joint kinematics at heel strike, toe off, and peak knee flexion, as well as peak knee joint kinetics. Additional measures (H1.2) of interest for Aim 1 include peak transverse and frontal plane kinematics and kinetics for the ankle and hip joint. For Aim 2, our primary measure (H2.1) of interest was medial joint contact force. We also looked at estimated total and lateral knee joint contact forces, knee adduction moment, knee flexion moment, summed muscle moment magnitude at 1st and 2nd peak contact force.

Exploratory Aim

MRI Segmentation and Geometry Generation

The tibiofemoral joint tissue geometry for one participant (Participant 3) was manually segmented using the 3D slicer software for analyzing medical images (Fedorov et al., 2012). The segmentation and geometry generation of the joint followed the protocol developed by the Open Knee Project (Erdemir & Sibole, 2010). MRI DESS scans of the symptomatic knee were imported into the MRI viewing software package, Slicer, where segmentation was completed (Fedorov et al., 2012) (Figure 3.5). The following tissues were manually segmented with the editor tool available in Slicer: femur, tibia, menisci, femoral and tibial cartilage.

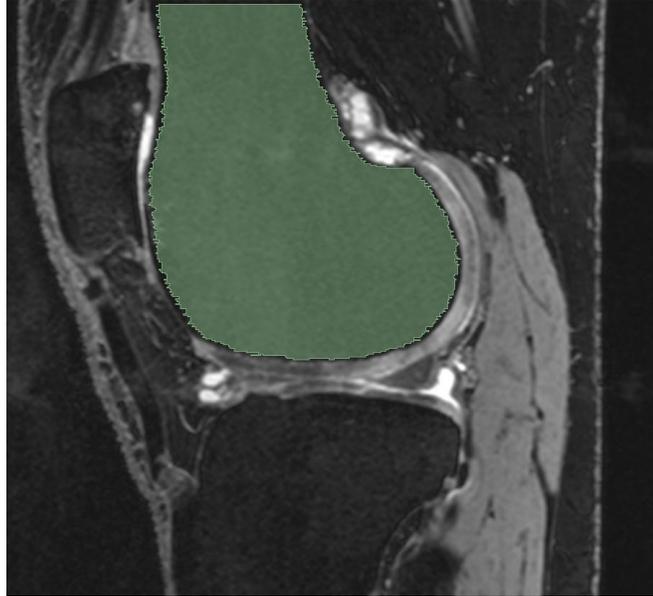


Figure 3.5: Segmentation of the femur from the MRI of participant.

Each tissue was then smoothed using a Gaussian Smoothing Algorithm with a Sigma of 0.7, equal to the MRI resolution, and 3D geometry volumes were generated and saved as stereolithography (STL) files. Further smoothing of the geometry consisting of Taubin Smoothing and iso-parametrization were completed in the MeshLab Software (Cignoni et al., 2008). After each tissue is smoothed, each 3D geometry was then converted from STL files into a NURBS (non-uniform rational B-spline) geometric solid using the skin surface tool within SapceClaim (Figure 3.6).

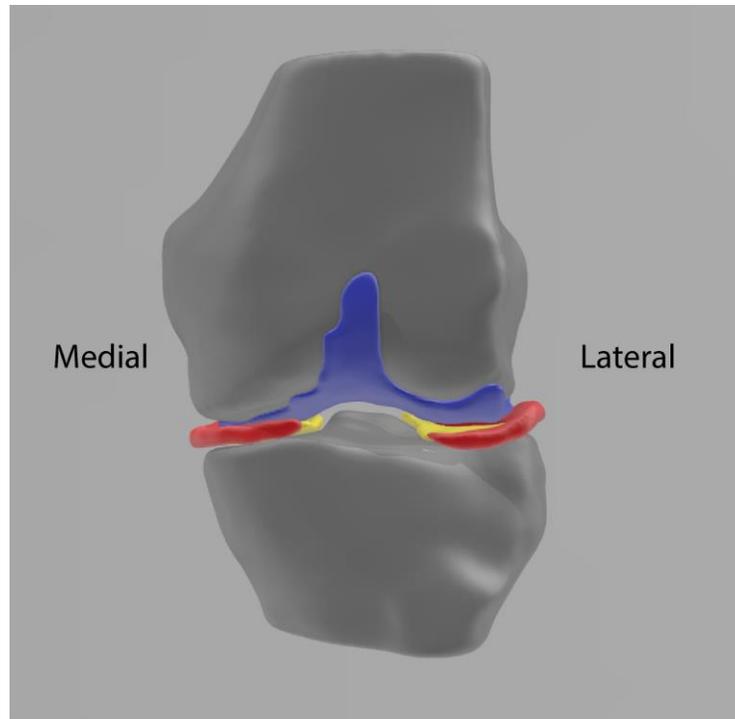


Figure 3.6: Smoothed tibiofemoral (femur, tibia, femoral cartilage, tibial cartilage, medial meniscus, and lateral meniscus) geometry imported into ANSYS and used for FEA.

FEA

Tibiofemoral joint geometry files was imported into the ANSYS software where the FEA was completed to investigate the impact of different loading conditions due to VSS and NS on menisci stress and strain. Static structural analysis in ANSYS was used to simulate a quasistatic loading of the knee joint at first peak contact force.

Material Properties

Material properties for each tissue were defined under the engineering data section of the ANSYS project block. The femur and tibia was modeled as rigid, non-deformable tissues due to the bones' significantly greater stiffness compared to the soft

tissues within the tibofemoral joint. This assumption has been shown to have negligible effects on FEA results and results in more efficient computation time.

The femoral and tibial cartilage were modeled as linear elastic material with an elastic modulus of 15 MPa and Poisson's ratio of 0.475 (Zielinska & Donahue, 2006). As the goal for this thesis was to investigate the impact of changing loading conditions during a quasi-static specific time point in the gait cycle, biphasic fiber-reinforced visco-hyperelastic nature of cartilage was not needed for this study. Furthermore, because the primary tissue of interest is the menisci, a less-complex cartilage material property did not hinder results and reduced computational time. The ACL, PCL, MCL, and LCL were not modeled as a downward displacement was prescribed to the femur to load the knee joint in compression and therefore these ligaments would not have an impact on this study to investigate menisci stress.

Medial and lateral menisci were modeled as linear elastic, orthotropic material with radial and axial moduli of 20 MPa, a circumferential modulus of 140 MPa, and shear modulus of 57.7 MPa (Donahue et al., 2002; Donahue et al., 2003; Netravali et al., 2011). The menisci had an in-plane Poisson's ratio of 0.2 and an out of plane ratio of 0.3 (Donahue et al., 2002). The menisci were attached to the tibia using linear spring elements for the anterior and posterior meniscal horns with total spring stiffness being 2000 N/mm (Zielinska & Donahue, 2006). Validated fiber-reinforced viscoelastic material properties for the menisci are less established and are not needed to determine the impact of changing gait mechanics on stress and strain.

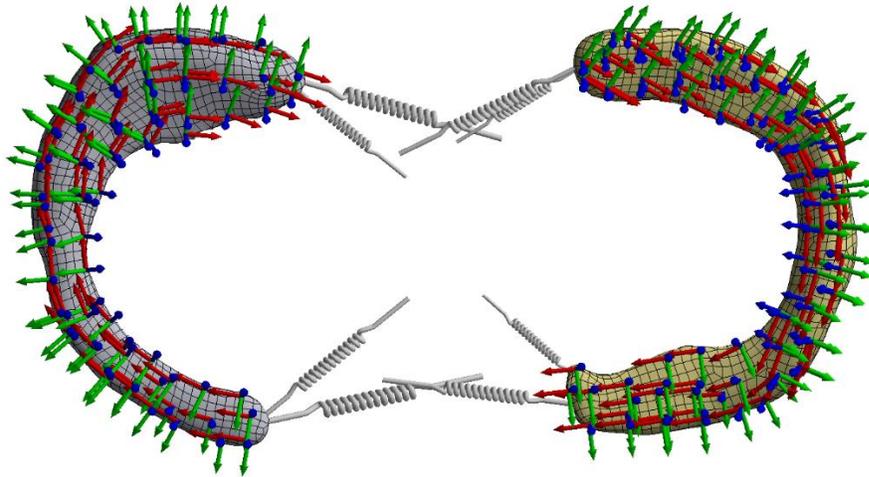


Figure 3.7: Axis direction for orthotropic material property of the menisci. Element orientation was designated under the geometry tab of ANSYS mechanical. Surface and edge guides of the menisci geometry were used to define orientation of the elements axis.

Interactions and Meshing

Following selection of material properties, the tibiofemoral joint was assembled and each tissue was meshed within ANSYS Mechanical. Solid-to-solid frictionless contact connections were established between the following pairs: femoral cartilage and the medial/lateral menisci and tibial cartilage, the lateral meniscus and lateral tibial cartilage, and the medial meniscus and medial tibial cartilage. Frictionless contact interactions are appropriate when modeling the tibiofemoral joint due to articular cartilage being considered such a low friction surface and the synovial fluid within the knee joint aiding in the smooth motion of the joint. Femoral cartilage and tibial cartilage had bonded connection to the femur and tibia, respectively. Meniscal – cartilage and femoral – tibial cartilage contacts were brought closer into contact using the offset function within ANSYS to ensure contact was maintained between the soft materials during compression of the femur into the tibia.

The medial and lateral menisci were meshed as hexahedral elements of 0.80mm size using the hexahedral dominant function. The femoral and tibial cartilage were meshed as tetrahedral elements ranging from 1.0 to 2.5 mm using the patch independent function. The rigid femur and tibia were meshed with quadrilateral surface elements. A mesh convergence was determined by first selecting a mesh quality that matched previous reported number of elements used in FE modeling the menisci within the literature (Netravali et al., 2011). The menisci mesh was then increased slightly to improve representation of the meniscal geometry and to ensure contact pressure did not change more than 5% between meshes (Table 3.2; Figure 3.7).

	<i>Total</i>	<i>Femoral Cartilage</i>	<i>Medial Tibial Cartilage</i>	<i>Lateral Tibial Cartilage</i>	<i>Medial Mensicus</i>	<i>Lateral Meniscus</i>
<i>Nodes</i>	85047	31931	5696	7293	18288	19832
<i>Elements</i>	38051	18287	3195	4235	5545	6134

Table 3.2: Number of nodes and elements for each deformable geometry included in FE model

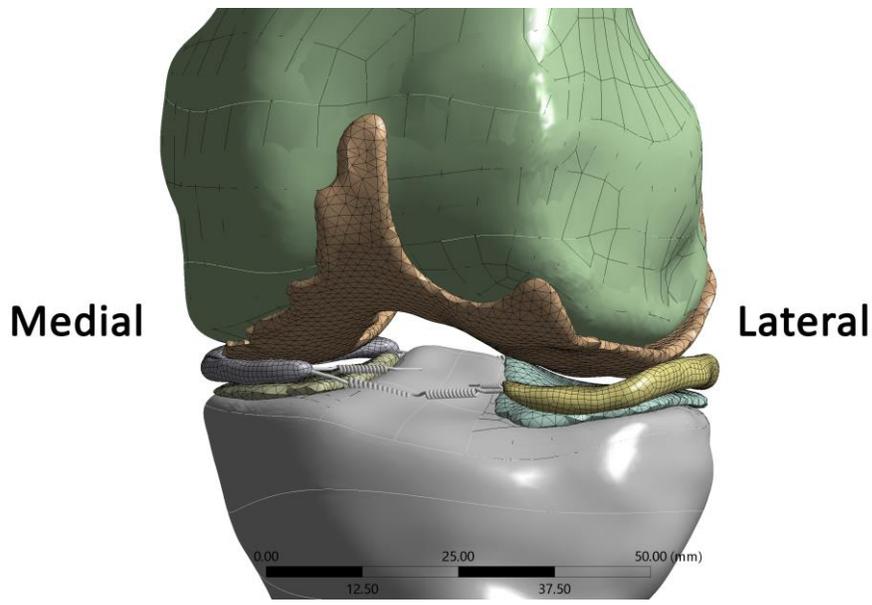


Figure 3.8: Geometry and mesh for femur, tibia, femoral cartilage, tibial cartilage, and menisci. Meniscal horn attachments are represented by springs connecting menisci to tibia.

Loading and Boundary Conditions

Loading and boundary conditions were established to induce a quasistatic compression of the knee joint during first peak contact force. The tibia was first established as a fixed support and was completely constrained during the simulation, while the femur was aligned to flexion-extension angle at the time of the peak joint contact force estimated by the musculoskeletal modeling in OpenSim and was constrained to allow only compression of the knee joint. A vertical displacement was then applied to the femur until a force reaction probe placed on the femur equaled the total contact force estimations from OpenSim.

This process was first completed for the participant whose knee was selected to construct the FE tibiofemoral model for both the VSS and neutral shoe loading conditions. Following successful solution convergence for the 1st participant, the loading conditions for 2 more participants for both shoe conditions were imposed on the FE

model. The 2 participants selected had the largest decrease and increase in knee contact forces with the VSS compared to the neutral shoe.

FEA Results

Due to the menisci's role in stabilizing the knee joint and resisting compressive and shear patterns, the outcomes assessed using FEA will be menisci contact pressure, max principal stress/strain, total deformation, and maximum shear stress/strain in both the VSS and control shoe conditions. Results from the FEA study were compared to several studies within the literature that have looked at the impact of gait mechanics on the menisci (Donahue et al., 2003; Netravali et al., 2011; Pena et al., 2006). Furthermore, cartilage contact pressure were compared to other finite element cartilage contact studies from the literature. Comparing these outcomes supported the FE model ability to find physiologically relevant results.

Summary

This study proposed to investigate the impact of a VSS intervention on gait mechanics, joint loading, and tissue mechanics in a symptomatic OA population. Outcomes from the proposed project looked to provide insight into the mechanisms that associate changing gait mechanics and OA progression. It is clear that altered gait mechanics have a significant impact on both radiographic and symptomatic OA progression; however, it is unclear what measures directly drive this change in progression. Knee loading and menisci function have been identified as a possible influence of pain in OA patients, and quantifying the impact associated with altered gait

mechanics, due to wearing VSS, on such outcomes may provide insight into the underlying mechanism leading to pain and poor clinical outcomes. Thus, this study explored such relationships between altered gait mechanics due to VSS and joint loading, which may identify how footwear can alter mechanisms for OA progression. Understanding the relationship between VSS and the mechanisms for OA progression may lead to improved application of the intervention to a clinical OA population.

CHAPTER 4

RESULTS

Participant Summary

Data was collected on 14 participants with medial compartment symptomatic knee osteoarthritis (OA) (Table 4.1). All participants' Knee Osteoarthritis Outcome Scores (KOOS) for pain, symptoms and activity of daily living scores indicate they have mild – moderate symptomatic OA (Table 4.1) (A score of 100 indicating no knee problems and 0 indicating severe problems). Modified physical performance battery results suggest participants are moderate to high physical functioning. All 14 participants were included in the Aim 1 results, 10 participants were included for musculoskeletal modeling for Aim 2 results (shown in grey and blue shade in Table 4.1), and 3 participants were modeled for finite element (FE) analysis for exploratory Aim results (only blue shade in Table 4.1). The first six female and four male participants to complete data collection were selected originally for musculoskeletal modelling. However, participant number four was difficult to scale properly and was replaced by participant number 11 who was randomly selected. FE modeling reflects analysis of the participant whose knee geometry was segmented as well as the participants with greatest increase and decrease in joint contact forces.

<i>Participant</i>	<i>Age</i>	<i>BMI</i>	<i>Gender</i>	<i>KOOS Pain</i>	<i>KOOS Symptom</i>	<i>KOOS ADL</i>	<i>MPPB Score</i>
1	72	25.46	F	94.44	100.00	92.65	0.52
2	70	33.37	F	77.78	82.14	94.12	0.54
3	69	18.60	F	58.33	57.14	57.35	0.60
4	67	24.94	F	77.78	82.14	95.31	0.72
5	57	23.35	F	86.00	71.00	90.00	0.71
6	67	28.95	M	75.00	78.57	85.29	0.63
7	64	24.75	F	81.00	75.00	91.00	0.70
8	61	28.35	F	72.22	71.43	72.06	0.68
9	67	22.30	F	75.00	75.00	76.47	0.69
10	70	22.91	F	66.67	78.57	82.35	0.73
11	65	22.86	F	31.00	46.00	50.00	0.66
12	62	28.89	M	69.00	93.00	75.00	0.70
13	68	23.58	M	80.56	82.14	92.65	0.81
14	61	25.75	M	78.00	79.00	91.00	0.80
<i>Mean ± SD</i>	65.71 ± 4.10	25.29 ± 3.52	<i>F:10</i> <i>M:4</i>	71.14 ± 15.61	75.47 ± 12.72	79.87 ± 14.37	0.68 ± 0.08

Table 4.1: Participant age, BMI, gender, KOOS pain, symptom and activity of daily living scores, and the MPOPB score. All 14 participants were included in Aim 1 results but only participants with shaded rows (both blue and grey) were included in Aim 2 results. Only blue shaded participants were included for the exploratory Aim.

Aim 1

Knee Joint Kinematics and Kinetics

No significant differences between shoe conditions were found for the knee adduction moment (KAM) ($p = 0.064$) (Table 4.2; Figure 4.2). However, 8 of 14 participants increased KAM by greater than $0.07 \%BW \times Ht$ with the VSS (Figure 4.4). Knee external rotation moment significantly increased with the variable stiffness shoes (VSS) ($p = 0.036$), whereas no differences were found between shoes in knee flexion moment or extension moment ($p = 0.185$; $p = 0.232$) (Table 4.2; Figure 4.2). Minimal effects of the

footwear on knee joint kinematics were observed (Table 4.2; Figure 4.1). However, knee flexion angle at toe off was less flexed in the VSS and neutral shoe condition ($p = 0.049$) (Table 4.2; Figure 4.1).

	<i>1st Peak KAM (%BW × Ht)</i>	<i>2nd Peak KAM (%BW × Ht)</i>	<i>Knee Flexion Moment (%BW × Ht)</i>	<i>Knee Extension Moment (%BW × Ht)</i>	<i>Knee External Rotation Moment (%BW × Ht)</i>
<i>NS</i>	2.63 ± 0.27	1.98 ± 0.27	2.03 ± 0.28	-2.22 ± 0.31	0.83 ± 0.07
<i>VSS</i>	2.72 ± 0.26	2.03 ± 0.27	2.14 ± 0.26	-2.31 ± 0.32	0.88 ± 0.08
<i>P-Value</i>	0.064	0.200	0.185	0.232	0.036
	<i>Knee Flexion at Heel Strike (°)</i>	<i>Peak Knee Flexion (°)</i>	<i>Knee Flexion at Toe Off (°)</i>	<i>Mean Knee Abduction (°)</i>	<i>Mean Knee External Rotation (°)</i>
<i>NS</i>	2.87 ± 1.27	16.1 ± 1.99	41.3 ± 1.58	4.82 ± 1.18	1.08 ± 1.01
<i>VSS</i>	3.10 ± 1.26	16.5 ± 1.65	40.5 ± 1.38	4.75 ± 1.06	1.27 ± 1.16
<i>P-Value</i>	0.708	0.560	0.048	0.878	0.813

Table 4.2: Mean ± standard error and p-value for primary knee kinematic and kinetic measures of interest in the neutral shoe and variable stiffness shoe.

Secondary Kinematics and Kinetics

Secondary changes in gait mechanics at the hip and ankle were also observed. Hip adduction moment ($p = 0.033$) and hip internal rotation moment ($p = 0.036$) (Table 4.3; Figure 4.2) increased significantly with the VSS compared to the neutral control shoe. While hip kinetics were influenced by the footwear, no effect of VSS on hip rotation or abduction angles was observed (Table 4.3; Figure 4.3). At the ankle, both eversion moment and angle did not differ between the footwear conditions ($p = 0.925$; $p = 0.140$)

(Table 4.3; Figure 4.3). Additionally, there was not a significant difference in medial-lateral center of pressure ($p = 0.062$) with the VSS (Table 4.4; Figure 4.4). First and second peak medial lateral ground reaction force (GRF) and first peak vertical GRF did not differ between footwear (Table 4.4). However, second peak GRF increased significantly with the VSS ($p = 0.001$) (Table 4.4).

	<i>1st Peak Hip Adduction Moment (%BW × Ht)</i>	<i>Hip Internal Rotation Moment (%BW × Ht)</i>	<i>Peak Hip Adduction (°)</i>	<i>Mean Hip External Rotation (°)</i>	<i>Peak Ankle Eversion (°)</i>	<i>Ankle Eversion Moment (%BW × Ht)</i>
<i>NS</i>	5.79 ± 0.26	-0.72 ± 0.09	-11.9 ± 1.05	0.45 ± 1.72	4.42 ± 1.07	-0.92 ± 0.17
<i>VSS</i>	5.95 ± 0.25	-0.77 ± 0.09	-12.1 ± 0.98	0.84 ± 1.87	5.69 ± 0.94	-0.93 ± 0.16
<i>P-Value</i>	0.033	0.021	0.705	0.280	0.140	0.925

Table 4.3: Mean ± standard error and p-value for secondary ankle and hip joint measure of interest in the neutral shoe and variable stiffness shoe.

	<i>1st Peak Medial – Lateral GRF (N)</i>	<i>2nd Peak Medial – Lateral GRF (N)</i>	<i>1st Peak Vertical GRF (N)</i>	<i>2nd Peak Vertical GRF (N)</i>	<i>Mean Medial Lateral Center of Pressure</i>
<i>NS</i>	44.4 ± 3.24	36.1 ± 3.22	754.5 ± 36.71	751.3 ± 32.97	-0.057 ± 0.010
<i>VSS</i>	43.1 ± 3.13	38.5 ± 3.87	764.1 ± 38.82	769.1 ± 34.77	-0.045 ± 0.010
<i>P-Value</i>	0.311	0.118	0.089	0.001	0.062

Table 4.4: Mean ± standard error and p-value for GRF and center of pressure in the neutral shoe and variable stiffness shoe.

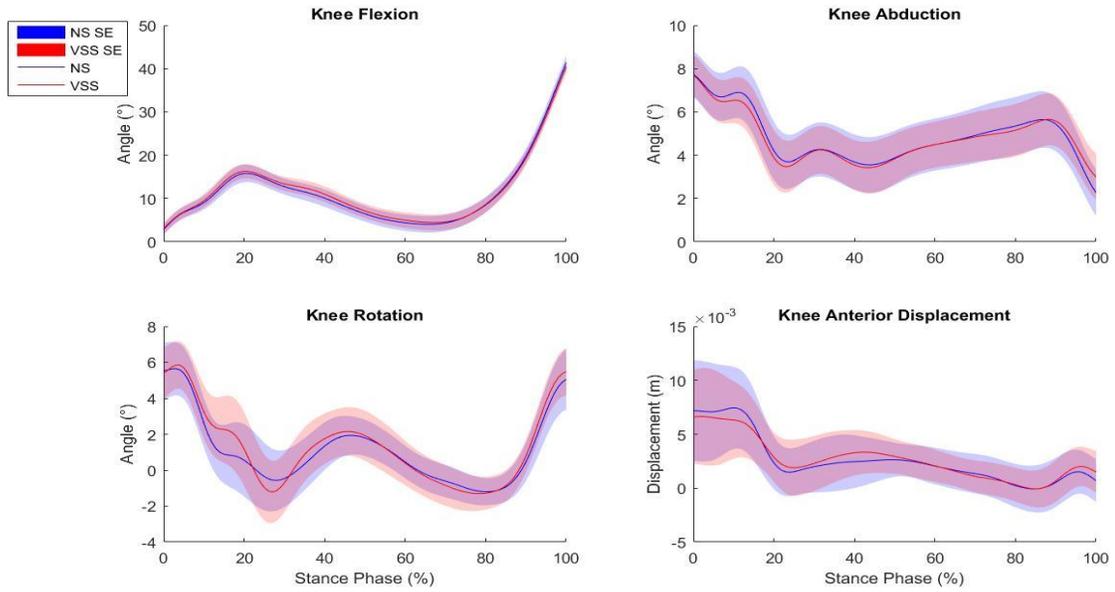


Figure 4.1: Mean and standard error waveforms of knee joint kinematics for the VSS and neutral shoe conditions for all 14 participants.

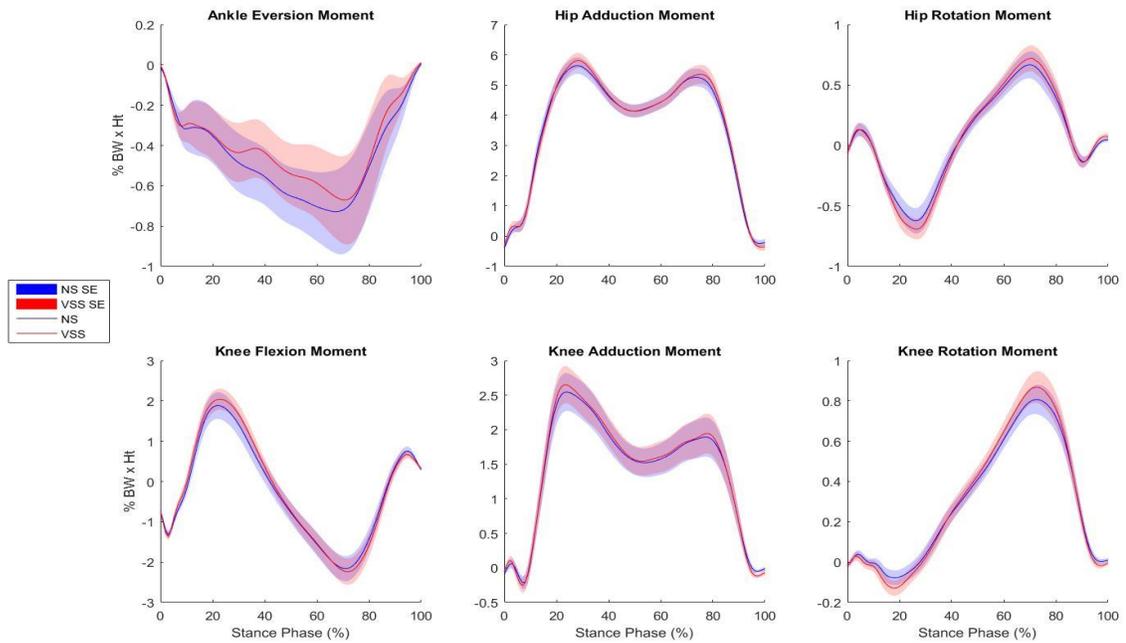


Figure 4.2: Mean and standard error waveforms of ankle, hip and knee joint kinetics for the VSS and neutral shoe conditions for all 14 participants.

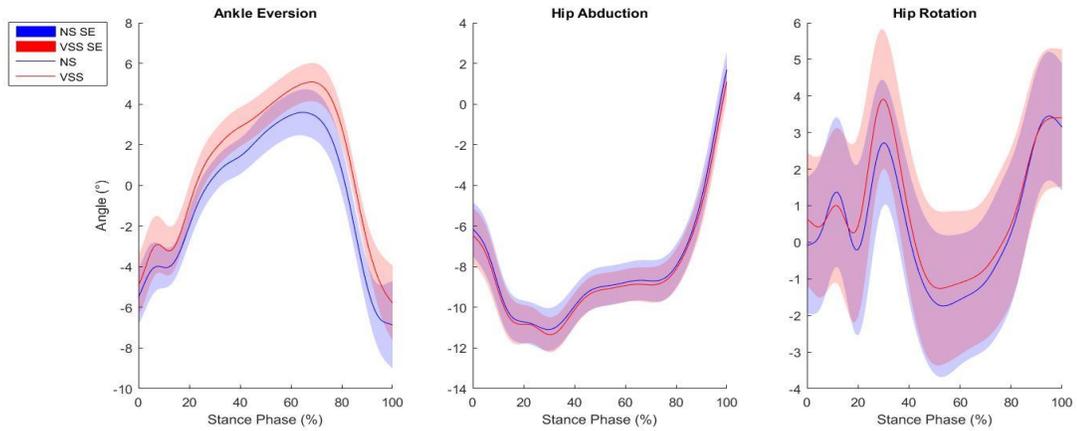


Figure 4.3: Mean and standard error waveforms of ankle eversion, hip abduction, and hip rotation for the VSS and neutral shoe conditions for all 14 participants.

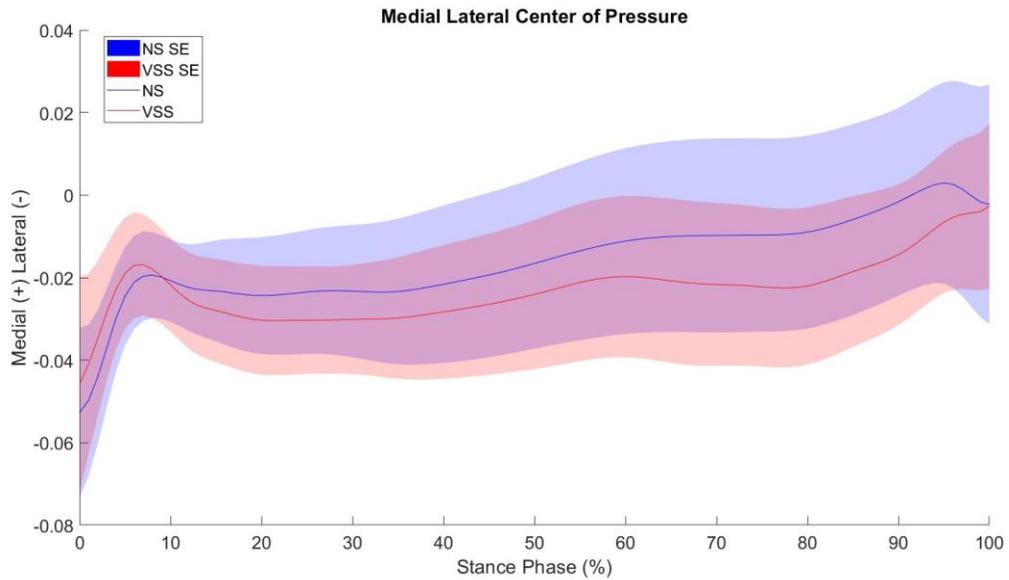


Figure 4.4: Mean and standard error in medial and lateral center of pressure trajectory over anterior-posterior center of pressure for all 14 participants.

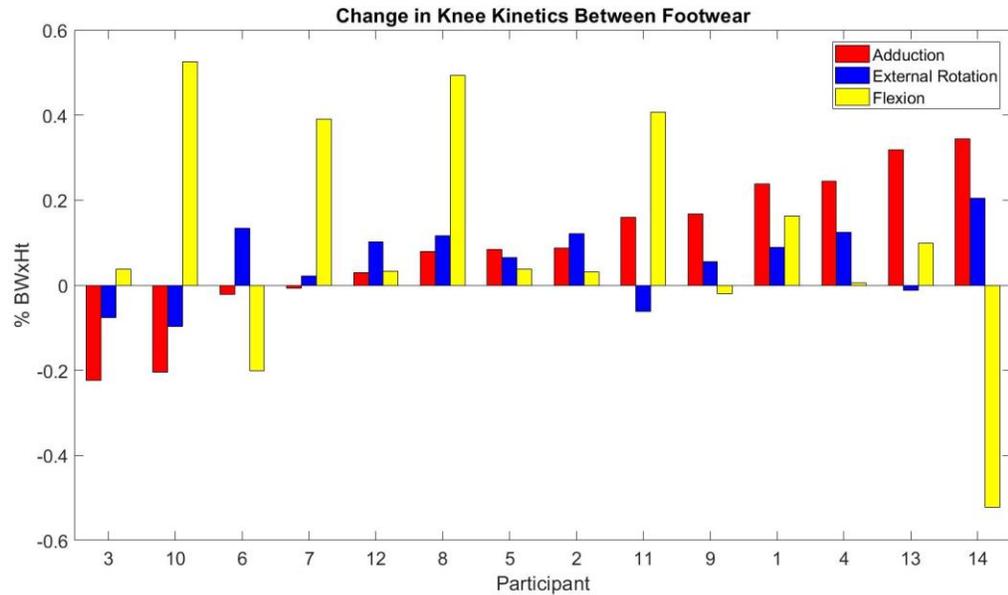


Figure 4.5: Change in external knee joint moments between the VSS and neutral shoe conditions for each participant (VSS – Neutral Shoe). Participants are ordered to match table 4.1.

Aim 2

First Peak

Similar to Aim 1, the musculoskeletal modeling results from Aim 2 of this study varied between participants with no significant differences in 1st peak knee contact forces (CF) or external knee moments between the two footwear conditions (KAM, $p = 0.30$; knee flexion moment, $p = 0.68$; total CF, $p = 0.29$; medial CF, $p = 0.088$; lateral CF, $p = 0.972$) (Table 4.5; Figures 4.6-7). There were no differences in summed muscle moment magnitudes to 1st peak medial and lateral CF ($p = 0.17$, $p = 0.26$) as well as no change in knee flexion angle at 1st peak contact force ($p = 0.12$) (Table 4.5; Figure 4.8). While not statistically significant, medial and lateral summed muscle moment magnitude did increase in a total of five and four participants by greater than 4%, respectively. Because the response to the VSS varied between individuals, participants were grouped based on

their change in KAM into positive responders who had a decrease in KAM (n = 5) and negative responders who had an increase in KAM (n = 5) (Figure 4.10). Participants 7, 11, 1, 2, and 3 and then 2, 14, 13, 5, and 12 were considered positive responders and negative responders, respectively. The splitting participants into groups of positive and negative responders allowed for further comparison between the footwear conditions. Three of the five positive responders experienced decreases in medial CF with VSS compared to the neutral control shoe, while all five negative responders had increased medial CF (Figure 4.9). The estimated summed muscle moment magnitudes increased in both positive responders who experienced increases in medial CF with VSS by 7.5% and 39%.

	<i>1st Peak KAM (%BW × Ht)</i>	<i>Knee Flexion Moment (%BW × Ht)</i>	<i>1st Peak Total CF (BW)</i>	<i>1st Peak Medial CF (BW)</i>	<i>1st Peak Lateral CF (BW)</i>	<i>Peak Knee Flexion (°)</i>	<i>1st Peak Medial Muscle Cont. (N × m)</i>	<i>1st Peak Lateral Muscle Cont. (N × m)</i>
<i>NS</i>	2.52 ± 0.18	3.06 ± 0.41	2.73 ± 0.23	2.27 ± 0.16	0.48 ± 0.07	20.4 ± 2.19	5.67 ± 3.90	4.88 ± 2.06
<i>VSS</i>	2.59 ± 0.19	2.96 ± 0.39	2.80 ± 0.23	2.35 ± 0.16	0.48 ± 0.08	21.1 ± 2.10	6.45 ± 3.90	5.36 ± 2.22
<i>P- Value</i>	0.298	0.681	0.293	0.088	0.972	0.118	0.167	0.261

Table 4.5: Mean ± standard error and p-value for external knee joint moments, knee joint contact force, knee flexion angle, and muscle contribution to joint contact forces during the first peak of knee joint contact force.

Second Peak

There was not a significant difference in 2nd peak KAM (p = 0.49), 2nd peak total CF (p = 0.44), and 2nd peak lateral CF (p = 0.784) between the footwear conditions (Figure 4.6,

4.7, & 4.11; Table 4.6). However, there was a significant increase in 2nd peak medial CF (p = 0.044) as 7 out of 10 participants experienced an increase in medial CF of more than 4% with the VSS compared to the neutral control shoe (Figure 4.6, 4.11; Table 4.6).

When looking at individual participants, 4 participants experienced a decrease in 2nd peak KAM (Figure 4.11). Of those 4, two participants experienced an increase in medial CF of 3% (Figure 4.11). Similar to first peak contact force results, these 2 participants again experienced a large increase in summed muscle moment magnitudes, however there was no significant group difference in medial and lateral summed muscle moment magnitude (p = 0.69 ; 0.38) contact forces (Figure 4.8).

	<i>2nd Peak KAM (%BW × Ht)</i>	<i>2nd Peak Total CF (BW)</i>	<i>2nd Peak Medial CF (BW)</i>	<i>2nd Peak Lateral CF (BW)</i>	<i>2nd Peak Knee Flexion (°)</i>	<i>2nd Peak Medial Muscle Cont. (N × m)</i>	<i>2nd Peak Lateral Muscle Cont. (N × m)</i>
<i>NS</i>	2.05 ± 0.21	2.12 ± 0.22	1.91 ± 0.15	0.33 ± 0.09	18.2 ± 2.04	5.33 ±3.23	4.37 ± 1.99
<i>VSS</i>	2.08 ± 0.22	2.16 ± 0.23	1.96 ± 0.15	0.33 ± 0.09	19.2 ± 2.23	5.65 ± 3.75	4.84 ± 2.06
<i>P-Value</i>	0.487	0.437	0.044	0.748	0.165	0.694	0.382

Table 4.6: Mean ± standard error and p-value KAM, knee joint contact force, knee flexion angle, and muscle contribution to joint contact forces during the first peak of knee joint contact force.

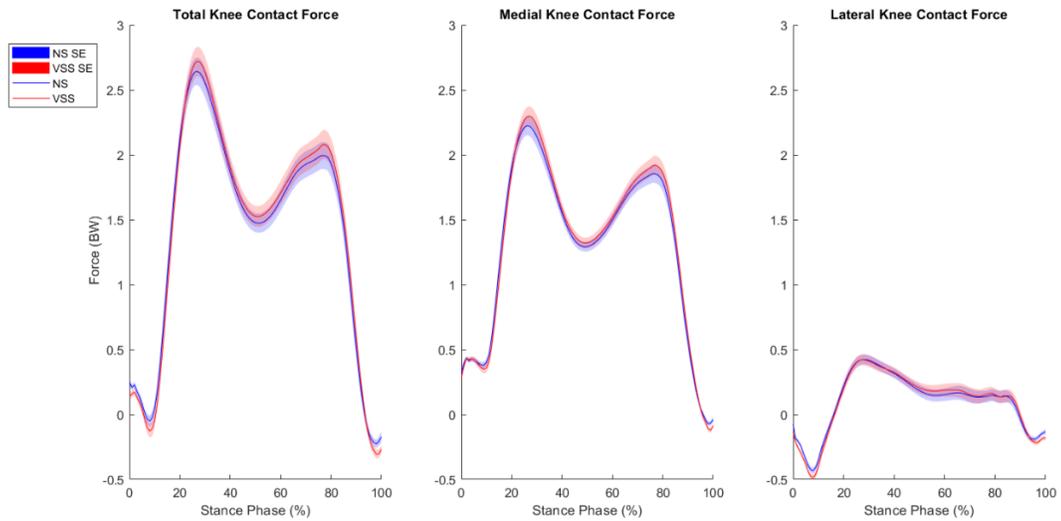


Figure 4.6: Mean and standard error waveforms of knee joint contact forces for the VSS and neutral shoe conditions for 10 participants included in musculoskeletal modeling.

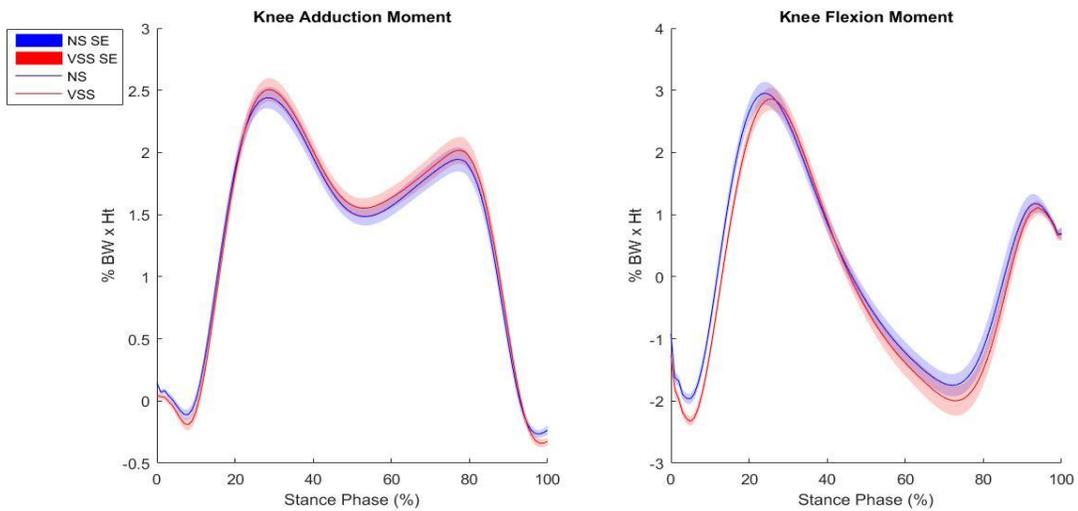


Figure 4.7: Mean and standard error waveforms of knee adduction and flexion moment for 10 participants in the VSS and neutral shoe conditions from the musculoskeletal modeling analyses.

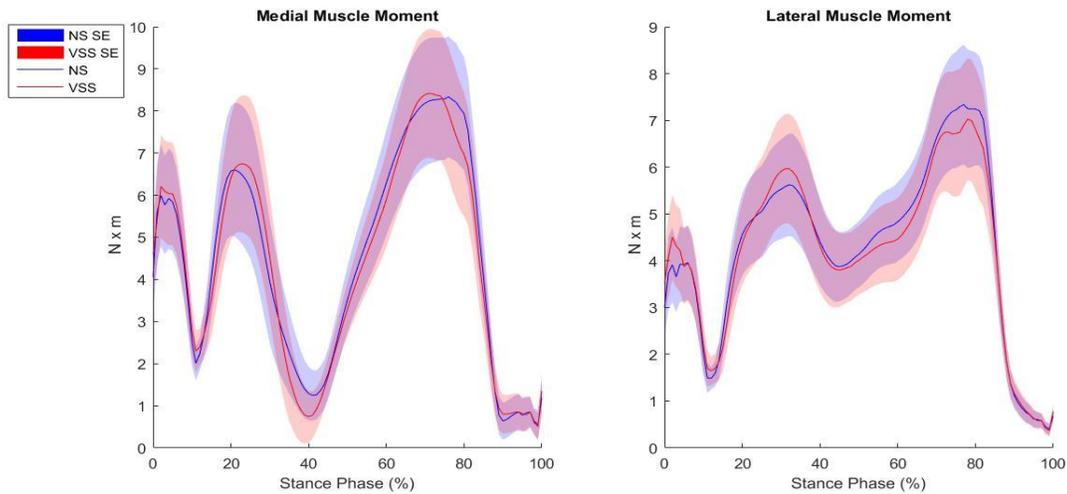


Figure 4.8: Mean and standard error waveforms of summed medial and lateral muscle moment magnitudes for the VSS and neutral shoe conditions. Muscle moments were calculated by summing the product of estimated individual muscle forces and moment arms.

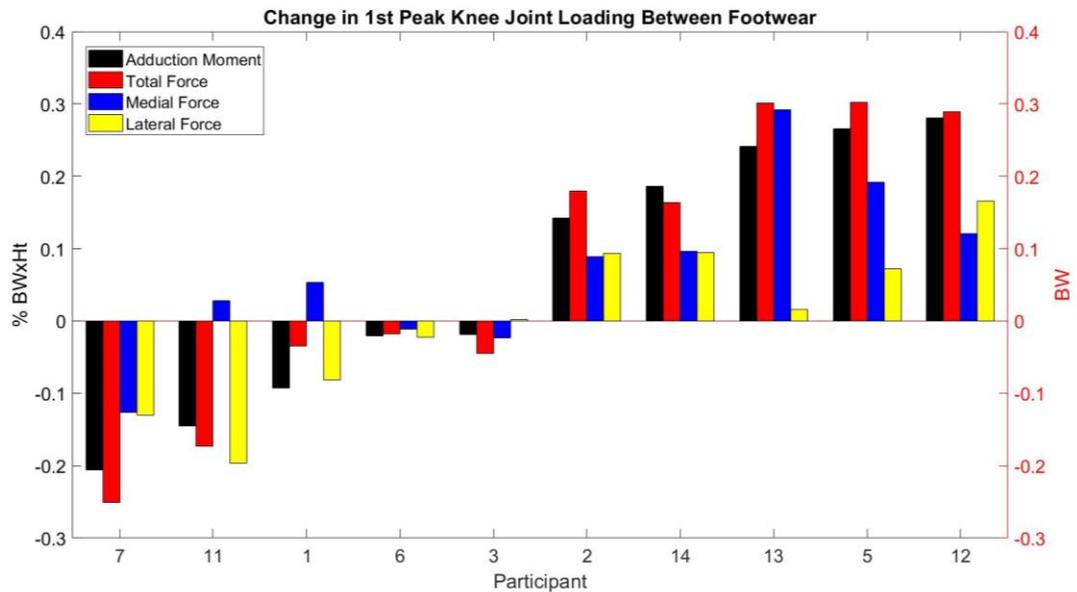


Figure 4.9: Change in first peak knee adduction moment and total, medial, lateral contact forces between the VSS and neutral shoe conditions for each participant. Participants are ordered from minimum to maximum differences between the VSS minus the neutral shoe (VSS – Neutral Shoe).

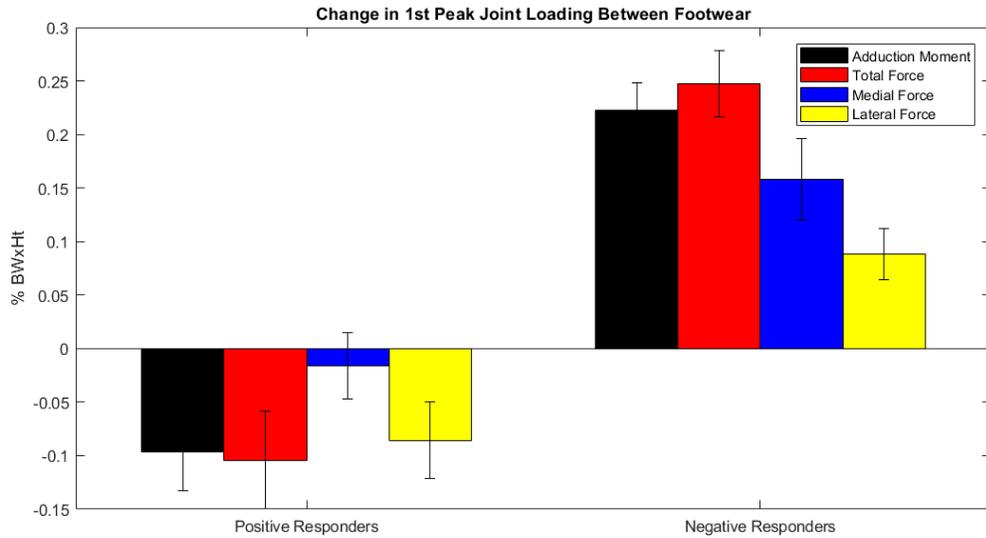


Figure 4.10: To further investigate the impact of footwear on joint loading, participants were divided into positive responders and negative responders groups based on if they had a decrease or increase in KAM. The mean change in first peak knee adduction moment and total, medial, lateral contact forces between the VSS and neutral shoe conditions for positive responders and negative responders (VSS – Neutral Shoe).

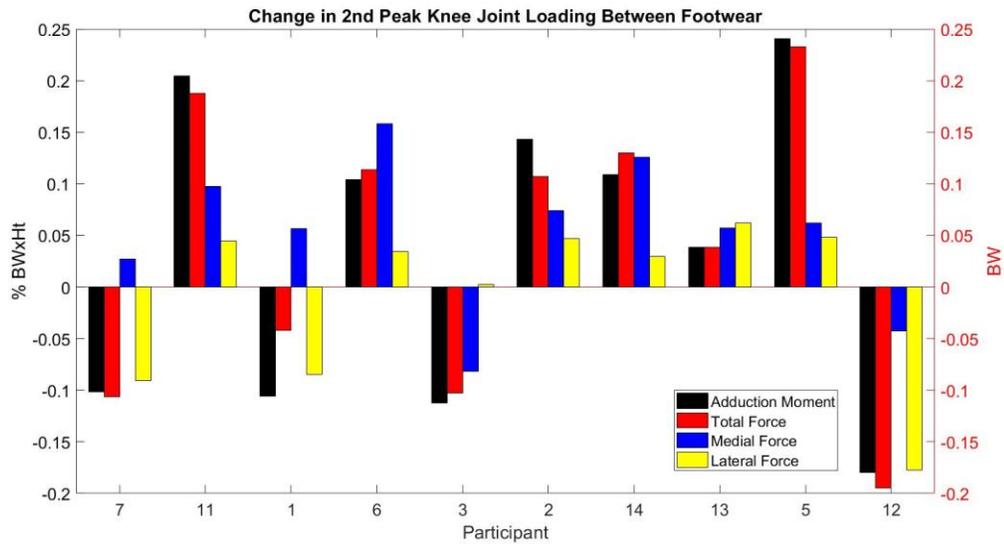


Figure 4.11: Change in second peak knee adduction moment and total, medial, lateral contact forces between the VSS and neutral shoe conditions for each participant (VSS – Neutral Shoe). Participants are ordered in same order as Figure 9 above.

Exploratory Aim

Participant 3 had a small reduction in peak joint contact force of 5% BW with the VSS and subsequently had varied changes in stress, strain, and contact pressure of the menisci (Table 4.7 – 9). Maximum principal and shear stress/strain were reduced in the medial menisci by 0.5 to 3% with the VSS compared to the control shoes. However, the lateral menisci experienced increases in maximum principal and shear strain by 30 and 12%, respectively (Table 4.8, 4.9; Figure 4.13 – 16). Furthermore, although there were small decreases in contact forces for Participant 3 with the VSS, meniscal contact pressure increased for both the medial and lateral contacts between the femoral and tibial cartilages (Table 4.8, 4.9; Figure 4.17, 4.18).

Participant 7 experienced the largest reduction in contact force with the VSS (25% BW) (Table 4.7), and consequently saw reductions in all outcomes of interest. Maximum principal and shear stress of the medial meniscus decreased by 6.3 and 5.5%, respectively with the VSS compared to the neutral control shoe (Table 4.8; Figure 4.14, 4.16). Similar reductions were seen in the lateral meniscus of Participant 7 as maximum principal and shear stress decreased by 5.4 and 6.6% with the VSS (Table 4.7; Figure 4.14, 4.16). Peak contact pressure also decreased in both menisci for Participant 7 while instituting the VSS loading condition (Table 4.8, 4.9; Figure 4.17, 4.18). Opposite to Participant 7, Participant 13 experienced the largest increase in contact force (30%) in VSS compared to the neutral shoe, which induced increases in contact pressure, stress, and strain (Table 4.7 – 9). Maximal principal and shear stress increased by 5.1 and 6.9% in the medial meniscus and by 6.8 and 8.2% in the lateral meniscus for Participant 13 for the VSS loading condition (Table 4.8, 4.9; Figure 4.14, 4.16). Contact pressure also

increased for Participant 13 for the VSS condition, especially within the medial meniscus where contact pressure increased by 2.10 MPa or 55% for the femoral – meniscus contact interaction (Table 4.8, 4.9; Figure 4.17, 4.18).

<i>Participant</i>	<i>NS Knee Flexion Angle (°)</i>	<i>NS Total CF (N)</i>	<i>NS Femoral Displacement (mm)</i>	<i>VSS Knee Flexion Angle (°)</i>	<i>VSS Total CF (N)</i>	<i>Femoral displacement (mm)</i>
3	19	1233	1.435	19	1210	1.425
7	27	2331	1.76	27	2150	1.73
13	7	1848	1.80	9	2093	1.832

Table 4.7: Knee flexion angle, total contact force, and imposed displacement of the femur for all 6 FEA simulations.

<i>Participant - Shoe</i>	<i>Total Def-ormation (mm)</i>	<i>Femoral - Menisci Contact Pressure (MPa)</i>	<i>Tibial – Menisci Contact Pressure (MPa)</i>	<i>Max Principal Strain (%)</i>	<i>Max Shear Strain (%)</i>	<i>Max Principal Stress (MPa)</i>	<i>Max Shear Stress (MPa)</i>
3-NS	1.637	2.86	1.69	4.92	15.5	5.01	3.49
3-VSS	1.635	3.14	1.82	4.82	14.9	4.96	3.47
7-NS	1.69	2.28	2.57	4.46	12.5	4.31	2.37
7-VSS	1.65	2.10	2.03	4.20	10.7	4.04	2.24
13-NS	1.80	3.84	3.22	7.79	15.0	7.81	4.77
13-VSS	1.87	5.94	3.85	7.92	16.5	8.21	5.10

Table 4.8: Peak total deformation, contact pressure, maximum principal stress/strain, and maximum shear stress/strain for the **medial menisci**.

<i>Participant - Shoe</i>	<i>Total Def- ormation (mm)</i>	<i>Femoral – Menisci Contact Pressure (MPa)</i>	<i>Tibial – Menisci Contact Pressure (MPa)</i>	<i>Max Principal Strain (%)</i>	<i>Max Shear Strain (%)</i>	<i>Max Principal Stress (MPa)</i>	<i>Max Shear Stress (MPa)</i>
<i>3-NS</i>	1.30	2.20	2.43	2.46	12.1	2.13	1.47
<i>3-VSS</i>	1.32	2.27	3.11	3.21	13.6	2.12	1.49
<i>7-NS</i>	1.12	2.35	1.74	2.85	12.7	2.80	1.52
<i>7-VSS</i>	1.08	2.24	1.60	2.59	11.8	2.65	1.42
<i>13-NS</i>	1.71	3.18	2.31	6.79	14.0	3.69	2.67
<i>13-VSS</i>	1.78	3.37	2.46	7.33	14.6	3.94	2.89

Table 4.9: Peak total deformation, contact pressure, maximum principal stress/strain, and maximum shear stress/strain for the **lateral menisci**.

Meniscal Deformation

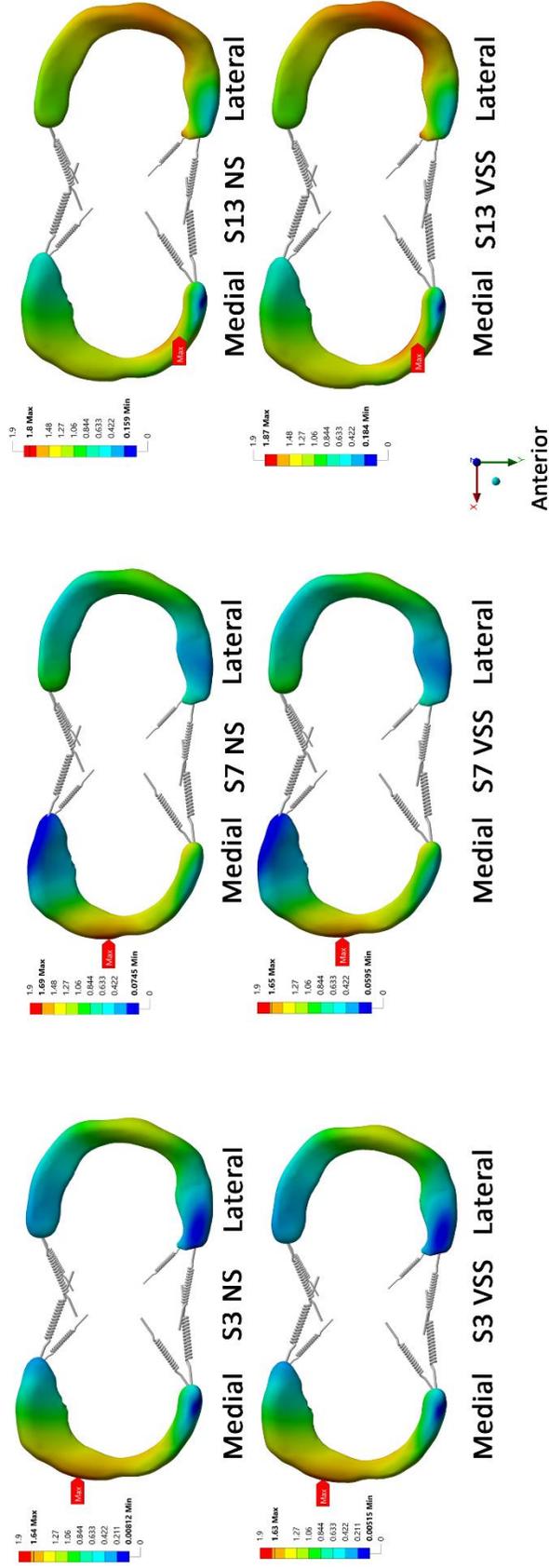


Figure 4.12: Total deformation (mm) of the menisci at peak total contact force for the neutral shoe (NS) and variable stiffness shoe (VSS). Peak deformation location is indicated by red arrow. Participant 3 had little difference in peak deformation between the footwear conditions. Peak deformation decreased for Participant 7 in VSS compared to NS. Participant 13 had an increase in peak total deformation with VSS.

Meniscal Maximum Principal Strain

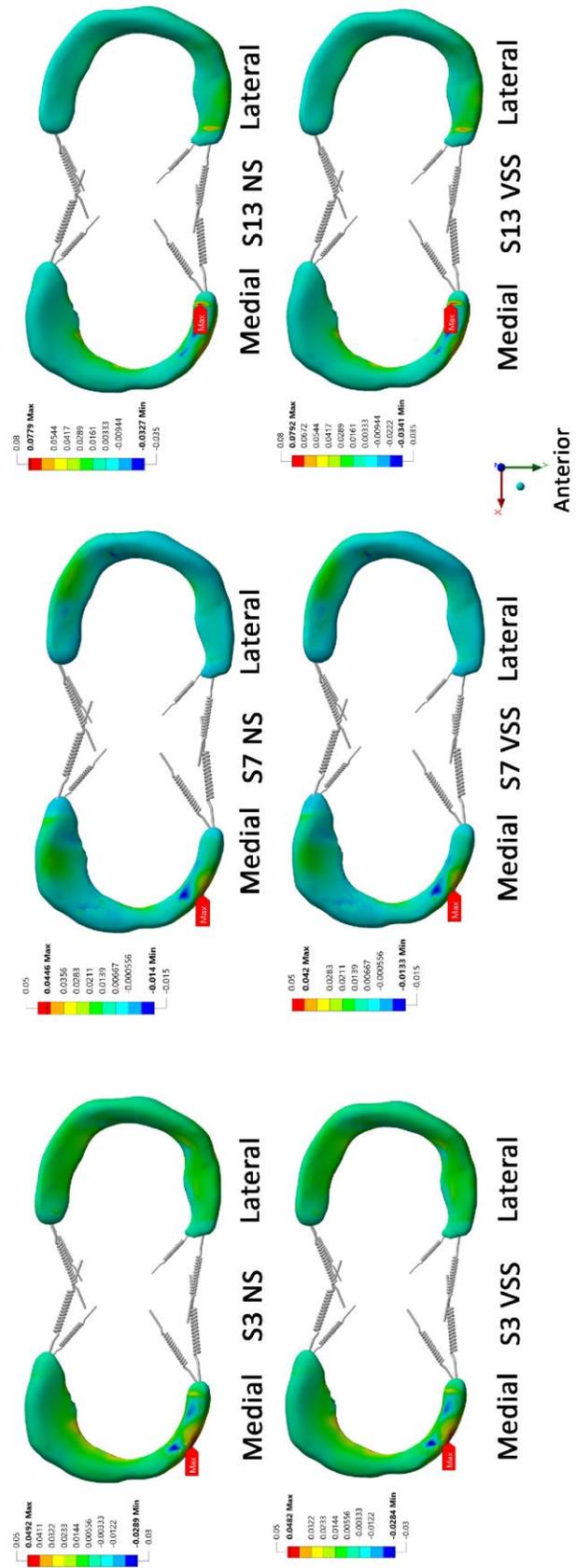


Figure 4.13: Maximum Principal Strain (mm/mm) of the menisci at peak total contact force for the neutral shoe (NS) and variable stiffness shoe (VSS). Peak Maximum Principal Strain location is indicated by red arrow. Participants 3 and 7 had decreases in peak Max Principal Strain in VSS compared to NS. Participant 13 had an increase in peak Max Principal Strain with VSS.

Meniscal Maximum Principal Stress

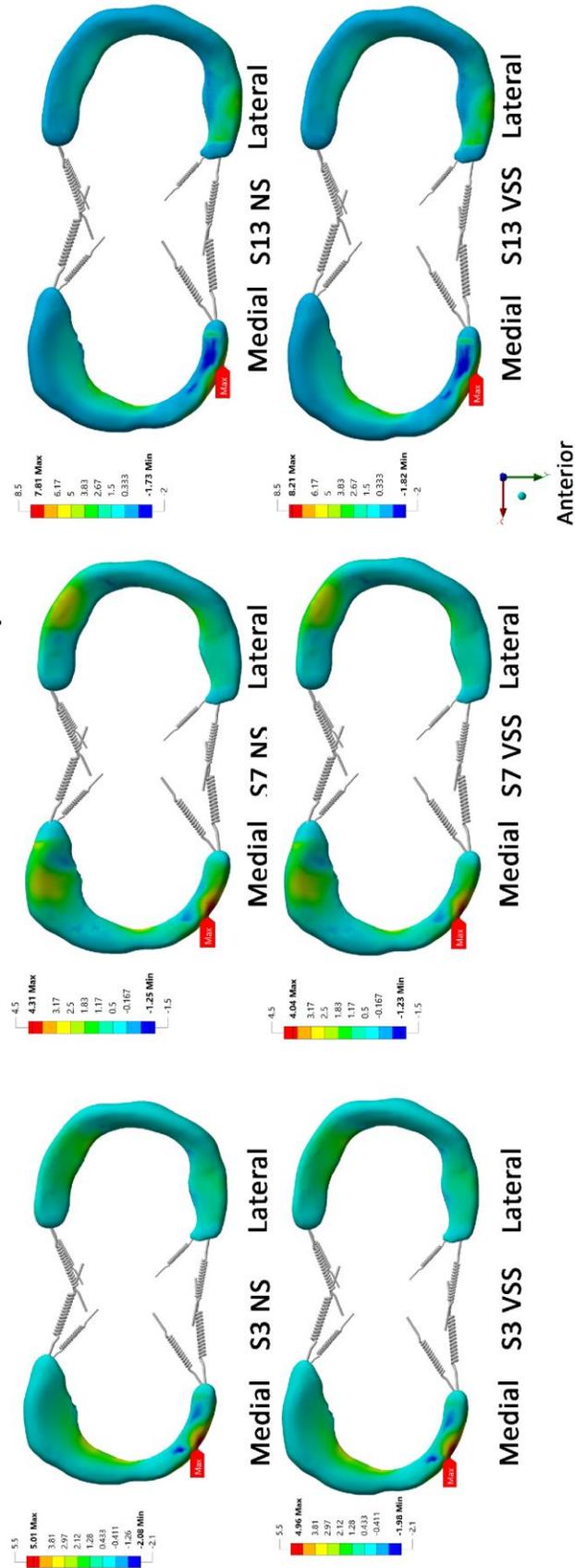


Figure 4.14: Maximum Principal Stress (MPa) of the menisci at peak total contact force for the neutral shoe (NS) and variable stiffness shoe (VSS). Peak Maximum Principal Stress location is indicated by red arrow. Participant 3 had little difference Max Principal Stress between the footwear conditions. Max Principal Stress decreased for Participant 7 in VSS compared to NS. Participant 13 had an increase in peak Max Principal Stress with VSS.

Meniscal Maximum Shear Strain

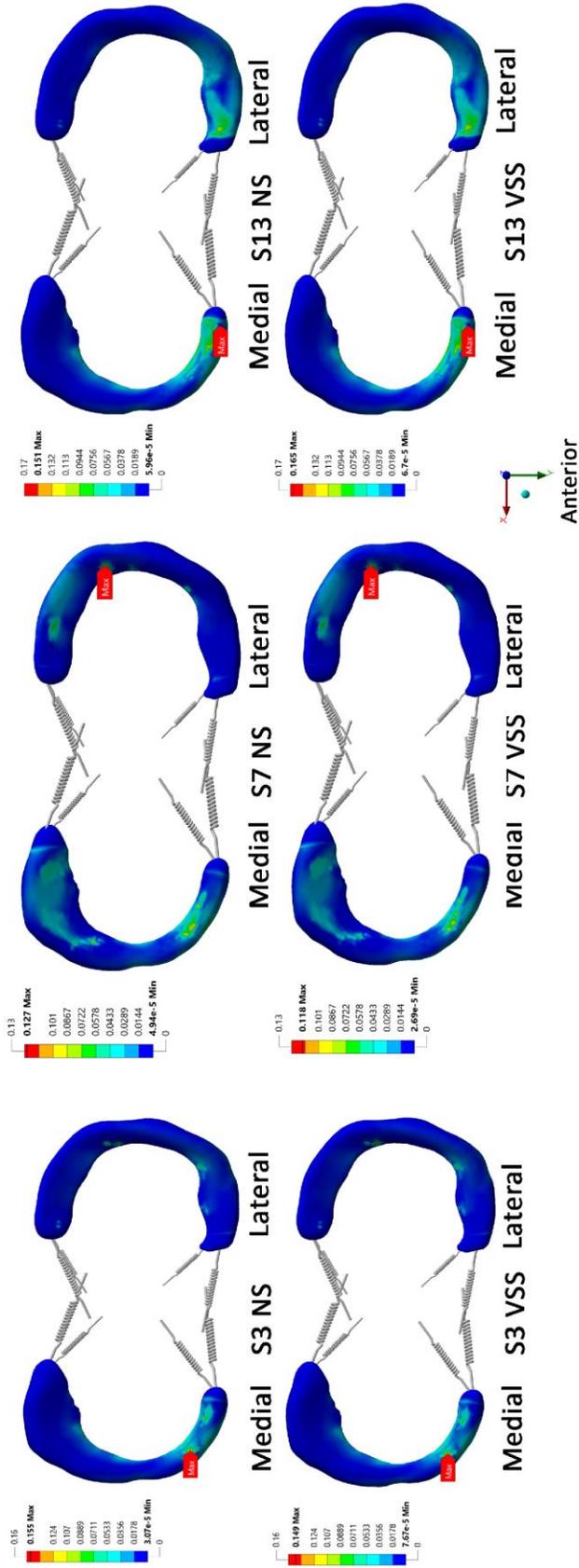


Figure 4.15: Maximum Shear Strain (mm/mm) of the menisci at peak total contact force for the neutral shoe (NS) and variable stiffness shoe (VSS). Peak Maximum Shear Strain location is indicated by red arrow. Participants 3 and 7 had decreases in peak Max Shear Strain in VSS compared to NS. Participant 13 had an increase in peak Max Shear Strain with the VSS.

Meniscal Maximum Shear Stress

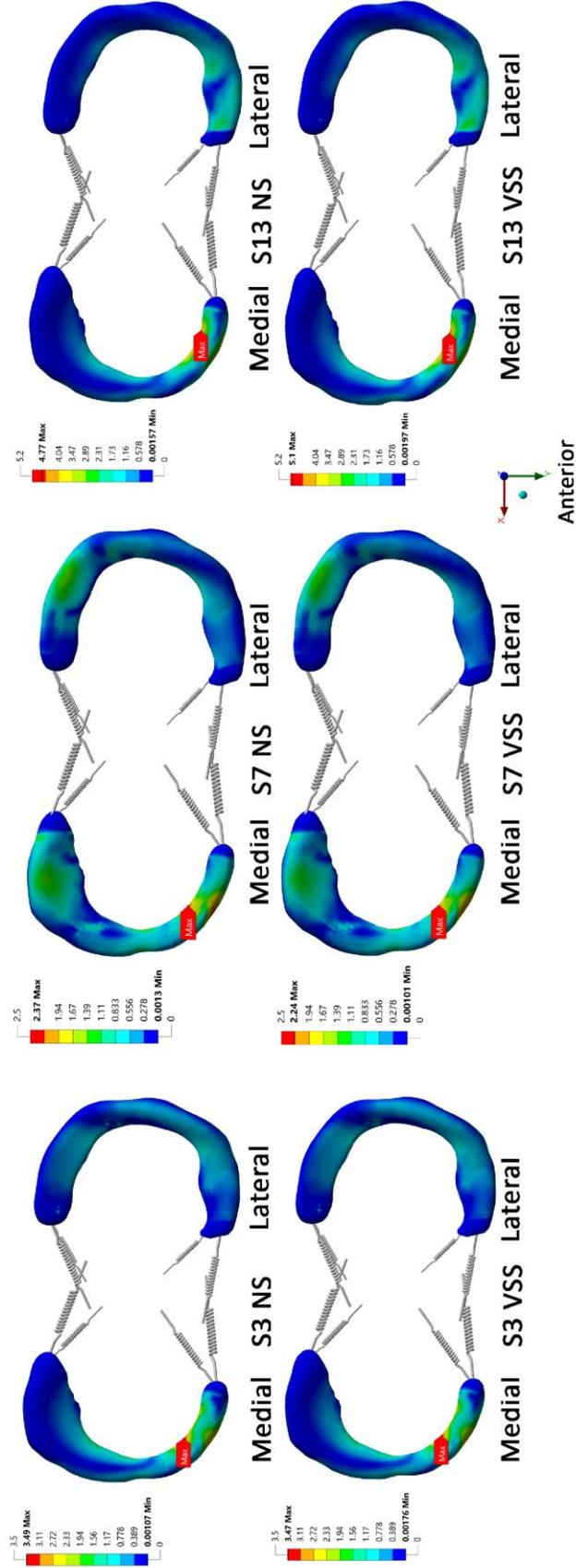


Figure 4.16: Maximum Shear Stress (MPa) of the menisci at peak total contact force for the neutral shoe (NS) and variable stiffness shoe (VSS). Peak Maximum Shear Stress location is indicated by red arrow. Participant 3 little differences between the footwear conditions. Peak Max Shear Strain decreased for Participant 7 in VSS compared to NS. Participant 13 had an increase in peak Max Shear Strain with the VSS.

Menisci - Femoral Cartilage Contact Pressure

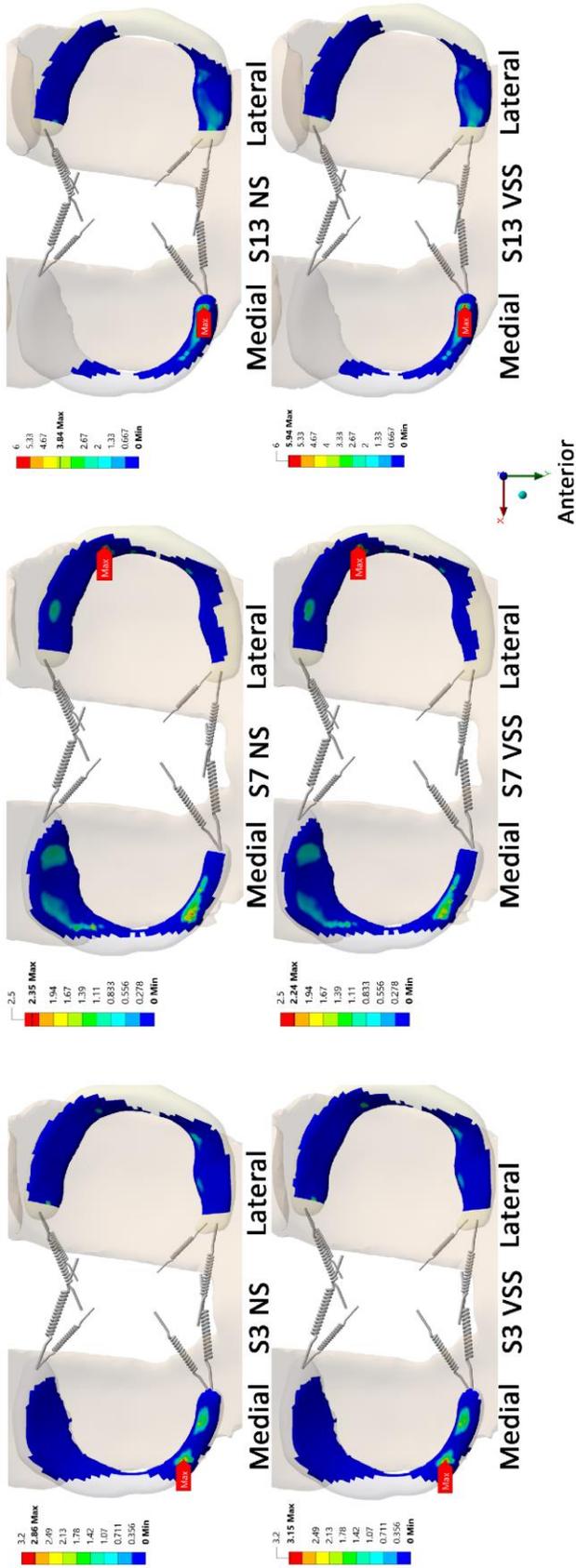


Figure 4.17: Contact pressure (MPa) of the menisci – femoral cartilage contact on the menisci surface at peak total contact force for the neutral shoe (NS) and variable stiffness shoe (VSS). Peak contact pressure decreased for participant 7 with the VSS. Participants 3 and 13 and an increase in peak contact force in VSS compared to NS.

Menisci - Tibial Cartilage Contact Pressure

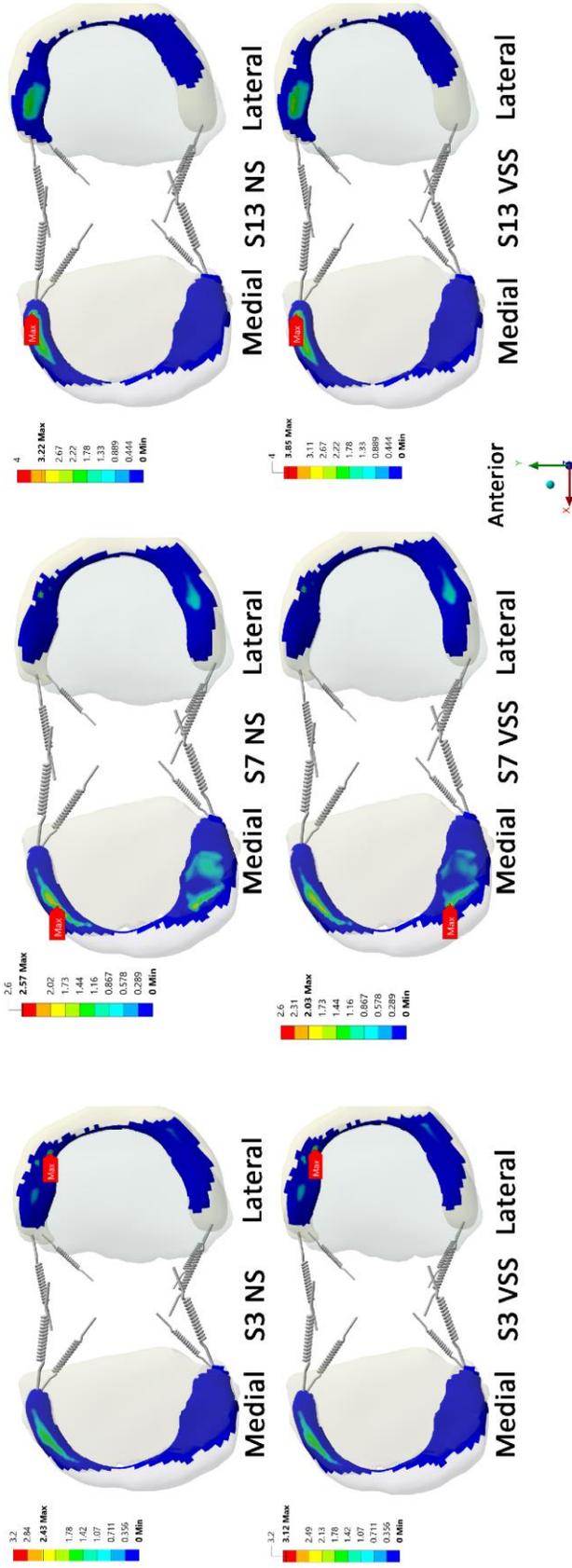


Figure 4.18: Contact pressure (MPa) of the menisci – tibial cartilage contact on the menisci surface at peak total contact force for the neutral shoe (NS) and variable stiffness shoe (VSS). Peak contact pressure decreased and changed from an anterior to a posterior position of the menisci for participant 7 with the VSS. Participants 3 and 13 and an increase in peak contact force in VSS compared to NS.

CHAPTER 5

DISCUSSION

The primary goal of variable stiffness shoes (VSS) is to act as a non-surgical treatment intervention to lower knee osteoarthritis (OA) symptoms and structural progression risk. Therefore, the overall aim of this study was to investigate the impact of VSS on mechanisms for progression of knee OA compared to a neutral control shoe. We quantified the effect of VSS compared to neutral control shoes using three different approaches; gait analysis, musculoskeletal modeling, and finite element modeling. These three approaches allowed us to determine the impact of VSS on general gait mechanics, knee joint contact forces, and menisci mechanics, providing a more comprehensive investigation into the relationship between VSS and the mechanical mechanisms for OA progression. Results from this study suggest individual response in gait mechanics to VSS vary substantially across participants. Furthermore, results indicate using only knee adduction moment (KAM) as a measurement for determining how VSS impacts joint loading and thus may alter knee OA progression may be inadequate. However, for participants who did have large reductions in joint moments and contact forces, VSS may reduce stress and strain placed on tissues within the joint, such as the meniscus, which could positively impact radiographic and symptomatic OA progression risk.

Aim 1

The first aim of this study was to quantify the impact of VSS on 3D lower extremity joint mechanics in OA patients. VSS are designed to decrease KAM and medial compartment loading, in an attempt to lower risk of structural and symptomatic

OA progression. We hypothesized that the KAM would decrease with the VSS compared to the neutral control shoe. However, in contrast to our first hypothesis and the literature, this study found there was not a significant decrease in the KAM for participants wearing VSS as compared to neutral control shoes. The first peak KAM increased on average by 4.6% for participant when wearing VSS compared to the neutral control shoe. These results are in contrast to the literature, which has found VSS can significantly reduce KAM by 6 – 8% (Bennell et al., 2013; Erhart-Hledik et al., 2012; Erhart et al., 2008). However, we found there was large variation in the response to the VSS and participant's change in KAM ranged from an 11% reduction to a 19% increase as compared to the control shoes (Figure 4.5). This variation in response to the footwear is supported in part by the literature. However, it has been typically shown that 15 – 20 % of participants experience an increase in KAM with VSS, while 57 % of our participants had an increase greater than $0.07 \% BW \times Ht$ with the VSS (Figure 4.5) (Bennell et al., 2013; Erhart-Hledik et al., 2012; Erhart et al., 2008; Fisher et al., 2007). Furthermore, only 28% (4 out 14) of the participants in this study had the expected reduction in KAM with the VSS.

The literature has previously found the mechanisms of action for VSS to alter gait mechanics and reduce KAM are through changes to medial-lateral ground reaction forces (GRF), center of pressure (COP), and lower extremity kinematics (Boyer, K. A. et al., 2012; Jenkyn et al., 2011). The increased lateral stiffness of the VSS is thought to lead to a medial shift in COP line of action and a reduction in medial GRF magnitude, which effectively lowers KAM by reducing the frontal plane lever arm at the knee joint (Boyer, K. A. et al., 2012; Jenkyn et al., 2011). These changes in COP and GRF are thought to

arise through an adaptive dynamic response characterized by increasing ankle eversion and knee abduction angles during gait (Boyer, K. A. et al., 2012). However, in the present study no such changes in COP, GRF, or ankle and knee kinematics were found. The lack of an adoption of an “adaptive dynamic response” or medial-lateral shift in COP or GRF may be an explanation for the lack of a reduction in KAM found in this study.

It was also hypothesized that the knee external rotation moment would increase while knee flexion moment would not change in VSS compared to the neutral control. Knee external rotation and flexion moments have not been previously reported by other studies that have investigated VSS (Bennell et al., 2013; Erhart-Hledik et al., 2012; Erhart et al., 2008; Erhart et al., 2010; Fisher et al., 2007). However, these outcomes are important to consider as external rotation and flexion moments both contribute to the knee joint contact force (Walter et al., 2010). We found a significant increase in external rotation moment, but opposed to our hypothesis it was coupled with KAM such that individuals who increased knee external rotation moment also increased their KAM with the VSS (Figure 4.5). This coupling is supported by a correlation between external rotation moment and KAM of $r = 0.64$. The rationale for the lack of an effect on the knee flexion moments is based on the prior findings of a minimal impact of the VSS on sagittal plane joint kinematics, which was also observed in our study (Table 4.2). In agreement with our hypothesis there was not a significant change in the knee flexion moment with the VSS. However, while we did not find a significant change in the knee flexion moment with the VSS, when looking at the individual responses to the footwear, it becomes evident that some participants do experience drastic changes in knee flexion moment with the VSS (Figure 4.5). The combination of a varied response in knee flexion

moment, a significant increase in external rotation moment, and a lack of reduction in KAM suggests for individuals tested for this study had an overall negative effect of VSS on knee joint loading. The negative effect of VSS on knee joint loading observed may explain previous findings showing there is little evidence footwear can positively impact risk of OA progression (Parkes et al., 2013).

The present study investigated differences in ankle and hip joint kinetics between the footwear conditions to gain a more complete understanding of how the VSS impacts an OA patient's overall gait. Changes in COP and GRF with VSS are expected to impact other lower extremity joints, as the literature has previously found increases in ankle eversion moment and a decrease in hip adduction moment with VSS (Erhart et al., 2008). However, in contrast to our second hypothesis, we did not find differences in ankle eversion moment between the footwear conditions, while hip adduction moment increased with the VSS. Given the large percentage of the participants that experienced an increase in the KAM with the VSS these findings are not unexpected. Furthermore, participants increased hip internal rotation moment with the VSS, which has not been previously shown within the literature. The increases in hip joint kinetics may be detrimental to individuals who suffer from both hip and knee osteoarthritis (OA) and may need further evaluation in future studies of VSS.

The discrepancies between what has been previously shown in the literature and our results may be attributed to multiple factors including the material properties of our neutral and VSS compared to that used in literature. The difference in medial-lateral stiffness for the VSS used in this study was very subtle. Results from mechanical impact testing indicated the VSS were 1.1 times stiffer on the lateral side (Table 3.1). The

literature has previously used VSS that had a lateral side that was 1.5 times stiffer (Erhart et al., 2008; Fisher et al., 2007). Furthermore, the longitudinal stiffness of the VSS was much greater compared to that of the neutral control shoe. These differences in material properties may have influenced gait results and lead to the larger variation in participant's response to the footwear in our work as compared to the literature. However as previously stated, variation in participant's response to VSS and footwear interventions in general (i.e. lateral wedges) is well documented, and has been considered a factor contributing to the lack of evidence that footwear interventions can make an impact on symptomatic progression of OA in the long term (Bennell, Bowles, Payne et al., 2011; Bennell et al., 2013; Erhart-Hledik et al., 2012; Parkes et al., 2013). The present study is limited to the number of participants evaluated as compared to the literature and does not have the scope to probe the question as to why this group of participants as a whole did not experience the expected response in KAM to VSS.

Overall, the results from this study may provide insight into factors contributing to the current limitations of VSS to make a positive impact on OA progression. The observation of variance in individual's response to VSS in the literature was also shown in this study, including in planes of motion outside of the previously reported frontal plane. With the high variance in response to the footwear, it is unclear if VSS have the capacity to consistently induce a reduction in knee joint contact forces and effectively impact OA progression risk. This lack of clarity is further exacerbated by the variation in participant's response to VSS outside of the frontal plane of the knee (Figure 4.5). Changes in the sagittal and transverse plane knee moments with the VSS, even with reductions in KAM, may lead to increases in joint forces. For example, Participants 3

and 10 experienced decreases in KAM but increases in knee flexion moment, and Participants 6 and 7 had slight decreases in KAM but increases in external rotation moment (Figure 4.5). Thus, moments outside the frontal plane should be considered when investigating the ability of footwear interventions to impact OA progression in future clinical trials.

Aim 2

The second aim of this thesis was to estimate the impact of VSS on medial compartment tibiofemoral contact forces in OA patients. For Aim 2, we used musculoskeletal modeling to estimate participants' joint contact forces while wearing neutral control shoes and VSS. Previously, joint contact forces while wearing VSS have only been measured in one study within the literature in a single participant with an instrumented knee replacement (Erhart et al., 2010). We hypothesized medial contact forces would decrease while participants wore VSS compared to a neutral control shoe; however, there was not a significant difference in estimated first peak medial contact force between the footwear conditions, and there was an increase in 2nd peak medial contact force with VSS (Figure 4.6). These are in contrast to the findings from Erhart et al. where they found measured medial contact force was reduced with VSS compared to a personal shoe for their single participant with an instrumented knee replacement (Erhart et al., 2010). However, the participant in Erhart's study had a reduced KAM as well as total knee joint contact force with VSS, neither of which were observed in the present study (Figures 4.6, 4.7). The overall lack in agreement between the findings of Erhart et al., and this study may be attributed to the increased external rotation moment and large variance in knee

flexion moment in VSS shown in our Aim 1 results. Increases in rotation moment or knee flexion moments may have contributed to the lack of a reduction in joint contact forces in VSS compared to the neutral control shoes for many individuals.

As the VSS is hypothesized to reduce the medial joint contact force via a reduction in the KAM and due to the variance in the KAM change in our population, participants were split into two sub groups, positive responders (n = 5) and negative responders (n = 5) (Figure 4.10). Participants were determined to be positive responders if they experienced a decrease in 1st peak KAM with the VSS (Figure 4.9). The splitting of the participants into two sub groups allowed for a more in depth analysis to look at individual's responses to the footwear and the relationship between changes in KAM and joint contact forces. Of the five positive responders with decreased 1st peak KAM, three experienced decreases in medial contact force and all five had reductions in lateral contact force (Figure 4.9). Thus, despite a decrease in 1st peak KAM, two participants (11 and 1) had increased 1st peak medial contact force in the VSS compared to the control shoe (Figure 4.9). A previous study by Walter et al. found similar results, where a decrease in KAM did not always result in a decrease in medial contact force. The observed differences between our two participants' responses in KAM and medial contact force due to the VSS are attributed to an increase in summed medial muscle moment magnitudes by 7.5% and 39%, respectively. Furthermore, Participant 11 and 1 both had a greater knee flexion moment in VSS compared to the control shoes from Aim 1. Participant 1 also had an increase in knee external rotation moment in Aim 1. In the second half of the stance phase, there was also two participants (7 and again 1) that experienced a decrease in 2nd peak KAM but increased medial contact force (Figure

4.11). They similarly had increases in summed medial muscle moment magnitude by 32% and 41%, respectively. The increases in muscle force and subsequent summed muscle moment magnitude to contact forces may have been a result of slight increases in vertical ground reaction forces and sagittal plane moments. As VSS are designed to reduce KAM (a measure of the distribution of load between compartments) and reduce loading within the medial compartment of the knee joint, the inconsistencies between changes in KAM and medial contact forces with the footwear are important to consider when examining the efficacy of VSS. The variations in changes to estimated medial contact forces with VSS may be a possible explanation for the varied response in participant reported changes in pain due to footwear (Erhart-Hledik et al., 2012; Erhart et al., 2010; Parkes et al., 2013).

As with any modeling study, the parameter selection and assumptions made can have a large impact on model accuracy and ultimate estimation of measures of interest. Of the five positive responders from Aim 2 who experienced a reduction in 1st peak KAM, three of them also saw a reduction in 1st peak KAM in Aim 1 when the anatomical and cluster coordinate system were defined using the PCT method. For the 10 participants modeled in OpenSim for Aim 2, the knee is modeled as a single hinge joint with translation in the sagittal plane being dependent on the knee flexion angle. However, for the 14 participants modeled in visual 3D for Aim 1, the knee was modeled as a 6 degree of freedom joint (Andriacchi, T. P. et al., 1998). The literature has previously found differences between knee degrees of freedom models impact estimations of KAM and knee joint contact forces (Walter & Pandy, 2017), and this may

be the cause of differences in KAM magnitudes from Aim 1 and Aim 2 (Table 4.2 and 4.4).

The modeling assumptions may have also had an impact on estimations of knee joint contact forces. The total, medial and lateral contact force estimations are within the physiological range that have been previously reported within the literature (DeMers et al., 2014a; Lerner et al., 2014; Lerner et al., 2015; Saxby et al., 2016; Smith et al., 2019; Steele et al., 2012). The combining of multiple methods used within the literature to improve contact force estimations by this study should be noted. A weighting constant was added to each muscle during static optimization. These weighting constants have been previously shown to lead to good agreement between estimated and measured contact forces (Smith et al., 2019; Steele et al., 2012). The weightings used in this study followed those described by Smith et al. and induced a heavy reliance on the hip muscles and soleus to produce most of the force production, which led to less activation particularly of the quadriceps and gastrocnemii. The bi-articulating muscles crossing the knee joint like the rectus femoris and gastrocnemii are of certain importance as their activation levels have been shown to impact joint contact forces greatly (DeMers et al., 2014a). The shifting in muscle reliance to the hip muscles and soleus brought about relatively low summed muscle contribution to estimated contact forces (between 20 to 30% contact force). The summed muscle contribution to joint contact force is the percentage that the summed muscle moment magnitudes ($M_{mus,Med}$) are to the moments produced by the joint contact forces ($d * F_{Lat}$), *Example: Lat Muscle Contribution =*
$$\frac{M_{mus,Med}}{d * F_{Lat}} * 100$$
 (Figure 3.4). A low summed muscle contribution to joint contact force signifies that the contact force is primarily due to external forces (i.e. the external KAM),

and a high summed muscle contribution indicates the muscle are primarily contributing to the estimated contact force. The percent summed muscle contributions to joint contact forces of 20-30% observed in this study are considerably lower than those previously shown within the literature, which are reported to be about 50% (Saxby et al., 2016; Winby et al., 2009). With the relatively low muscle contribution to joint contact forces, the lateral contact force was unloaded (when the contact force is negative) in the beginning and end of the stance phase (Figure 4.6). Some previous studies have estimated unloading of the lateral contact point (Hurwitz, Sumner, Andriacchi, & Sugar, 1998; Shelburne, Torry, & Pandy, 2006), but other modeling studies estimates and experimentally measured contact forces have found no such results (Erhart et al., 2010; Kutzner et al., 2013; Saxby et al., 2016; Winby et al., 2009).

This studies' findings of a low percentage of summed muscle contribution to joint contact forces and an unloading of the lateral compartment are possibly due to the muscle weights chosen and the method in which contact forces were estimated. Contact forces were estimated using a knee model described by Winby et al., where contact points were appointed within the tibiofemoral joint and contact forces were solved for by summing the net moment about each contact point (Figures 4.3). The net moments were comprised of external knee moments, internal muscle generated moments, and moments generated by the contact forces. This method was chosen as it allows for estimation of both medial and lateral contact forces, which is currently not possible using the OpenSim joint reaction analysis tool. A study by Sritharan et al., found that muscles that do not span the knee joint contribute to the knee adduction moment and tibiofemoral compartment loading (Sritharan, Lin, & Pandy, 2012). Importantly, they found that knee-spanning

muscle appeared to compress both compartment of the tibiofemoral joint, while non-knee spanning muscles tended to compress the medial compartment and unload the lateral compartment. As our muscle weights focused muscle activation to non-knee spanning muscles, this is a possible explanation for the observed unloading of the lateral compartment of the knee joint. Furthermore, this provides another possible reason for why two participants discussed above experienced a decrease in KAM but had an increase in medial contact force. The reliance of non-knee spanning muscles likely increased medial compartment loading past the reduction in KAM but still allowed for the observed decrease in lateral contact force. As Saxby and Winby both used EMG driven models to estimate force production, their medial and lateral contact estimates saw no unloading of the lateral compartments due to greater contributions of the gastrocnemii, hamstrings, and quadriceps (Saxby et al., 2016; Winby et al., 2009). In the future, the inclusion of an EMG driven model to estimate muscle force production may alter or improve estimated results from this study.

In summary, the results from this study may provide insight into how KAM may not adequately capture the entire impact of VSS at the whole knee joint level. Participants overall had varied responses to the VSS with five participants decreasing and five increasing KAM in the footwear. However, reductions in KAM with VSS did not always translate to reductions in medial contact forces. Decisions made while performing the musculoskeletal modelling for this study likely had a slight impact on the results; however, previous studies have found similar findings in disagreement between reduced KAM and medial contact forces (Walter et al., 2010). Nevertheless, the ineffectiveness of VSS to consistently reduce medial contact forces with KAM would

impact the efficacy of the footwear to lower OA progression risk. This may be a factor contributing to the lack of evidence within the literature that VSS and load modifying footwear in general can have a significant effect on structural or symptomatic progression of OA (Bennell et al., 2013; Erhart-Hledik et al., 2012; Parkes et al., 2013).

Exploratory Aim

The exploratory aim of this thesis was to use finite element (FE) analysis to develop a model of the tibiofemoral joint in order to evaluate the impact the VSS may have on knee tissue stress and strain. Knee joint contact forces calculated in Aim 2 were used as inputs into the FE simulation to allow for estimation of meniscal stress and strain at the time of the 1st peak contact force in the VSS and neutral shoe conditions for three different participants, for a total of six simulations. Combining the musculoskeletal modeling results from Aim 2 with FE modeling provided an innovative way to investigate the effect VSS may have on tissues within the knee joint. For each of the 6 FE simulation performed, the femur and femoral cartilage were manipulated to the corresponding knee flexion angle at the time of the 1st peak contact force for the loading condition, while the tibia was fixed to allow no rigid-body motion. The femur was then compressed into the menisci and cartilage by instituting a displacement that resulted in a reaction force within the FE model joint equal to the 1st peak total contact force calculated from Aim 2 musculoskeletal modeling. First peak contact force was chosen as the static loading instant in time of interest due to 1st peak KAM being strongly related to OA structural progression (Andriacchi, Thomas P. et al., 2004; Miyazaki et al., 2002).

Results from the six FE simulations were generally in good agreement with the literature. Peak contact pressure of 2.20 to 5.94 MPa for the medial meniscus and 1.60 to 3.85 MPa for the lateral meniscus were observed during the different loading conditions (Table 4.8, 4.9). These values are within the range of previously reported peak contact pressures from the literature (Lee et al., 2006; Pena et al., 2006; Zielinska & Donahue, 2006). Contact pressures between the femoral cartilage and menisci were generally greater than contact pressure between the menisci and tibia (Table 4.8, 4.9). Meniscal max principal stress and strain were similar to that previously reported from the literature (Guess et al., 2010; Mononen et al., 2013; Mononen, Jurvelin, & Korhonen, 2015; Netravali et al., 2011). Peak contact pressure of the medial and lateral cartilage ranged from 7 to 20 MPa, which also has been previously found within the literature (Adouni et al., 2012; Adouni & Shirazi-Adl, 2014; Halonen et al., 2017; Kłodowski et al., 2016a).

Footwear appeared to have a small to moderate effect on menisci mechanics. Participant 3 had a small decrease in joint contact forces with the VSS, and accordingly had small changes in maximum principal and shear stress for both the medial and lateral menisci ranging from -0.99% to +1.36% . However, Participant 3 did have relatively large increases in medial and lateral contact pressure (7.7% – 28.0%) with the VSS. This change in contact pressure may be attributed to smaller contact area in the VSS model for Participant 3. Therefore, while small decreases in 1st peak contact force for Participant 3 were observed, the small and varied response on the menisci stress and contact pressure would suggest the VSS would not have a beneficial effect on OA progression risk for this single participant. Conversely, the VSS for Participant 7 may be beneficial to slow OA progression. Contact pressure, maximum principal stress/strain, and maximum shear

stress/strain all decreased by greater than 3.6% during the VSS loading condition for Participant 7. These reductions in tissue stress were brought on by a $\approx 180\text{N}$ decrease in joint contact force in the VSS for Participant 7 (6 X greater reduction than that of participant 3). In contrast, Participant 13 had a 245N increase in joint contact force resulting in an increase in contact pressure, maximum principal stress, and maximum shear stress/strain by greater than 4.3%. These results suggest that the magnitude of change in joint contact force between the VSS and neutral shoe conditions plays a significant role in the level of change in tissue stress within the joint. Currently, only one other study has looked at the effect of different footwear loading conditions on tissues within the knee joint (Halonen et al., 2017). While they focused on changes to the tibial cartilages, they similarly found large changes in joint loading can influence contact pressure by several MPa (Halonen et al., 2017). Our results, along with Halonen et al. indicate that large changes in joint loading due to footwear has the ability to impact tissue mechanics within the joint. These changes in tissue stress and strain may influence OA progression risk over prolonged exposure to the footwear.

Select modeling assumption and decision were made to improve simulation time and improve results but may be considered as limitations of the current study. Specifically, one limitation may be the use of orthotropic meniscus and linear elastic cartilage material properties that were used for this thesis. Attempts to institute a hyperelastic cartilage properties were made. However, obtaining a solution that converged was particularly difficult and resulted in unrealistic cartilage deformation. For the scope of this thesis project, the chosen material properties for both the meniscus and cartilage are adequate and resulted in simulation results that are consistent to what has

been previously found within the literature. However, since participants were OA patients with degraded and damaged cartilage, inclusion of a viscoelastic fibril-reinforced osteoarthritic cartilage material model in the future may improve on the current work (Mononen et al., 2015; Mononen et al., 2016).

Another limitation of the current study was the use of only 3 different participants. However, the 3 participants chosen provide a good representation of how participants generally respond to VSS. Participant 3, whose knee geometry was selected for the FE model development, had a very slight decrease in KAM and total contact force with the VSS, which is a very common response shown throughout the literature (Bennell et al., 2013; Erhart et al., 2008; Erhart et al., 2010). Participant 7 had a large decrease in KAM and total contact force in the VSS compared to the neutral shoe that would be considered the optimal response and thought to be beneficial to the knee joint. On the other hand, Participant 13 had a large increase in KAM and contact force while wearing the VSS which is also been shown to occur for some participants within the literature (Bennell et al., 2013; Erhart et al., 2008; Erhart et al., 2010). Comparing these three drastically different responses to VSS allowed us to investigate if changes in joint loading due to VSS can actually impact tissues within the joint. Future work with a greater number of participants modeled for FE analysis may provide an opportunity to find a range in KAM magnitude change between footwear that results in considerable change to stress within the joint tissues.

In addition to more participants, the development of subject specific tibiofemoral geometry for each participant may be a goal of future work. The current FE model was developed from only one of the participant's knee geometry. Applying the large joint

contact force magnitudes of Participants 7 and 13 to Participant 3's relatively small joint geometry certainly affected the estimations of Participants 7 and 13's meniscal stress and strain. The development of three subject-specific FE models would likely have been beneficial as such models has shown to improve model accuracy (Guo, Santner, Lerner, & Maher, 2017; Henak et al., 2013; Kłodowski et al., 2016b; Navacchia et al., 2016). However, development of multiple subject-specific models adds a considerable amount of time to data processing. As the goal of this study was to investigate if different loading conditions between footwear were sensitive enough to assess changes in tissue stresses within the joint, the use of a single tibiofemoral geometry with different loading conditions matching estimated joint contact forces was sufficient.

Lastly, future work should aim to use a dynamic analysis instead of the static analysis performed for this current study. The static analysis selected for the current study was appropriate for assessing the effect of different loading conditions at one specific moment in time; however, improvement to a dynamic analysis would allow for implementation of the entire gait cycle as loading and boundary conditions. Inclusion of the entire gait cycle through a dynamic analysis is a more realistic loading and boundary condition than the compressing the tibiofemoral joint through a described displacement of femur, which was performed for this study. Implementation of loading over the entire gait cycle would allow for a better understanding of tissue stress while participants walk in VSS compared to a neutral shoe. However, when comparing within subject conditions, the FE approach used for this thesis was appropriate in evaluating the possible differences in tissue mechanics brought on by different footwear conditions.

We were able to develop a FE model that estimates values for menisci and cartilage stress that have been previously shown from the literature. When comparing the different loading conditions due to footwear, results from this exploratory aim show significant differences in contact forces can impact stresses occurring with the joint. However, small changes to joint loading appeared to have varying effects on tissue stress, which may be a factor contributing to the lack of evidence supporting VSS ability to impact OA progression. Average reductions in KAM with VSS range from 6% – 8 % and may be not be large enough to enact changes in contact forces that can influence stress placed on the tissues within the joint. Future work that improves on the FE model used in this study may allow for detection of a boundary defining specific changes in KAM or joint contact force that lead to significant changes in tissue stress.

CHAPTER 6

CONCLUSION

The overall objective of this thesis was to investigate whether a VSS intervention could alter knee joint loading and menisci mechanics in a symptomatic medial compartment knee OA population. We used gait analysis, musculoskeletal modeling, and FEA to determine the effect of VSS on gait mechanics, knee joint contact force, and menisci stress and strain, compared to a control shoe in medial compartment knee OA patients. These methods provided a more in-depth approach into investigating if VSS have the capacity to impact mechanical mechanisms for knee OA progression. We found participants' did not decrease KAM while wearing VSS, which is in contrast to what has been previously shown in the literature. Furthermore, participants who did experience a decrease in KAM did not always experience a decrease in medial compartment contact force. Participants also had a greater knee external rotation moment in the VSS compared to the neutral control shoe. The observed lack in ability of VSS to decrease medial compartment loading, along with the increase in knee joint moments outside of the frontal plane, suggests KAM should not be the only measure used when considering if VSS can positively impact an OA population. However, results from our FE modeling of the tibiofemoral joint indicate significant changes in knee joint contact force can influence stress placed on the menisci. The present study findings suggests the VSS may be able to positively influence mechanisms for OA progression in select individuals who experience large decreases in knee joint loading. Future work should focus on what determines if an individuals will experience a significant decreases in medial

compartment joint loading with VSS and if prolonged exposure to VSS improves OA structural and symptomatic progression.

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