ABSTRACT

Title of Dissertation:	MODELING THE MECHANICAL CONSEQUENCES OF PREGNANCY ON KNEE JOINT LOADING AND FUTURE KNEE HEALTH
	Elizabeth Mae Bell, Doctor of Philosophy, 2023
Dissertation directed by:	Associate Professor Ross H. Miller and Professor Jae Kun Shim, Department of Kinesiology

Clinical evidence suggests that experiencing pregnancy increases a woman's risk of knee osteoarthritis, a painful and mobility limiting disease that results from cartilage deterioration. While understanding the underlying causes and the association with pregnancy is complex, the mechanical load on cartilage during walking appears to be important to the initiation and progression of the disease, especially if walking mechanics are abnormal. Pregnancy involves various changes in mechanical factors like mass, center of mass, and joint laxity which are known to progressively change walking mechanics throughout gestation. However, it is unknown if mechanical changes associated with pregnancy, which may be substantial in magnitude but may be limited in duration, can explain the osteoarthritis risk since osteoarthritis is diagnosed later in life. Given that women typically experience pregnancy early in their lifetime and will need healthy knees for decades after they become mothers, this research aimed to model the mechanical consequences of pregnancy on knee joint loading and knee joint health over the lifetime. Specifically, this dissertation sought to (i) determine how pregnancy influences variables like resultant knee joint kinetics, which more directly indicate the load on cartilage over a range of walking speeds (ii) estimate the impact of pregnancy on internal knee joint forces and tibiofemoral cartilage load during walking and (iii) evaluate the isolated effect of altered loading experienced during pregnancy on cartilage degeneration and the risk of knee osteoarthritis throughout a woman's lifetime. Results suggest that (i) 3D knee joint moments over a range of walking speeds are greater in pregnant vs. non-pregnant individuals and knee adduction moments are altered as pregnant women walk faster. Similarly, pregnant women experience greater total knee joint loading and greater medial knee joint loading which results in additional and altered peak strain on knee cartilage with greater walking speed. Finally, the elevated and altered compressive load experienced over one or more pregnancies resulted in a greater cartilage failure probability, with differential effects when women experience multiple pregnancies later in their lifetime. These

findings support the notion that the mechanical factors associated with pregnancy significantly alter knee joint loading and mechanical changes may, in part, contribute to the known association between pregnancy and risk for knee osteoarthritis risk over a woman's lifetime. Further, present-day American mothers who are conceiving at later stages of life compared to previous generations may be more susceptible to knee osteoarthritis. Future investigations are needed to explore effects postpartum and for populations beyond healthy, active pregnant women. Further research could also investigate if biomechanical adjustments could be used as potential interventions to lessen knee joint loading and potentially decrease the risk of knee osteoarthritis among this population.

MODELING THE MECHANICAL CONSEQUENCES OF PREGNANCY ON KNEE JOINT LOADING AND FUTURE KNEE HEALTH

by

Elizabeth Mae Bell

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Advisory Committee:
Associate Professor Ross H Miller, Chair
Professor Jae Kun Shim, Co-chair
Associate Professor Timothy Kiemel
Associate Professor Sushant Ranadive
Professor Norman Wereley

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Dedication

I would like to thank and dedicate my work to my Family. First, thanks to my husband, Morgan, for his continued patience, understanding, and encouragement throughout graduate school and our life together. Thanks to my mother, for her enduring understanding regarding my big ideas and life choices. Thanks to my grandmother Sylvia, for her encouragement, assistance, and guidance. I’m thankful and fortunate that my mother-in-law, Felicitie, provided help and care for my young boys over the last few years. Finally, many thanks to my sons, Harrison, who attended many meetings and virtual courses as an infant and John-Britt who was in the womb for almost every dissertation data collection.

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List of Abbreviations

Analysis of Variance	ANOVA
Body Mass Index	BMI
Electromyography	EMG
Standard Deviation	SD
Self-selected “comfortable” walking speed	SSW
Statistical Parametric Mapping	SPM

Chapter 1: Introduction

1.1 Background

Knee osteoarthritis is a prevalent chronic disease characterized structurally by cartilage loss and symptomatically by pain and loss of mobility. Symptomatic knee osteoarthritis is a serious condition that develops over the lifetime and affects nearly 50% of adults aged 45-85 years (Murphy et al., 2008). The pathology of osteoarthritis is complex, with disease initiation and development resulting from the interplay of mechanical factors such as joint loading and physiological factors like inflammation. Although neither factor alone is a convincing root cause of osteoarthritis**,** simple conceptual models focused on mechanical or physiological factors alone can provide insight into the causes and prevention of knee osteoarthritis (Berenbaum, 2013; Felson, 2013). Although understanding the pathology of knee OA is complex and the causal relationship behind this association is poorly understood, the mechanical load on cartilage during walking appears to be important to the initiation and progression of the disease,[1] especially if walking mechanics are abnormal.[2,3] As such, this dissertation will attempt to better understand some of these relationships using models of pregnant walking.

Pregnancy is associated with many changes in mechanical factors like mass, center of mass, and joint laxity that happen over 40 weeks which is a relatively short amount of time (Figure 1.1), with significant changes by 20 weeks. These changes are known to progressively change walking mechanics. [4–8] Clinical, observational evidence suggests that pregnancy is a sex-specific risk factor with as few as four births being associated with a greater risk for knee osteoarthritis (Wise et al., 2013). Still the effect of pregnancy on the mechanical properties of tissues around peripheral joints such as the knee is limited (Bey et al., 2019). If there is a sustained effect on mechanical properties of knee joint tissues, it is unknown if these mechanical changes, which are substantial in magnitude but limited in duration, can explain the osteoarthritis risk associated with pregnancy since osteoarthritis is typically diagnosed many years after pregnancy.

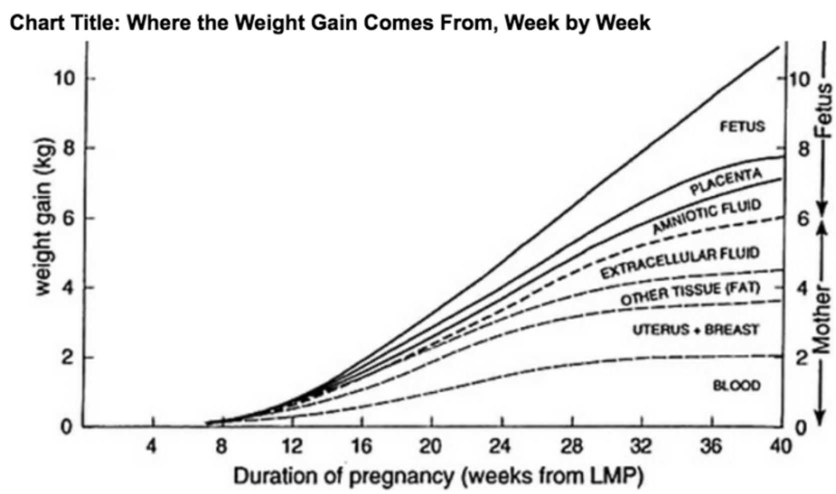

Figure 1.1. Components of gestational weight gain in pregnancy (Pitkin, 1973). Note: LMP = last menstrual period.

An important factor in the initiation and progression of knee osteoarthritis seems to be the mechanical load on cartilage during gait where altered or excessive local mechanical loading at the knee contributes to cartilage loss and accelerates joint degeneration. Increased or abnormal loading mechanics may affect knee joint health as experimental measures of fatigue via mechanical testing of articular cartilage suggests that the stress-life, or cycles until failure, of this tissue is exhaustible within the human lifespan and is sensitive to even small increases in the peak stress per cycle (Riemenschneider et al., 2019; Weightman et al., 1978). Therefore, increased and/or altered forces experienced at the knee during pregnant walking may accelerate degeneration via mechanical fatigue (Riemenschneider et al., 2019; Seedhom, 2006). Pregnant women may experience increased or altered knee joint loading as they walk for exercise (American College of Obstetricians and Gynecologists' Committee on Obstetric Practice, 2015) and this type of loading may affect many women over their lifetime as over 80% of females in the United States will experience at least one pregnancy by the end of their childbearing years (Pew Research Center, 2018). Accordingly, understanding the mechanical consequences of pregnant walking on knee joint health is important knowledge for women's health - even if contribution over the time course of one pregnancy is insignificant.

Knee osteoarthritis is a progressive disease that develops over the lifetime and the influence of these factors on the risk for knee osteoarthritis must be understood since women typically experience pregnancy in their early 20's and will need healthy knees for decades after they become mothers. Commonly, to quantify the risk of knee osteoarthritis due to altered walking mechanics, magnitudes of resultant knee moments in walking are compared as they seem to relate to the development of knee osteoarthritis (Amin et al., 2004; M. Hall et al., 2015; Lynn et al., 2007). With this common technique variables such as resultant knee joint moments or model-based estimates of joint contact forces are assessed between clinical and healthy populations. Inadequate information is currently available to use this standard approach to estimate how knee joint loading changes during pregnancy. In fact, no studies provide model-based estimates of knee joint loading and the few available studies that examine knee joint kinetics (Bagwell et al., 2020; Branco, Santos-Rocha, Aguiar, et al., 2016) provide only sagittal plane moments or compare results to post-partum instead of non-pregnant values.

It's currently unclear how factors like knee joint moments, that more directly indicate the load on cartilage, are affected while walking at a range of speeds in pregnancy. Current knowledge is limited to joint level descriptions of knee kinetics near a comfortable walking pace (Bagwell et al., 2020; Branco, Santos-Rocha, Aguiar, et al., 2016; Foti et al., 2000). Longitudinal analyses through pregnancy suggest that the anthropometric and associated body composition changes are largely associated with identified increases in joint kinetics (Branco, Santos-Rocha, Vieira, et al., 2016). Analysis of knee joint moments suggest that compared to nulliparous females, knee joint loading is increased in late pregnancy at least when knee joint moments are normalized to pre-pregnancy mass and participants walk at fast (1.5 m/s) preferred speeds (Bagwell et al., 2020). However, some are limited to sagittal plane analysis (Branco et al., 2014), self-selected walking speed(Bagwell et al., 2020; Branco et al., 2014; Branco, Santos-Rocha, Aguiar, et al., 2016; Foti et al., 2000) or make comparisons to postpartum measures (Branco et al., 2014; Branco, Santos-Rocha, Aguiar, et al., 2016). Further, to my knowledge, no estimates of joint force, are available for this population. Still, evaluations of resultant knee joint moments or even of joint contact force in pregnant walking give only a snapshot of information about how loading may be altered by the mechanical effects of pregnancy. Evaluating the effect of walking in the third trimester does not give insight into how any increased or altered loading which is experienced over a certain number of months may contribute to the risk for osteoarthritis in the long-term.

A more complete understanding of the consequences of pregnant walking on knee joint health requires a simulation of the mechanical consequences of cyclic loading on medial knee cartilage deterioration over time. A phenomenological model of cartilage fatigue and a probabilistic model of tissue failure (such as Edwards, 20210; Miller and Krupenevich 2020) can be used to evaluate the effect of walking in pregnancy or pregnancies over time would enable an objective evaluation of how increased or altered forces on cartilage may contribute to joint degeneration throughout a woman’s lifetime. This mechanical approach to investigating knee joint loading would be advantageous since it will allow for the evaluation of the long-term effect of altered or increased loading experience in pregnancy on knee joint health without conducting longitudinal observational studies over many years.

To summarize, the general walking biomechanics changes and changes in knee loading specifically with pregnancy are unclear, and the impact of these changes on the lifetime risk of knee osteoarthritis is uncertain. Therefore, the purpose of this dissertation was to model the mechanical consequences of pregnant walking on knee mechanics, knee joint loading and future knee joint health to determine if the increased risk of knee osteoarthritis after pregnancy is at least in part explained by the mechanical effects of pregnancy. Clarifying these gaps in knowledge is important to understand if the mechanical factors associated with pregnancy significantly alter knee joint loading and contribute to the known association between pregnancy and risk for knee osteoarthritis risk over a woman's lifetime. Results will have implications for pregnant physical activity recommendations and may provide insight into how biomechanical modifications may be used as interventions to reduce knee joint loading and possibly reduce future knee osteoarthritis risk.

1.2 Objectives and Hypotheses

To address this purpose three studies were designed which aimed to 1) define the effect of pregnancy on preferred speed and resultant walking mechanics 2) determine if pregnancy increases or alters internal knee joint land cartilage loading and, 3) evaluate how the mechanical loading experienced while walking throughout pregnancy may contribute to an increase in the lifetime risk for knee osteoarthritis. The objectives and hypotheses of each study are detailed in this section.

Study 1: Define the effect of pregnancy on preferred speed and resultant knee joint mechanics.

Objectives: Compare self-selected, preferred walking speed between pregnant and non-pregnant women to 1.1) determine the effect of pregnancy on preferred walking speed and 1.2) examine knee joint kinetics and determine group (pregnant, non-pregnant) by speed (preferred, 1.0m/s, 1.5m/s) effects on 3D joint moments.

Hypotheses: Based on results of available literature on temporospatial parameters throughout pregnancy is expected that 1.1) pregnant individuals will slow their preferred self-selected waling speed compared to non-pregnant controls which will result in 1.2a) similar self-selected knee joint moments between pregnant and non-pregnant women. However, 1.2b) when knee joint moments are compared between groups at controlled paces it is expected that pregnant knee joint moments will be greater than non-pregnant moments due to the increased and altered body mass shifts associated with pregnancy. These expectations will be indicated by a significant group by speed interaction within the statistical parametric mapping repeated-measures Analysis of Variance (ANOVA) with post hoc indications of the trends described.

Study 2: Determine if pregnancy increases or alters internal knee joint forces and model the mechanical response of cartilage.

Objectives: Estimate 2.1) how total joint contact forces in the knee 2.2) and the internal distribution of force between the lateral and medial compartments is changed while walking in late pregnancy over a range of walking speeds. Evaluate 2.3) the effect of increased or altered medial knee joint loading on the deformation experienced by medial knee joint cartilage.

Hypotheses: It is expected that pregnant subjects, who experience significant mass gain, altered knee mechanics, and possible increases in joint laxity/instability which challenge balance will exhibit amplified muscular co-contraction which will result in 2.1) greater overall compressive knee joint loads. This increase in joint load combined with shifted mass distribution and possible changes in gait mechanics will result in 2.2) elevated and medially shifted medial knee contact forces for pregnant vs. non-pregnant subjects. Increased or altered contact mechanics in pregnancy will 2.3) cause medial knee cartilage strains to be increased compared to non-pregnant walking.

Study 3: Estimate the lifetime effect of Pregnant walking on knee joint health.

Objectives: 3.1) Determine if cumulative damage over the lifetime is increased with experiencing one or more pregnancies or 3.2) with experiencing pregnancy later in life.

Hypotheses: Increased or altered contact mechanics and greater medial knee cartilage strains will increase the damage accumulated on cartilage per distance traveled and result in more damage accumulated from walking in one or more pregnancies which, over the lifespan will 3.1) contribute to a significant increase of cartilage failure suggesting a greater risk of knee osteoarthritis due to mechanical wear and tear. Experiencing pregnancy later in life, when tissue is more susceptible to the effects of biomechanical risk factors, will increase the failure probability of medial knee cartilage over the lifetime.

Chapter 2: Review of Literature

2.1 Introduction

Clinical evidence suggests that experiencing multiple pregnancies influences future knee joint health. For example, pregnancy increases the relative risk for knee replacement by 8% per birth (Liu et al., 2009). Parity, or the number of times a female has given birth, significantly increases the risk for osteoarthritis particularly for females who have more than four children (Wise et al., 2013). Being pregnant more than six times has been found to be an independent risk factor for knee osteoarthritis (Zhou et al., 2018). However, having more than two children than is rather extreme for most American females, who average 2.07 children during their lives (Pew Research Center, 2018). Having more than two children is even extreme for the proportion of American females who are mothers - who on average give birth to 2.47 children throughout their lifetime (Pew Research Center, 2018). Overall, these findings support that pregnancy is a crucial sex-specific factor to consider as a potential contributor to knee osteoarthritis, however the exact mechanisms behind the development and progression of this disease are complex. Focusing just on the mechanical consequences of walking in pregnancy may help with understanding how a more common scenario of a one or two pregnancies influences the risk for knee osteoarthritis over a woman's lifetime.

This chapter will focus on reviewing literature to see if there is a compelling reason for the increased risk associated with pregnancy. Initially the mechanical changes associated with pregnancy and their connections with knee osteoarthritis will be reviewed. Additionally, any available research which investigates the effect of pregnancy on knee joint mechanics will be examined to see what current knowledge is available surrounding mechanical consequences of pregnancy on knee joint loading and future knee joint health.

2.2 Anthropometrics

Throughout pregnancy the body undergoes tremendous physical changes to accommodate the growing fetus. Even healthy pregnancy is associated with significant increases in mass, with the Institute of Medicine recommending an overall gain of 11.5-16kg (The American College of Obstectricians and Gynecologists, 2020) comprised of increasing weight gain for the mother and fetus (Pitkin, n.d.; Figure 1.1) for healthy women who were initially in a normal BMI range (Nehring et al., 2011). Gestational weight gain may be an important factor to consider with respect to knee osteoarthritis, as increased weight presumably increases joint stress and may contribute to wear and tear of the knee joint. Most studies suggesting that increased knee joints loads when walking are a risk factor for knee osteoarthritis have been on the progression of the disease from a milder case at baseline to a more severe case at follow-up. However, high knee joint loads have also been reported as a risk factor for development of the disease, starting from a healthy baseline, in older adults, individuals with prior knee surgeries (Chang et al., 2015; Chehab et al., 2014), and recently even in healthy middle-aged adults (Erhart-Hledik et al., 2021). As such the mechanical effect of increased body mass on magnitudes of knee joint loads experienced in walking is one mechanical factor to consider with respect to the consequences of walking in pregnancy.

Alongside mass increases, the expanding uterus and increased breast tissue shifts the distribution of mass within the trunk resulting in displacement of the whole-body center of mass (Catena et al., 2018, 2019; Jensen, Doucet, et al., 1996; Jensen, Treitz, et al., 1996). These distribution changes alter the whole-body of mass anteriorly and superiorly (Catena et al., 2019) which may alter the application point of loads in the knee in static and dynamic movement tasks. As previously mentioned, excessive loading caused by altered walking mechanics could accelerate joint degeneration, as the stress life of cartilage, or cycles until failure, is very sensitive to increases in the peak stress per cycle (Weightman et al., 1978). Understanding how the application point of knee joint loads are affected by pregnancy may be an important factor to understand with respect to knee joint health over a woman's lifetime.

2.3 Maternal Hormones and Joint Laxity

A recent, large-scale, nationally representative health survey from Korea, the 5th Korean National Health and Nutritional Examination Survey (KNHANES 2010-2012), demonstrated associations between factors such as pregnancy and parity with knee osteoarthritis prevalence (Jung, You Hwa et al, 2015). For the first time, analysis from this survey indicated that the association between radiographic knee osteoarthritis diagnosis and pregnancy/parity is stronger in women who have ever had an abortion. This association suggests that even when pregnancy is terminated early and when risk is adjusted for confounders such as age, income, education, occupation, smoking status, body mass index, and mental health status, the female body experiences changes that affect cartilage heath – so clearly knee joint laxity is one mechanical factor that is initiated within the first few weeks of pregnancy.

The relaxation of joints is a normal physiologic consequence of pregnancy, mediated by increases in hormones such as relaxin, estrogen, and progesterone that are necessary to relax pelvis ligaments and allow for the pelvic joints to accommodate vaginal delivery. Yet, these effects are not localized to the pelvis and result in increased peripheral joint laxity throughout pregnancy (Schauberger et al., 1996) and into post-partum (Chu et al., 2019). Available research into the effect of maternal hormones in pregnancy on peripheral joint laxity find that effect during pregnancy is difficult to characterize since hormonal changes do not correlate well with maternal levels of estrogen, progesterone, or relaxin (Forst et al., 1997; Marnach et al., 2003). Still, even if a direct effect or clinical correlation is not found through the evaluation of one hormone level it's commonly speculated that the prolonged exposure to multiple pregnancy hormones during contributes to overall joint laxity. For example, both Estrogen and Relaxin contribute to decreased stiffness, or greater compliance, of ligaments and tendons and increases in serum Relaxin concentration has been reported to correlate with joint laxity outside of pregnancy (Dragoo 2011, Lubahn 2006). These hormones alter the mechanical properties of ligaments and tendons by activating collagenase or breaking down collagens within the tissue and this collagenolytic effect is thought to reduce the stiffness and strength of the tissues.

Overall, pregnancy results in greater knee joint laxity which may be due to increasing tendon length instead of the common assumption that tendons become more compliant. If this increased knee joint laxity decreases joint stability, then the central nervous system may react by increasing co-contraction which may change the way that cartilage within the knee joint is loaded. As such, knee joint laxity, especially the resulting knee instability, is a mechanical factor that could affect knee joint loading during pregnant walking.

Commonly it is assumed that tendons become more compliant throughout pregnancy and lead to increases in knee joint laxity. Mechanically, ligaments and tendons need to be stiff enough to transfer the force produced by muscle to the bone and maintain joint stability. Increased tendon stiffness can limit a muscle from isometrically contracting and instead cause the muscle to stretch, or eccentrically contract, during a certain motion. Eccentric stretching is associated with higher rates of muscle injury, so muscles connected to a very stiff tendon are more likely to be injured than muscles connected to more compliant tendons. So, a ligament or tendon should be stiff enough for performance but compliant enough to prevent eccentric injuries of muscle. It's thought that increased compliance of tendons in pregnancy can allow for isometric muscle contraction and an overall lessening of muscle injury. A more compliant tendon may also be less prone to injury as it can be strained more without breaking.

Still, a recent investigation that evaluated the relative strain and stiffness of the patellar tendon throughout a maximum knee extension moment throughout pregnancy and postpartum suggests that the mechanical properties of the knee, specifically patellar tendon stiffness are not universally affected by pregnancy (Bey et al., 2019). This study, which was the first to ever provide evidence on the mechanical properties of human tendons throughout different stages of pregnancy, did not detect changes in patellar tendon mechanical properties but did find a change in the morphological property of tendon length. Bey et al. (2019) reported a continuous increase in the tendon rest length measured at a 90° resting knee joint angle from early pregnancy to postpartum which may contribute to the increased knee joint laxity that is frequently reported in pregnant women.

2.4 Joint Strength

Hormonal changes and fluid retention associated with pregnancy are though to affect peripheral joint strength. Reduced hand grip strength is associated with pregnancy (Abdullahi et al. 2021). Measures of knee joint strength in pregnancy are limited in literature, but one investigation of the mechanical properties of human tendons throughout pregnancy found that, on average, muscle strength as well as patellar tendon stiffness force, and relative strain did not change during pregnancy and was not different from non-pregnant controls (Bey et al., 2019). Bey et al. (2019) did not observe any effect of pregnancy on knee extensor muscle strength which suggest that leg strength is maintained in pregnancy due to the associated increase in body mass.

2.5 Walking Mechanics

Remaining healthy and active during pregnancy is important for immediate and life-long health (Gilmore et al., 2015; Mayo Clinic, 2017; World Health Organization, 2016). To achieve the recommended amount of physical activity, pregnant individuals are generally encouraged to walk for exercise (American College of Obstetricians and Gynecologists' Committee on Obstetric Practice, 2015). Walking at any pace is recommended for pregnant patients that are new to exercise and brisk walking of at least 2.5 miles per hour (1.1 m/s) is recommended as a moderate-intensity aerobic activity (American College of Obstetricians and Gynecologists' Committee on Obstetric Practice, 2015; American Heart Association, 2018; World Health Organization, 2016). Although walking is important for daily activity and encouraged for physical activity, pregnancy progressively changes walking mechanics (Branco et al., 2014; Forczek et al., 2018). For example, at a self-selected pace pregnancy results in adaptations in hip mechanics (Branco et al., 2013; Branco, Santos-Rocha, Aguiar, et al., 2016; Forczek et al., 2018) and postural realignments in the pelvis and trunk (Foti et al., 2000; Hagen & Wong, 2010). While pregnancy progressively changes walking mechanics, the effect on knee joint loading is relatively unknown.

As previously mentioned, it is typical to quantify the risk of knee osteoarthritis due to altered walking mechanics by comparing surrogate measures of resultant knee moments or joint forces between clinical and control populations. However only limited information on these variables exists for pregnant individuals. The few available studies that examine knee joint kinetics during pregnant walking (Bagwell et al., 2020; Branco, Santos-Rocha, Aguiar, et al., 2016) provide only sagittal plane moments or compare results to post-partum instead of non-pregnant values. Still, these investigations gather an impressive amount of data on walking mechanics throughout pregnancy and post-partum. Overall, outcomes suggest that, compared to nulliparous females, knee joint loading is increased in late pregnancy at least when knee joint moments are normalized to pre-pregnancy mass and participants walk at fast (1.5 m/s) preferred speeds (Bagwell et al., 2020).

Yet, these analyses are limited to joint level descriptions of mechanics near a comfortable walking pace. The preferred walking pace of the available studies ranges from relatively slow walking paces of 1.0 m/s and 1.1 m/s (Branco, Santos-Rocha, Aguiar, et al., 2016) to faster paces of 1.5 m/s (Bagwell et al., 2020). Further, each available investigation reports that preferred pace did not change significantly between time points – this consistency in walking pace is surprising since it is commonly reported that pregnant individuals prefer to walk slower as pregnancy progresses (DiNallo et al., 2008). No available report of pregnant knee mechanics controls for walking speed. This limitation may influence interpretations since speed effects could confound between-group comparisons of joint moments and result in bias. For example, sagittal and coronal plane moments generally increase when walking faster (de David et al., 2015). Additionally, the tendency to collect walking data at a preferred pace significantly limits the current understanding of pregnant walking, as it is unrealistic to assume that pregnant individuals always walk at a preferred velocity. In daily life, a range of speeds are necessary. In pregnancy a slow pace, of at least 1.1m/s, is recommended for exercise. Although walking faster may not be easy women may walk faster to keep up with others, cross the street to catch a bus, or for exercise.

Overall, current knowledge surrounding knee joint loading in pregnancy is limited to resultant knee joint analysis at a preferred walking pace but suggests that mechanics may be altered during pregnancy especially when walking at a relatively fast pace. An approach that evaluates the consequences of pregnant walking on knee mechanics over a range of speeds is necessary to comprehensively evaluate how pregnant walking is different than non-pregnant walking. Additionally, more advanced modeling techniques are necessary to understand if the gait adaptations associated with pregnancy may contribute to greater risk of knee osteoarthritis. Specifically, estimates of compressive knee joint contact force, the medial knee joint load on cartilage and analysis of the effect of any increased or altered loading on cartilage throughout a woman's lifetime are not currently available.

2.6 Limitations

Limiting the investigation to just the mechanical effects experienced in pregnancy does not account for the mechanical effects that last after giving birth.

Sustained effects seem likely postpartum since morphological changes associated with pregnancy joints with increased laxity may not fully return to pre-pregnancy values after the first pregnancy and laxity has develops more rapidly during subsequent pregnancies (Dumas & Reid, 1997). Further, there is evidence that walking mechanics remain altered in parous women 1-5 years after giving birth (Stein & Boyer, 2020). Still, the findings of these dissertation studies will provide a more complex examination of knee loading experienced in late pregnancy. Examining the mechanical effects of knee joint loading experienced in pregnancy will serve as a starting point for future research which could look at post-partum effects.

2.7 Summary

Generally, available results indicate that mechanical factors like increased and altered segment mass and increased knee joint laxity in pregnancy may contribute to altered knee mechanics while walking. Although there are multiple longitudinal analyses of pregnant gait at a preferred walking pace it is currently unclear what the influence of walking speed is on 3D joint kinetics. Further there are currently no model based estimates of the internal joint loading experienced during walking or the consequences of any altered or increased knee joint loading on cartilage health throughout a woman's lifetime. Filling these gaps in literature is necessary to objectively assess if the mechanical changes in gait may contribute to the increased risk of knee osteoarthritis for women who have experienced pregnancy or pregnancies in their lifetime.

Chapter 3: Experimental Data Collection

3.1 Introduction

Data for the studies planned in this dissertation, including walking mechanics, muscle activation and valuations of joint strength, were collected from pregnant and non-pregnant individuals during a one-time visit to the Neuromechanics Research Core between July 2021 and April 2022. This chapter will focus on details about the human subject research participants as well the collection and analysis methods used for the data obtained.

3.2 Participants

Healthy pregnant women in their third trimester (28-35wk gestation) and healthy non-pregnant controls were recruited to participate in this research. All participants were recruited without regard to race, national origin, creed, educational background, socioeconomic status, or non-pertinent factors. Emails, flyers and in-person recruitment which included contact through local healthcare offices, parent list-servs and daycare centers were used as recruitment techniques for pregnant participants.

Participants were asked verbally about exclusion and inclusion criteria before they performed written consent procedures. Pregnant women were required to bring or send a letter from their obstetrician which cleared them to participate in walking for moderate exercise. Pregnant participant inclusion criteria required that each pregnant volunteer be pregnant with a single fetus and visit the laboratory for data collection in the early part of their third trimester (28-35wk gestation). These volunteers were required to be young (age 18-35 years), healthy adults who were cleared by primary physician to walk for daily exercise, and non-smokers. Non-pregnant volunteers were included if they were young (18-35 years old) healthy women who performed walking as a normal part of daily exercise. Pregnant or non-pregnant volunteers were excluded if they had spinal cord injury, burns, contractures, joint fusions other orthopedic conditions that limited their range of motion, strength, or the ability to perform higher level activities independently and safely or may impede performance, or complete or partial peripheral nerve injury that will limit physical performance or increase risk of injury. Volunteers were excluded if they had a history of allergic reaction to skin products/adhesives, any cardio-pulmonary, metabolic, or integumentary diagnosis where exercise is contraindicated (e.g., chronic hypertension, preeclampsia-eclampsia, preeclampsia superimposed on chronic hypertension, gestational hypertension or known ongoing cardiovascular disease) or pain level greater than 6/10 (very painful) on a 0-10 scale.

3.3 Instrumented Gait Analysis

Each volunteer visited the Neuromechanics Research Core Laboratory in College Park, Maryland for a single data collection session after completing written consent procedures approved by the internal review board of the University of Maryland (UMD; IRB 1552283). Participants refrained from exercise and caffeine before the appointment, were asked to stay hydrated and did not eat for at least four hours before data collection. Pregnant women were required to bring or send a letter from their Obstetrician clearing them to walk for moderate exercise which was reviewed before consent.

After completing informed consent procedures self-reported information about race and ethnicity, pre-pregnancy weight, and date of last menstrual cycle were recorded. Height was measured using a freestanding stadiometer. Limb dominance was determined by asking the participants, “Which leg would you kick a soccer ball with?” Resting blood pressure measures were taken with an arm cuff (Omron Health Care) to ensure that participants were within a normal range.

Following intake, each participant was asked to change into athletic shorts that fit below the waist, a comfortable sports or nursing bra and their own athletic shoes. Then each participant was fit with a chest worn heart-rate monitor (Garmin), a wearable metabolic system which included a face mask and backpack-worn wireless transceiver (Cosmed K5), fourteen surface electromyographic (EMG) sensors (Delsys Trigno ®), a terry cloth headband and a full body retroreflective marker set (Figure 3.1). All EMG electrodes were placed on the skin using a Delsys Adhesive Interface, which is a precisely cut piece of double-sided tap that fits on the bottom of the surface sensor. All EMG electrodes were placed parallel to the muscular line of action, as recommended by The Surface Electromyography for the Non-Invasive Assessment of Muscles project which is a European concerted action in the Biomedical Health and Research Program of the European Union (Hermens, 1999). Instrumented gait analysis was performed, and data was collected with a system that was comprised of thirteen motion capture cameras (200hz; T-Series, Vicon Inc., Oxford, UK) which were focused on the 12m section of the 50m oval shaped track where the 10 six-degree-of-freedom force plates (1000hz; 9260AA, Kistler Instrument Corp.) were placed in a single row located within a raised platform. Retroreflective markers, surface EMG sensors, and the wearable metabolic system were placed by the same researcher in all data collection sessions.

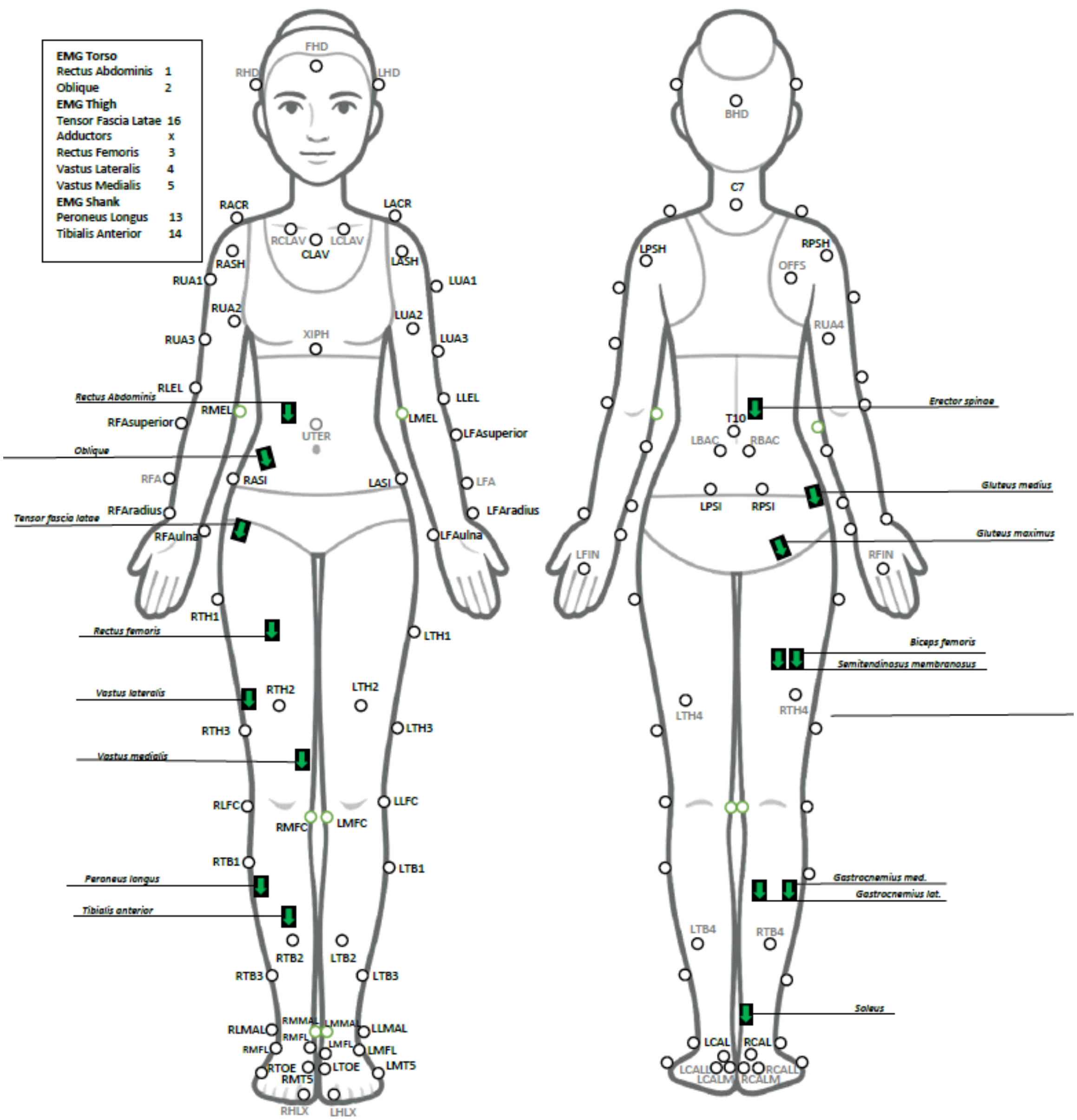

Figure 3.1. Full body marker set (each black circle is one marker) and surface electromyographic sensors (black rectangles with green arrows). Markers that were taken off for dynamic walking trials are edged in green.

Once participants were fit with all equipment the data collection process started. During data collection positions of all the retroreflective markers, force data, EMG signals, and breath-by-breath measures of oxygen consumption and carbon dioxide production were collected simultaneously. For post-processing purposes, data collection included a static trial were the participant each participant was directed to step onto two of the force plates and stood in anatomical position so that a static picture of the marker set could be collected. After the static trial, each participant walked to a chair at the side of the track and sat and rested quietly for five minutes so that a resting metabolic rate could be collected. Next, metabolic data was collected while participants walked for 3-7 minutes total at each targeted speed (self-selected walking (SSW) speed, 1.0m/s and then 1.5m/s). Dynamic walking trials were collected during every lap as participants walked around the track at each pace for 3-7 minutes. If markers or sensors fell off while walking around the track participants were asked to ignore it and keep walking at the correct pace. After obtaining a steady state oxygen consumption for at least two minutes markers or sensors were replaced and participants were asked to walk back and forth on the straight section of track with the embedded force plates for an additional collection of up to 10 trials before they sat and rested. After each walking condition participants were asked to rest quietly and blood pressure was checked after five minutes. Walking conditions (preferred, 1.0m/s, 1.5m/s) were not randomized, and heart rate was monitored continuously to make sure that each woman was able to progressively increase activity while monitoring participants to ensure that they did not exceed moderate levels of exercise, or 6/10 on a pain scale. Direction of walking was randomized and balanced between groups. Once data collection was complete the metabolic unit, retroreflective markers, and EMG electrodes were removed. At the end of the collection, participants were then asked to eat a snack and rest, if needed. Participants could also change into their own work-out clothing for the rest of the data collection session.

3.4 Self-Reported Levels of Physical Activity Level

To assess recreational physical activity levels self-reported measures of physical activity level were recorded using the pregnancy activity questionnaire (PPAQ; Chasan-Taber et al., 2004) which is an instrument developed to measure a broad range of physical activities performed during pregnancy and rank individuals. Specifically, this instrument provides a way to categorized individuals into categories that range from sedentary to most active within a narrower range than nonpregnant samples.

3.5 Isometric Strength Testing

After completing instrumented gait analysis and filling out questionnaires, participants were able to change out of shorts and wear their own comfortable clothes (e.g., sweatpants or long-sleeve shirt) for the dynamometer testing. Isometric strength testing was performed to provide an objective measure of muscular strength and to complement self-reported measures of physical activity level. Maximal isometric strength was measured at the hip (-15, 0, and 30 degrees of flexion and 0 degrees of adduction), knee (40, 60, 90 degrees of extension), and ankle (-20, 0, 20 degrees of plantar flexion) using an isometric dynamometer (Biodex Medical Systems, Shirley, NY, USA). Participants performed three sets of maximal voluntary contractions at each angle in both the flexion and extension or adduction and abduction directions. Each trial lasted five seconds. Details about participant setup are included in Figure 3.2).

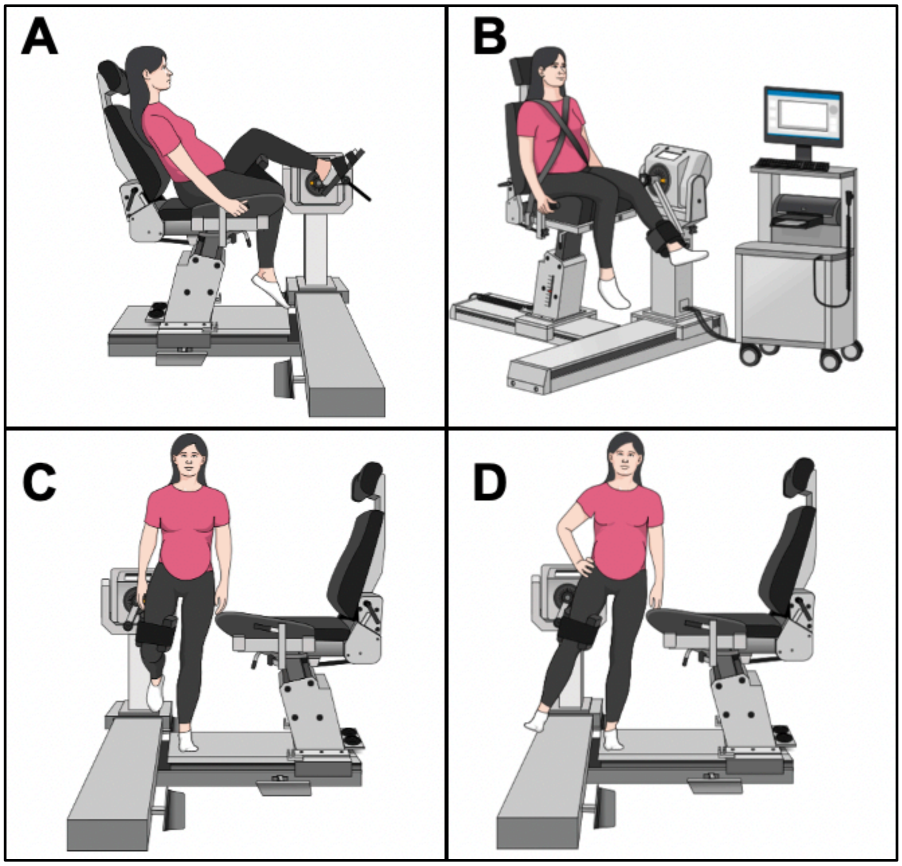

Figure 3.2. Dynamometer testing procedures for (a) ankle flexion and extension, (b) knee flexion and extension, (c) hip flexion and extension, and (d) hip adduction and abduction.

Chapter 4: Pregnancy and Walking Speed Influence External Knee Joint Moments

4.1 Introduction

Pregnant individuals face a variety of mobility challenges that can affect their quality of life and risk for various secondary conditions (Lee & Zaffke, 1999; Moccellin & Driusso, 2012; Sabino & Grauer, 2008; Tendais et al., 2011; Vullo, 1996). For example, experiencing pregnancy increases the relative risk for knee replacement, the end-stage treatment for knee osteoarthritis, by 8% per birth (B. Liu et al., 2009). While understanding the pathology of knee osteoarthritis is complex, the mechanical load on cartilage during walking appears to be important to the initiation and progression of the disease,(Andriacchi, T. P., & Mündermann, A., 2006) especially if walking mechanics are abnormal.(Amin et al., 2004; Lynn et al., 2007) As such, the effect of pregnancy on walking mechanics, especially at the knee, may indicate if the risk of osteoarthritis is, at least in part, explained by changes in knee joint loading.

Pregnancy is associated with many changes in mechanical factors which likely change knee joint loading in walking. For example, even healthy pregnancy results in increased body mass, typically upwards of 11 kg (The American College of Obstectricians and Gynecologists, 2020) and shifts in segmental mass distribution (Haddox et al., 2020; Jensen et al., 1996) which displace the whole-body center of mass anteriorly (Catena et al., 2018, 2019; Haddox et al., 2020). Further, even early pregnancy is associated with increases in peripheral joint laxity which are sustained throughout pregnancy (Schauberger et al., 1996) and into post-partum (Chu et al., 2019). Greater knee joint laxity may result in changes in perceived knee joint stability which may challenge balance and increase muscular co-contraction or change how the knee is loaded. Current literature suggests that these anatomical and physiological changes progressively change walking mechanics (Branco et al., 2013, 2014; Branco, Santos-Rocha, Aguiar, et al., 2016; Forczek et al., 2019; Forczek & Staszkiewicz, 2012)(Branco et al., 2013; Branco, Santos-Rocha, Aguiar, et al., 2016; Forczek et al., 2018) and postural realignments in the pelvis and trunk (Foti et al., 2000; Hagen & Wong, 2010). However, little information is available with respect to knee joint moments and forces that more directly indicate the load on cartilage. This gap in knowledge is important because high knee joint moments relative to body mass during walking have been associated with the initiation and progression of knee osteoarthritis (Chang et al., 2015; Chehab et al., 2014). Since these pregnancy-related changes happen relatively quickly compared to changes associated with other osteoarthritis risk factors such as aging or obesity, they could result in knee joint loads that are unusual or unfamiliar, which have been suggested as a general mechanical risk factor for osteoarthritis (Seedhom, 2006).

If knee joint mechanics are increased or altered by pregnancy, non-invasive gait interventions may potentially be applied to prevent the risk of knee osteoarthritis for this population. Such interventions would be beneficial since knee osteoarthritis is a progressive disease that develops over the lifetime and women who typically experience pregnancy in their twenties(Ely, 2018) will need healthy knees for decades after becoming mothers. Further, remaining healthy and active during pregnancy is important for immediate and life-long health(Gilmore et al., 2015; Mayo Clinic, 2017; World Health Organization, 2016) and walking is encouraged for physical activity (American College of Obstetricians and Gynecologists' Committee on Obstetric Practice, 2015).

The mechanical loading of cartilage during walking is commonly assessed indirectly through evaluating measures like resultant knee joint moments. These surrogate variables are useful since measures like knee adduction moment are commonly interpreted as reflections of medial knee joint loading in gait and are associated with the development of the knee osteoarthritis (Amin et al., 2004, p. 20; Hall et al., 2015; Lynn et al., 2007). Few available studies have reported knee joint moments as pregnant women walk at a self-selected pace(Bagwell et al., 2020; Branco, Santos-Rocha, Vieira, et al., 2016; Foti et al., 2000). Still, results within these analyses are mixed, with one study indicating that knee adduction moments may be increased in pregnancy compared to nulliparous (women who have never given birth) controls at least while walking at a relatively fast pace of 1.5 m/s on average (Bagwell et al., 2020). Although the aforementioned studies report no between-group differences in preferred walking speeds, between-study walking speeds range considerably. For example, Branco et al. (2016) reported women in their third trimester preferred walking an average walking speed of 1.1 ± 0.1 m/s while Foti et al. (2000)'s group walked at 1.2 ± 0.2 m/s and Bagwell et al. (2020) recorded a speed of 1.5 ± 0.1 m/s. This range is considerable, and since sagittal and coronal plane moments generally increase when walking faster (de David et al., 2015), walking speed likely confounds the interpretation of available results when comparing between studies. Additionally, the tendency to collect walking data at a preferred walking speed significantly limits the current understanding of pregnant walking, as it is reasonable to assume that pregnant individuals may walk at a variety of speeds. It's likely that pregnant individuals may prefer to walk slower as pregnancy progresses (DiNallo et al., 2008) but in daily life, a range of speeds are necessary. In pregnancy a relatively slow pace of at least 2.5mph (1.1 m/s) is recommended for exercise.(Colgrove, n.d.) Even if walking faster is difficult, pregnant women may need to walk faster, for example to keep up with others, cross the street to catch a bus, or for exercise.

Beyond limitations caused by analysis at a preferred walking speed, comparison of available results is difficult due to the control groups used and the way that kinetics are normalized to pregnancy or pre-pregnancy mass. For example, Foti et al. (2000) reports no differences in mass-normalized peak knee adduction moments of pregnant women in their third trimester compared to measures taken 1-year post-partum, but Bagwell et al. (2020) reports greater knee adduction peaks between pregnant women in third trimester compared to nulliparous controls when data are normalized to self-reported pre-pregnancy mass. Control group comparisons should be considered when interpreting available information since the effect of pregnancy on knee mechanics may extend beyond gestation (Stein & Boyer, 2020). For example, pregnancy results in lasting changes in knee joint laxity (Chu et al., 2019) and greater internal muscular co-activation may be required in pregnant and postpartum walking to stabilize the knee during stance. Overall, a more comprehensive approach that evaluates the consequences of pregnant walking on knee mechanics over a range of speeds is necessary to understand if the gait adaptations associated with pregnancy may contribute to altered or increased knee joint loading which may lead to an increased risk of knee osteoarthritis.

Therefore, the purpose of this study was to determine the effect of pregnancy on walking speed and on resultant knee joint kinetics. Healthy pregnant women in the first half of the third trimester and healthy non-pregnant, female controls and were recruited from the same local population and (H2.1a) were not expected to differ with regards to age, height, or pre-pregnancy/non-pregnant mass. The self-selected preferred speed of individuals walking in late pregnancy was compared to non-pregnant controls. Based on available literature it was expected that (H2.1b) pregnant individuals will slow their preferred self-selected walking speed compared to non-pregnant controls, which would result in similar three-dimensional (3D) knee joint moments between pregnant and non-pregnant groups. Second, due to the increased and altered body mass and greater knee joint laxity associated with pregnancy, it was expected that (H2.2) pregnant knee joint moments would be greater than non-pregnant moments when both groups walk at the same speed.

4.2 Methods

This study collected experimental gait data from pregnant and non-pregnant women walking at self-selected "comfortable" and controlled walking speeds and used inverse dynamics modeling to estimate 3D resultant knee joint moments.

4.2.1 Participants

An *a priori* power analysis was performed using available data from literature (Branco, Santos-Rocha, Vieira, et al., 2016) for planned one-dimensional statistical parametric mapping (SPM) using a two-factor (pregnant vs. non-pregnant) repeated measures Analysis of Variance (ANOVA) within-group factors (walking speeds: self-selected, 1.0m/s, 1.5m/s) to compare 3D joint moments and indicated that with an expected effect size of at least 0.30, $\alpha = 0.05$ and a power of at least 80% (typical in the biomechanics field), at least 8 participants should be collected in each group for a target total of 16 participants.

Pregnant participants were required to bring or send a signed doctor's note from their obstetrician clearing them to walk for moderate exercise. Pregnant participant inclusion criteria required that each volunteer be pregnant (single fetus) and visit the laboratory for data collection in the early part of their third trimester (28-35wk gestation). These volunteers were required to be young (age 18-35 years), healthy adults who were cleared by primary physician to walk for daily exercise, and non-smokers. Non-pregnant volunteers were included if they were young (18-35 years old) healthy women who performed walking as a normal part of daily exercise. Pregnant or non-pregnant volunteers were excluded if they had spinal cord injury, burns, contractures, joint fusions other orthopedic conditions that limited their range of motion, strength, or the ability to perform higher level activities independently and safely or may impede performance, or complete or partial peripheral nerve injury that will limit physical performance or increase risk of injury. Volunteers were excluded if they had a history of allergic reaction to skin products/adhesives, any cardio-pulmonary, metabolic, or integumentary diagnosis where exercise is contraindicated (e.g., chronic hypertension, preeclampsia-eclampsia, preeclampsia superimposed on chronic hypertension, gestational hypertension or known ongoing cardiovascular disease) or pain level greater than 6/10 (very painful) on a 0-10 scale.

4.2.2 Data Collection

Each volunteer visited the Neuromechanics Research Core Laboratory at the University of Maryland School of Public Health in College Park, Maryland for a single data collection session. After completing informed consent procedures, self-reported information about race and ethnicity, pre-pregnancy weight, and date of last menstrual cycle were recorded. Height was measured using a freestanding stadiometer.

Following intake, each participant was asked to change into athletic shorts that fit below the waist, a comfortable sports or nursing bra and their own athletic shoes. Then each participant was fit with a full body retroreflective marker set (Figure 3.1), a chest worn heart-rate monitor (Garmin), a wearable metabolic system which included a face mask and backpack-worn wireless transceiver (Cosmed K5), and fourteen surface electromyographic (EMG) sensors (Delsys Trigno ®; Figure 3.1). All equipment was placed by the same researcher for all participants. Instrumented gait data was collected with a system that was comprised of thirteen motion capture cameras (200 Hz; T-Series, Vicon Inc., Oxford, UK) which were focused on the 12-m section of the 50-m oval shaped track where the 10 six-degree-of-freedom force plates (1000 Hz; 9260AA, Kistler Instrument Corp.) were placed in a single row located within a surrounding custom platform.

During data collection positions, retroreflective marker positions, force data, and muscle activation signals were collected simultaneously as participants walked. For post-processing purposes, data collection included a static trial where each participant was directed to step onto two of the force plates and stood in anatomical position so that a static picture of the marker set could be collected. All trials were collected as part of a larger protocol that involved simultaneous metabolic data collection and marker position and force plate data was collected while participants walked around the 50-m track until a steady state oxygen consumption was reached for at least two minutes (5-7 minutes total at each targeted speed: self-selected walking (SSW) speed, 1.0 m/s and then 1.5 m/s) around the 50-m track. If markers or sensors fell off while walking around the track participants were asked to ignore it and keep walking at the correct pace. If pelvis markers fell off during the metabolic data collection, then markers were replaced, a new static was taken, and participants were asked to walk back and forth on the straight section of track with the embedded force plates for an additional collection of up to 10 trials before they sat and rested. After each walking condition participants were asked to rest quietly and blood pressure was checked after five minutes. To keep the data collection protocol "minimum risk," all walking conditions were performed in the same order by all participants (preferred, 1.0 m/s, 1.5 m/s) and heart rate was monitored continuously to make sure that each participant was able to progressively increase activity while monitoring participants to ensure that they did not exceed moderate levels of exercise, or ratings of 6/10 on a pain scale. The direction of walking for each participant, clockwise or counterclockwise, was randomized and balanced between groups.

4.2.3 Data Processing

Marker position and ground reaction force data were labeled in Vicon Nexus software (v. 2.12.1.133760h x86; Vicon inc., Oxford, UK). Labeled files (.c3d) that included full steps from the right side with foot strikes isolated on a single force plate were exported to Visual3D (v.6.03.6 C-Motion, Germantown, MD, USA). Within Visual3D marker coordinates and raw analog signals were smoothed using a 4^{th}-order-dual-pass Butterworth filter with cutoff frequencies of 6 Hz and 50 Hz, respectively. Heel strike an toe off events were automatically determined using an algorithm that detected on the minimum and maximum position of the toe and heel markers with respect to the distal end of the pelvis segment during walking (Zeni et al., 2008). Temporospatial parameters were calculated (per side, where relevant) and included cadence, step length, stride width and the duration of stance and swing. Walking speed was computed from stride length and stride time measures from multiple gait cycles within at least five walking trials for each participant. Each temporospatial variable was computed using the default pipeline command in Visual3D software and averaged for each individual participant across 5-7 trials for each speed condition. Group means and standard deviations were computed for pregnant and non-pregnant groups.

A linked-segment model of the body was created for each subject from marker positions collected during a standing calibration trial. Non-pregnant magnitudes of segment masses, segment moment of inertias, and the locations of the mass centers were estimated from the position data using a mathematical model (Hanavan, 1965) segmental masses and moments of inertia reported by (Haddox et al., 2020), and the subjects own height and mass. Pregnant model magnitudes of segment masses, segment moment of inertias and the location of mass centers were estimated from the position data using a custom model built to match an established musculoskeletal model representing healthy pregnant women near 32 weeks' gestation (Haddox et al., 2020) which was based on published anthropometric data from healthy, active pregnant women near 32 weeks' gestation (Perkins & Blackwell, 1998). Pregnant and non-pregnant model segment mass and inertia properties are shown in Table 4.1. Within the pregnant model, segment center of mass location for each participant was scaled by a ratio of participant height divided by the mean height of USAFRL group (1.655m).

In this analysis we chose to not normalize joint moments to body size (mass or body weight) in order to estimate how the absolute moment experienced at the knee may change in order to estimate changes in loading (Robbins et al., 2011). This choice differs from other available kinetic analyses of pregnant walking which tend to compare mass normalized peak knee joint moments between groups. Although scaling by mass can remove the effect of mass and better isolate kinetic changes due to movement, here we wanted the effect of mass because mass in pregnancy changes quickly, likely too quick for cartilage to adapt its material properties.

Within both linked segment models the knee joint center was defined as the midpoint of the malleoli markers. These joint centers were then reconstructed as “virtual” markers during the walking trials based on their positions relative to other markers in the standing trial. The long axis of the shank was the cross product of the anteroposterior and longitudinal axes with joint angles about these axes calculated using a Cardan Xyz rotation sequence. (Wu & Cavanagh, 1995) Iterative Newton-Euler inverse dynamics within Visual3D were used to calculate joint moments which were expressed in the shank reference frame.(Robertson et al., 2014) Three-dimensional knee joint moments were computed for the stance phase of three to seven steps (average 4 steps per speed condition) for the right leg. Peak values for knee adduction moment in early and late stance and knee flexion moment in early stance were averaged from the same steps.

Table 4.1 Pregnant Model Parameters for Linked Segment Model used in Inverse Dynamics Modeling

	Segment	Segment % Body Mass	Anterior/Posterior Segment Center of Mass (m)	Axial Segment Center of Mass (m)	Medial/Lateral Segment Center of Mass (m)	Inertia XX ($kg \cdot m^2$)	Inertia YY ($kg \cdot m^2$)	Inertia ZZ ($kg \cdot m^2$)
Non-Pregnant Model	Head	8.1%	0.0000	100% · Head Length	0.0000	0.0288	0.0288	0.0288
	Thorax	35.5%	0.0000	50% · Trunk Length	0.0000	0.4154	0.6029	0.3124
	Pelvis	14.2%	0.0000	50% · Pelvis Length	0.0000	0.0475	0.0755	0.0854
	Thigh	10.0%	0.0000	43.9% · Thigh Length	0.0000	0.1532	0.1532	0.0265
	Leg	4.7%	0.0000	43.3% · Seg Length	0.0000	0.0475	0.0044	0.0475
	Foot (talus & calcaneus)	1.5%	0.0000	38.1% · Foot Length	0.0000	0.0020	0.0020	0.0004
	Toes	-	-	-	-	-	-	-
	Humerus	2.8%	0.0000	53.0% · Humerus Length	0.0000	0.0149	0.0149	0.0017
	Ulna & Radius	1.6%	0.0000	48.3% · Lower Arm Length	0.0000	0.0102	0.0102	0.0012
	Hand	0.6%	0.0000	100% · Hand Length	0.0000	0.0020	0.0020	0.0020

	Segment	Segment % Body Mass	Anterior/Posterior Segment Center of Mass (m)	Axial Segment Center of Mass (m) * HT/1.65m	Medial/LateralSegment Center of Mass (m)	Inertia XX ($kg \cdot m^2$)	Inertia YY ($kg \cdot m^2$)	Inertia ZZ ($kg \cdot m^2$)
Pregnant Model	Head	-	-	-	-	-	-	-
	Thorax	34.6%	0.0293	0.2016	0.0000	0.5177	0.2557	0.5047
	Pelvis	24.6%	-0.0705	-0.0242	0.0000	0.1758	0.2233	0.1617
	Thigh	7.5%	-0.0088	-0.1933	0.0122	0.0529	0.0160	0.0529
	Leg	5.6%	-0.0048	-0.1819	0.0122	0.0475	0.0044	0.0475
	Foot (talus & calcaneus)	1.9%	0.0926	0.0278	0.0000	0.0014	0.0039	0.0041
	Toes	0.3%	0.0346	0.0060	0.0175	0.0001	0.0002	0.0010
	Humerus	2.8%	0.0000	-0.1645	0.0000	0.0119	0.0041	0.0134
	Ulna & Radius	1.7%	0.0000	-0.1253	0.0000	0.0030	0.0006	0.0032
	Hand	0.6%	0.0000	-0.0681	0.0000	0.0009	0.0005	0.0013

4.2.4 Statistical Analysis

Outcome variables were average self-selected walking speed, demographic parameters such as age, height and mass and 3D resultant knee joint moments. Shapiro-Wilk tests were used to check the assumption of normal distribution. One-way independent *t*-test were planned to (H2.1a) compare average demographic attributes between pregnant and non-pregnant groups. Average self-selected walking speed was (H2.1b) compared between pregnant and non-pregnant groups using a one-way independent *t*-test. One-way tests were used because the walking speed hypothesis was directional. One-dimensional statistical parametric mapping (SPM) analysis using a two-factor (Group: pregnant, non-pregnant) repeated measures (Speed: preferred, 1.0 m/s, 1.5 m/s) Analysis of Variance (ANOVA) model was used to determine (H2.2) the extent to which pregnancy and walking speed influence resultant knee joint kinetics.

One-dimensional SPM analysis is different than available results from literature which commonly decompose their one-dimensional outcome variable, for example knee joint flexion over normalized stance time, into zero-dimensional peaks and test for group differences. Previous analyses of peak knee joint moments may be problematic as each vector component is treated as independent which may result in bias (Pataky et al., 2013) and this reduction of the dimensionality of the data to a singular value may result in missing true differences between populations. Additionally, comparisons of peak variables from movement trajectories may inflate the risk of type I error unless there is an explicit a priori identification of the metrics tested, or family-wise experimental error is controlled (Pataky et al., 2016). To overcome such limitations, parametric 1D hypothesis testing provides a framework for hypothesis testing that considers magnitude and variation differences in patterns of data and compares each time step of a 1D signal statistically then corrects for multiple comparisons using Random Field Theory. Such procedures have become more common in biomechanics recently as this procedure can address biases of traditional peak analyses (Pataky et al., 2015) and has the added benefit of displaying differences visually over the cycle of interest. Still, it is important to note that differences detected by SPM within biomechanical analyses could be due to either magnitude or temporal shifts(Honert & Pataky, 2021) within the normalized cycle. Between-group statistical analyses were performed using the SPM plugin (http://spm1d.org/) within MATLAB 2022a (MathWorks Inc.) software. To avoid problems of heteroscedasticity the same number of trials, three steps, were pulled for each participant at each walking speed. Significance was set at $\alpha = 0.05$ and post hoc tests were planned to determine if there were within-speed differences in joint moments between pregnant and non-pregnant groups.

4.3 Results

4.3.1 Participants

In total, 10 healthy pregnant women in their third trimester with (mean ± SD) age 33 ± 2 years, height 1.65 ± 0.06 m, mass 77.3 ± 13.2 kg, and 10 non-pregnant nulliparous women with age 27 ± 3 years, height 1.64 ± 0.07 m, mass 66.9 ± 7.6 kg, volunteered to participate. The self-reported participant race distribution was 8 White, 1 Black, 1 Asian American pregnant participant and 8 white, 1 Iranian, and 1 Asian American non-pregnant participants. Participants gave written informed consent prior to participating and pregnant volunteers were required to bring a letter from their Obstetrician which cleared them to “walk for moderate exercise.” All protocols were approved by the University of Maryland’s Internal Review Board (#1552283). Participants were excluded if they reported any injury that would limit range of motion, strength, or the ability to walk or if they had any cardio-pulmonary, metabolic, or integumentary diagnosis where exercise was contraindicated.

Nulliparous (women who had not given birth) non-pregnant controls were significantly younger ($p < 0.001$; Group Mean (SD): 27 (3) years) than pregnant participants (33 (2) years). Height was not different ($p = 0.460$) between pregnant and non-pregnant groups. Groups had similar heights and pre-pregnancy mass (all $p > 0.334$). The current mass of pregnant participants (77.3 (13.2) kg) was significantly greater ($p = 0.022$) than non-pregnant participants (66.9 (7.6) kg).

4.3.2 Temporospatial Parameters

The average preferred walking speed for the pregnant group of participants was not significantly ($p = 0.13$) slower than the non-pregnant group walking speed (Table 4.2). Group mean (SD) temporospatial parameters are listed in Table 4.2. Pregnant participants took significantly wider steps ($p = 0.02$) than non-pregnant participants while walking at 1.5m/s.

Table 4.2 Mean (SD Temporospatial parameters for pregnant and non-pregnant groups at each walking speed.

Mean (SD) temporospatial parameters

	Self-Selected "Comfortable"		1.0m/s		1.5m/s		
Parameter	Pregnant	Non-Pregnant	Pregnant	Non-Pregnant	Pregnant	Non-Pregnant	
Speed (m/s)	1.19 (0.19)	1.28 (0.13)	1.05 (0.04)	1.01 (0.03)	1.46 (0.04)	1.47 (0.04)	
Cadence (step/s)	108.95 (6.16)	117.14 (9.04)	104.26 (5.09)	104.71 (6.42)	119.82 (6.99)	121.98 (5.33)	
Foot off (%)	67.77 (4.22)	66.16 (3.89)	67.18 (2.09)	68.10 (2.80)	64.09 (3.81)	65.72 (2.80)	
Step Length (m)	0.65 (0.09)	0.67 (0.04)	0.60 (0.05)	0.59 (0.03)	0.73 -0.04	0.73 -0.04	
Stride width (m)	0.15 (0.03)	0.13 (0.02)	0.15 (0.04)	0.13 (0.03)	0.16 (0.05)	0.13 (0.03)	*

* indicates a significant between group difference

4.3.3 Resultant Knee Joint Moments

From the SPM ANOVA, there were significant speed, group, and group-by-speed interaction effects (all p £ 0.05), indicated in Figure 4.1. Post hoc analysis of between-group differences within each speed condition indicated significant differences in knee flexion moment for all speeds with more extension for the pregnant group at heel strike ($p_{self\text{-}selected} = 0.007$, $p_{1.0m/s} = 0.011$, $p_{1.5m/s} = 0.005$) and greater flexion for the pregnant group near toe-off ($p_{self\text{-}selected} = 0.005$, $p_{1.0m/s} = 0.011$, $p_{1.5m/s} = 0.004$). Post hoc analysis of between-group knee adduction moments reveled significantly larger pregnant moments at all speeds (all $p < 0.001$) throughout a wide range of stance (~15% - 90%). Post hoc analysis of between-group knee rotation moments reveled more internal rotation for pregnant walkers at all speeds during loading response ($p_{self\text{-}selected} = 0.001$, $p_{1.0m/s} = 0.002$, $p_{1.5m/s} = 0.003$) and greater external rotation for pregnant walkers at all speeds throughout mid to late stance (all $p < 0.001$).

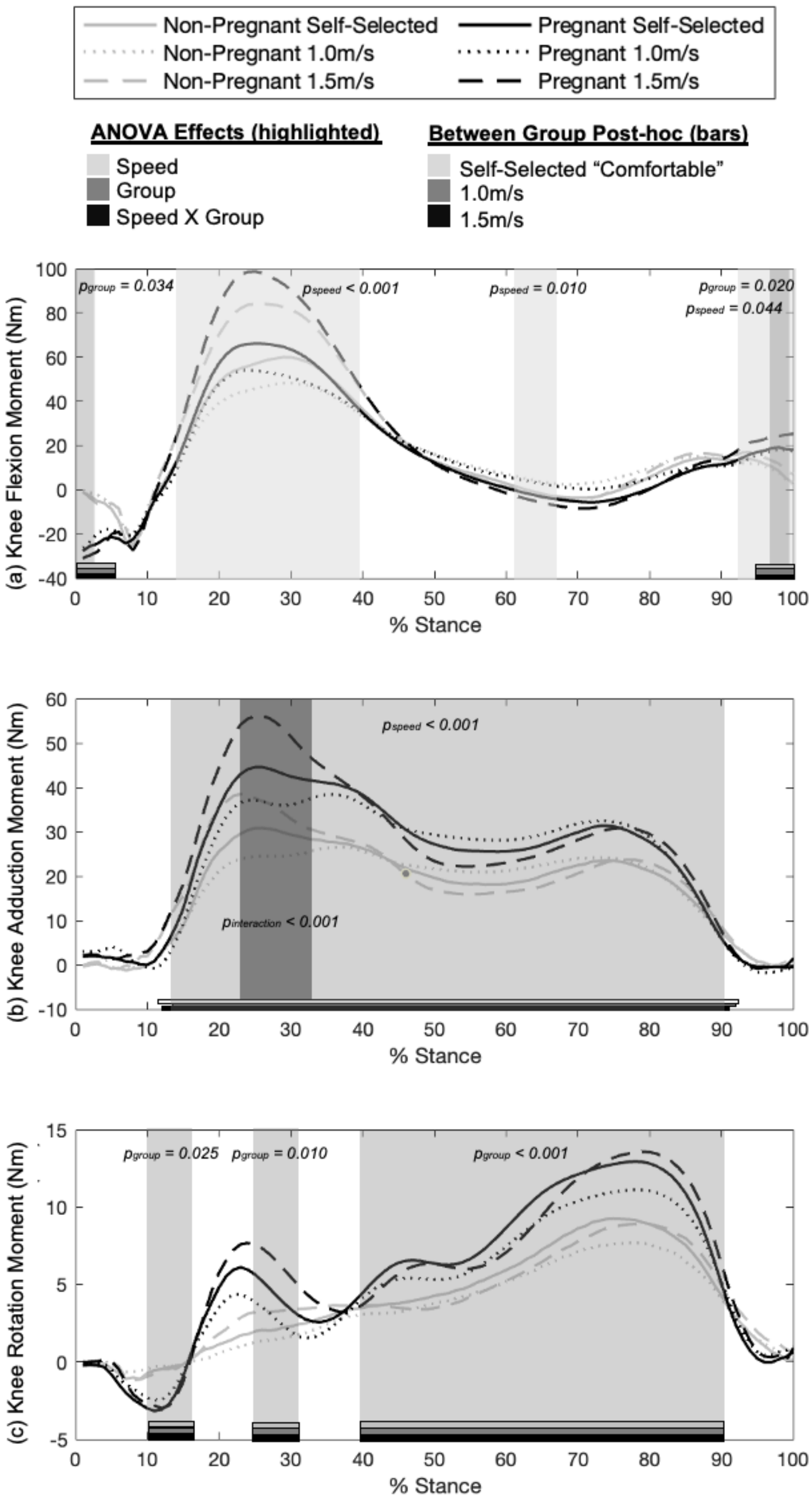

Figure 4.1. Average external 3D knee joint moments over the stance phase of walking for pregnant (black) and non-pregnant groups (gray) at self-selected "comfortable" (solid line), 1.0 m/s (dotted line), and 1.5 m/s (dashed line) speed conditions. Highlighted regions indicate significant ($p < 0.05$) main (Speed = light gray, Group = gray) and interaction (Speed X Group = black) effects. Bars on the x-axis indicate significant between-group differences within each walking speed (Pregnant > non-pregnant; $p < 0.017$)

4.4 Discussion

The purpose of this study was to determine if knee joint moments differ between pregnant and non-pregnant individuals as they walk at a range of walking speeds. Consistent with our hypotheses, pregnant individuals self-selected a “comfortable” walking speed slower than non-pregnant controls and knee joint moments across were significantly greater for pregnant women vs. controls across self-selected and controlled speeds. The present findings suggest that walking in pregnancy affects external knee joint mechanics and pregnant walking may result in increased and altered loading at the knee.

Pregnant individuals in this study self-selected a “comfortable” walking speed that was not significantly different from the walking speed of non-pregnant controls. Although some studies of daily activity in pregnancy report reduced self-selected speed throughout pregnancy (e.g., Van Raaij et al., 1990) this result seems to agree with many other published accounts of self-selected walking speed during instrumented gait analysis testing which also report no difference between self-selected speed in late-pregnancy and postpartum (Lymbery et al., 2005), throughout the first, second and third trimester (Forczek et al., 2019; Krkeljas, 2018), between pregnant women in the third trimester and non-pregnant controls.(Branco et al., 2013) Compared to other available kinetic analysis of late pregnant walking, the average self-selected, “comfortable” speeds of pregnant women in this current study (1.19 (0.19) m/s) were faster than self-selected walking speeds (1.13 (0.13) m/s) from Branco et al. (2016), comparable to self-selected speeds 1.2 (0.2) m/s) reported by

Foti et al. (2000), but slower than self-selected speeds (1.51 (0.10) m/s). reported by Bagwell et al. (2020)

As anticipated, faster walking speeds resulted in significantly increased knee flexion and adduction moments in both pregnant and non-pregnant women. However, this is the first biomechanical analysis of pregnant walking to consider speed effects on knee kinetics. A significant speed effect on knee flexion moment and a significant speed by group interaction during early stance for knee adduction moments indicate that between-group differences in walking speeds of pregnant and non-pregnant individuals is a confounder that must be controlled for when comparing joint moments between pregnant and non-pregnant walkers.

The present study found that when walking speed is increased knee adduction moment in early stance may be affected in a different way across pregnant and non-pregnant groups. This group-by-speed interaction suggests that joint moments experienced in pregnant walking may not only be increased with faster walking speeds but altered across early stance compared to non-pregnant gait.

The present study used non-normalized kinetic data to estimate how joint loading at the knee maybe affected by the relatively quick changes in mass experienced in pregnancy. Our results suggest that pregnant individuals experience greater knee joint moments compared to non-pregnant walking. This conclusion is different than Branco et al. (2016) who compared mass normalized peak 3D knee moments of pregnant women in their third trimester to nulliparous controls walking at comparable preferred walking speeds of 1.1 m/s (Branco, Santos-Rocha, Aguiar, et al., 2016) and found no significant differences between 3rd trimester participants and nulliparous (never-pregnant) controls. Our findings agree with available analysis of pregnant and postpartum women walking a similar walking pace of 1.5 m/s (Bagwell et al., 2020) which found increased peak knee adduction moments during the third trimester and post-partum compared to nulliparous controls. However, within Bagwell et al. (2020) peak moments were normalized to pre-pregnancy body mass instead of body mass of participants at the time of data collection. Although Bagwell et al. (2020) state that "…pre-pregnancy body mass for normalization of kinetics throughout pregnancy is a novel solution that could be used to identify changes in demand at the joint level." We agree that scaling by pre-pregnancy weight may be relevant for investigations are interested in the possible damage caused since pregnancy is associated with relatively quick changes in mass and tissues may have not accumulated to new heavier mass levels. relevant for investigations which aim to estimate loading changes. However, normalizing to pre-pregnancy body mass may be a problematic technique since it relies on self-reported pre-pregnancy weight which may involve recall error. Combined with the results of previous evaluations, it seems that resultant knee joint kinetics increase during late pregnancy compared to non-pregnant walking when knee joint kinetics are considered without gestational mass normalization.

Overall, the present results suggest that knee adduction moments may be altered as pregnant women change walking speeds and 3D knee joint moments over a range of walking speeds are greater in pregnant vs. non-pregnant individuals. Resultant knee joint moments are important measures related to knee joint loading and joint health and these present findings may indicate that the mechanical changes experienced during walking in late pregnancy may increase the loading experienced at the knee in multiple dimensions, with possible effects in not only the magnitude but pattern of knee joint adduction moments. Knee adduction moment is a well-documented indicator of medial compartment loading during walking and an important predictor of the severity (Astephen et al., 2008) and progression (Hatfield et al., 2015) of knee osteoarthritis. Increases in knee flexion moment across a range of speeds is also associated with increased medial compartment loading and likely contributes to knee osteoarthritis risk (Chehab et al., 2014). Results of the current study suggest that women experience greater and altered knee joint mechanics while walking in late pregnancy which may result in an increased risk of knee osteoarthritis and, in part, help explain the known increase in risk of knee osteoarthritis for women who experience pregnancy/pregnancies. Still, resultant knee joint moments are outcome measures that are commonly used as surrogate measures of knee joint loading in adult populations at risk of or who have knee osteoarthritis, but not direct measures of the load on cartilage and more information is required to understand how these measures relate to knee joint health.

4.5 Limitations

Quasi-experimental designs, such as this comparison between healthy pregnant and healthy non-pregnant women are limited since it is susceptible to selection differences in groups. Although groups were as matched as possible, the control group was significantly younger than the pregnant group. Although age may have an external effect on validity of the comparison, all participants were in the typical "young adult" age range (18-35 years), so the age difference is likely not a major factor. The groups in this study were recruited from the same local population and were similar in terms of height, pre-pregnancy weight, and race/ethnicity.

It's possible that the effect sizes within this study are smaller than what was originally projected in the *a priori* power analysis for this study which was based on analysis of only peak sagittal plane joint moment available in the closest related literature. However, even if resultant knee joint moments are similar between-groups, these results support the importance of analysis at a range of speeds and show the importance of controlling for speed as a potential confounder when comparing joint kinetics even when designing within-subjects analyses.

Pregnant participants visited the lab one time in the first half of the third trimester (weeks 28-35 gestation) and the present results do not necessarily generalize to the entire period of pregnancy nor necessarily to pre- vs. mid- vs. post-pregnancy longitudinal comparisons. Other factors which change with gestational time such as fetal position in the pelvis, hormonal changes, or walking comfort at the end of pregnancy may change walking ability, knee mechanics when walking, or the sensitivity of cartilage to mechanical loading.

The pregnant model parameters were based on Haddox et al. (2020) who gathered anthropometrics from a military population of pregnant women (Perkins & Blackwell, 1998)who had an initial BMI below 26 kg/m^2. We believe this model fairly represents the healthy, non-military population of pregnant women who participated in this research. Although pre-pregnancy mass was a self-reported value, the pregnant women in this study reported an average pre-pregnancy BMI of 23.99 (3.65) kg/ m^2.

4.6 Conclusion

The present results suggest that 3D knee joint moments over a range of walking speeds are greater in pregnant vs. non-pregnant individuals and knee adduction moments may be altered as pregnant women change walking speeds. Since pregnancy is associated with relatively quick changes in mass and tissues may have not accumulated to new heavier mass levels, we speculate that these changes in walking mechanics may contribute to osteoarthritis initiation or cartilage damage. Additional work is needed to determine if changes in resultant knee joint moments result in increased or altered knee joint loading in walking.

Chapter 5: The Mechanical Requirements of Walking in Late Pregnancy Elevate and Alter Internal Knee Joint Loading

5.1 Introduction

Experiencing multiple pregnancies has been associated with an increased risk of developing radiographically diagnosed knee osteoarthritis (Wise et al., 2013; Zhou et al., 2018). Although the causes behind this increased risk are complex, mechanical loading may play a major role (Felson, 2013). Pregnancy, which is associated with many changes in mechanical factors, such as increased and altered mass, likely results in altered or excessive local mechanical loading during walking (STUDY 1). If pregnancy results in abnormal loading mechanics, then additional "wear and tear" may significantly affect knee joint health. Experimental measures of fatigue via mechanical testing of articular cartilage suggests that the stress-life, or cycles until failure, of this tissue is exhaustible within the human lifespan and is sensitive to even small increases in the peak stress per cycle (Riemenschneider et al., 2019; Weightman et al., 1978). Therefore, increased and/or altered forces experienced at the knee during pregnant walking may accelerate degeneration via mechanical fatigue (Riemenschneider et al., 2019; Seedhom, 2006). Pregnant women may experience increased or altered knee joint loading as they walk for exercise (American College of Obstetricians and Gynecologists' Committee on Obstetric Practice, 2015) and this type of loading may affect many women over their lifetime as over 80% of females in the United States will experience at least one pregnancy by the end of their childbearing years (Pew Research Center, 2018). Accordingly, understanding the mechanical consequences of pregnant walking on knee joint loading is important to understand if the increased risk for osteoarthritis may be partially explained by mechanical effects.

Although, to our knowledge, estimates of knee joint loading in this population are not currently available in literature, there are many descriptions of pregnant knee joint moments at a self-selected pace which indicate that the resultant knee joint moment is similar in walking to non-pregnant adults (Branco, Santos-Rocha, Vieira, et al., 2016; Foti et al., 2000). External moments are commonly used as a surrogate measure for joint loading in gait (Simic et al., 2010) and can provide an accurate estimate of peak medial joint loading (Manal et al., 2015). However, even if external knee mechanics are sustained in pregnant walking, known changes in mechanical factors such as increased and altered mass distribution, increased knee joint laxity, and possible reductions in joint strength which make it likely that internal compensations may be necessary. Further, changes in knee adduction moment do not fully describe changes in medial knee joint contact force especially when total contact force may be changing (Meyer et al., 2013). Accurate interpretation of knee adduction moment effects on medial joint contact force requires consideration of muscle forces (Miller et al., 2015). An estimation of the distribution of the internal joint load is necessary to understand if sustaining external knee joint moments under the constraints of late pregnancy results in abnormal loading on knee joint cartilage.

Gaining an objective estimate of the internal joint forces experienced during pregnant walking would be useful to understand how walking in pregnancy may cause abnormal loading within the knee. Abnormal loading may be particularly worrisome if altered gait mechanics result in greater compressive medial knee loading since it is associated with medial knee osteoarthritis (Andriacchi et al., 2004) which is 5-10 times more prevalent than lateral knee osteoarthritis (Felson et al., 2002; S. Ahlbäck et al., 1968; Wise et al., 2012). Further, predicted medial knee contact force has been related to cartilage loss and disease progression (Brisson et al., 2021). Although medial knee joint contact force cannot be directly measured without taking invasive joint instrumentation (e.g., Bergmann et al., 2014; D'Lima et al., 2006) knee adduction moment is commonly used as a surrogate estimation for compressive knee joint contact force, and results from study 1 suggest knee adduction moment may be differentially affected by changing walking speed in late pregnancy.

Therefore, the purpose of this study was to estimate how joint contact forces, the internal distribution of force, and specifically, medial knee joint loading is changed while walking at a range of speeds in late pregnancy. It was hypothesized that pregnant subjects, who experience significant mass gain which shifts the body center of mass will experience (H2.1) greater overall compressive knee joint loads. This increase in joint load combined with shifted mass distribution will also result in (H2.2) elevated and medially shifted medial knee contact forces for pregnant vs. non-pregnant subjects. Finally, increased or altered contact mechanics in pregnancy will cause (H2.3) greater peak medial knee cartilage strains compared to non-pregnant walking.

5.2 Methods

5.2.1 Input data from Experimental Data Collection

Experimentally obtained kinematic and kinetic data from the gait analysis of 20 female volunteers (10 pregnant and 10 non-pregnant, see section 4.2.1 Participants) who walked at self-selected and controlled walking paces (see section 4.2.2 Experimental Setup) was input data for the mechanical models used in this analysis. Joint angle (Figure 5.1), joint moment (Figure 5.2), and resultant knee joint force (Figure 5.3) data from inverse dynamics modeling (Study 1; see section 4.2.3 Data Processing) was used as input for joint contact force modeling. Temporospatial values (Table 5.1 & Table 5.2) from the experimental gait collections were input for the cartilage mechanics model and probabilistic model of fatigue.

Table 5.1 Walking Speed for each pregnant and non-pregnant participant and speed condition

	Pregnant			**Non-Pregnant**		
Participant	Self-selected "Comfortable"	1.0 m/s	1.5 m/s	Self-selected "Comfortable"	1.0 m/s	1.5 m/s
1	0.96	0.96	1.41	1.44	1.00	1.47
2	1.54	1.12	1.50	1.22	1.01	1.41
3	1.09	1.07	1.41	1.23	1.05	1.52
4	1.16	1.09	1.46	1.27	1.00	1.56
5	1.04	1.06	1.43	1.24	1.00	1.46
6	1.37	1.05	1.51	1.59	0.96	1.45
7	1.00	1.05	1.44	1.18	1.04	1.44
8	1.38	1.05	1.48	1.25	1.03	1.50
9	1.18	1.02	1.46	1.19	1.00	1.46
10	1.20	0.99	1.52	1.16	1.01	1.47
Mean	**1.19**	**1.05**	**1.46**	**1.28**	**1.01**	**1.47**
SD	0.19	0.05	0.04	0.13	0.03	0.04

Table 5.2 Step Length for each participant and speed condition

	Pregnant			Non-Pregnant		
Participant	Self-selected "Comfortable"	1.0 m/s	1.5 m/s	Self-selected "Comfortable"	1.0 m/s	1.5 m/s
1	0.53	0.53	0.71	0.69	0.56	0.71
2	0.81	0.69	0.79	0.64	0.55	0.68
3	0.69	0.64	0.76	0.68	0.64	0.77
4	0.62	0.61	0.67	0.64	0.58	0.71
5	0.61	0.62	0.76	0.65	0.58	0.71
6	0.75	0.63	0.78	0.76	0.57	0.73
7	0.58	0.60	0.71	0.62	0.59	0.73
8	0.75	0.65	0.79	0.65	0.55	0.72
9	0.64	0.58	0.72	0.65	0.58	0.71
10	0.62	0.57	0.75	0.69	0.65	0.81
Mean	**0.66**	**0.61**	**0.74**	**0.67**	**0.59**	**0.73**
SD	0.09	0.05	0.04	0.04	0.03	0.04

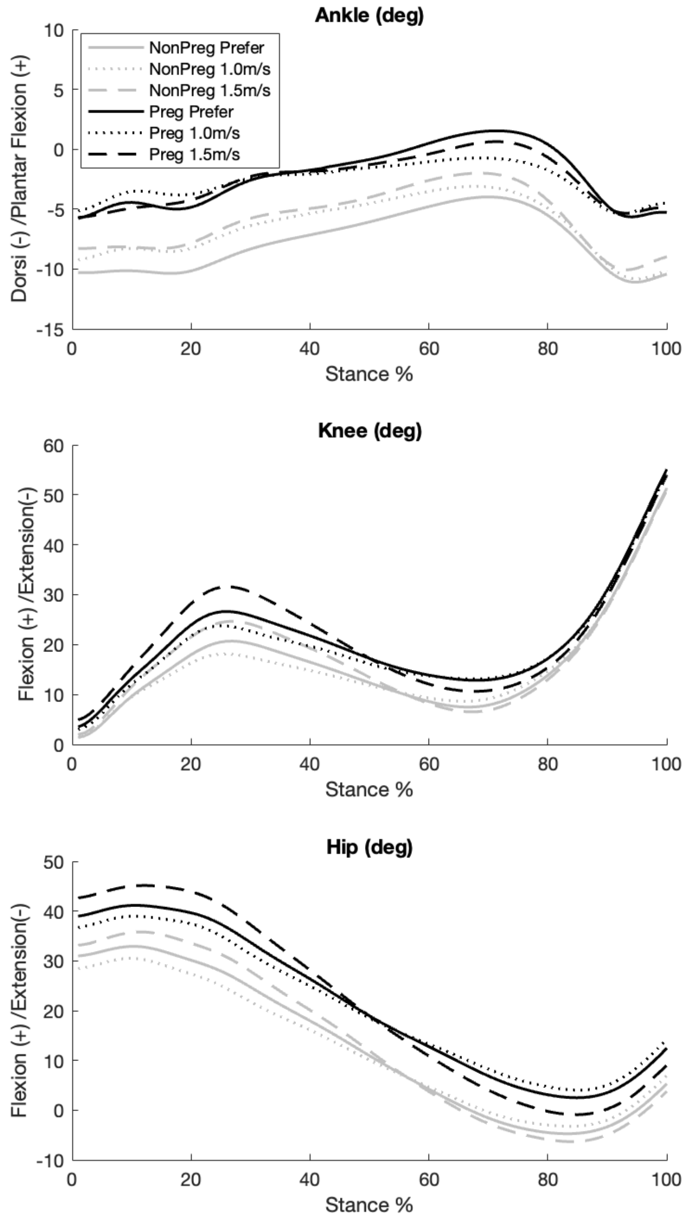

Figure 5.1 Joint angles for pregnant and non-pregnant groups at each walking speed (self-selected "comfortable", 1.0m/s, 1.5m/s)

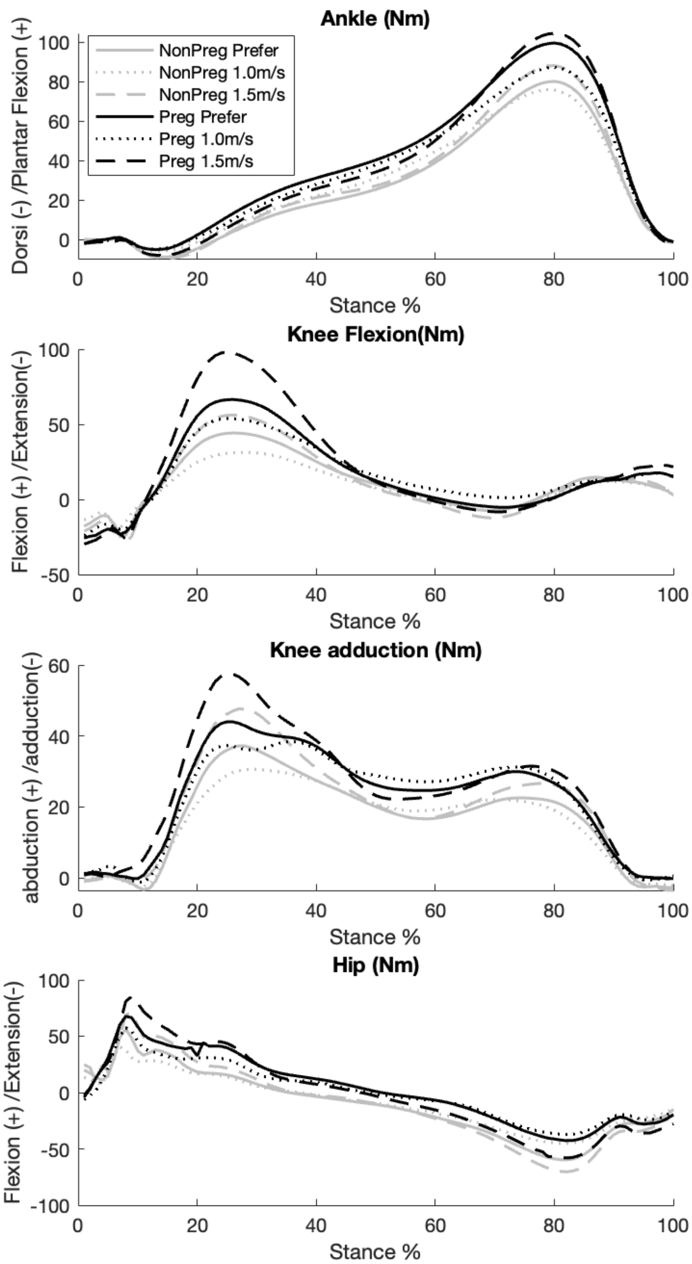

Figure 5.2. Joint moments from inverse dynamics analysis for pregnant and non-pregnant groups at each walking speed (self-selected "comfortable", 1.0m/s, 1.5m/s)

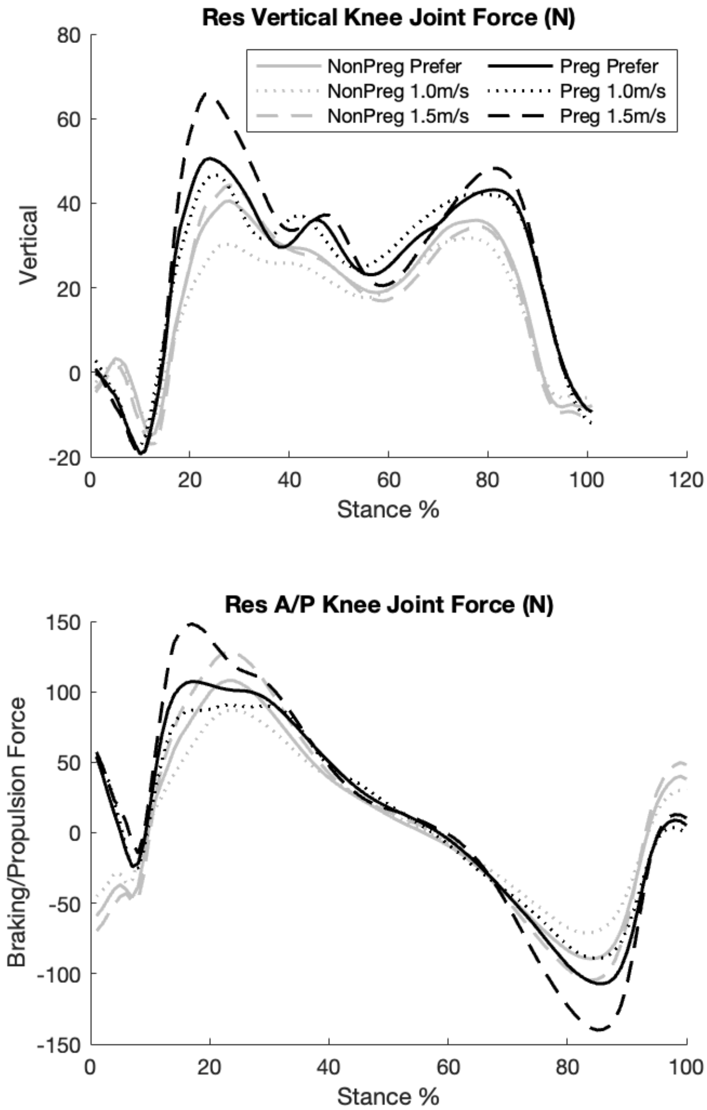

Figure 5.3. Resultant joint force measures from inverse dynamics for pregnant and non-pregnant individuals at each walking speed (self-selected "comfortable", 1.0m/s, 1.5m/s)

5.2.2 Muscle Force Estimation

Static optimization is a techniques which can overcome the force-sharing problem caused by anatomic redundancy, which can estimate muscular and allow for the estimation of joint contact forces by using a musculoskeletal model to represent the body (e.g., Figure 5.4; DeVita & Hortobagyi, 2001). Such modeling is useful since *in-vivo* determination of internal knee forces would be impossible or extremely difficult to perform in human subjects' research. For example, it is impossible to measure internal forces without taking invasive actions such instrumented knee replacement (D'Lima et al., 2006; Bergmann et al., 2014) but musculoskeletal modeling enables non-invasive estimation of knee contact forces. and solves the force sharing problem around complex joints such as the knee. Static optimization is time-independent (with estimates calculated separately for each point in time) and assumes that its cost function is representative of human gait. Static optimization is fast and easy method to implement within current software and personal computer processing power.

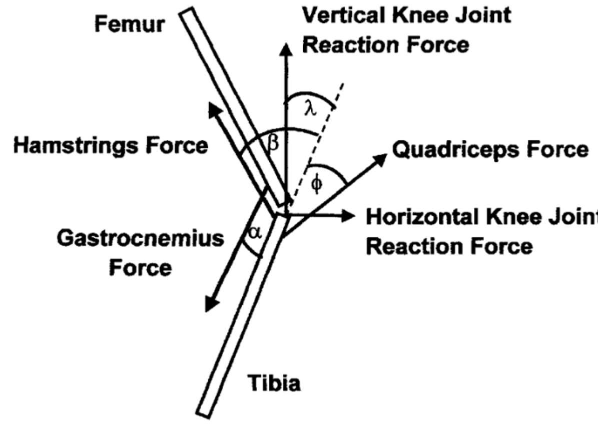

Figure 5.4. Schematic of mathematical model used within static optimization (taken from DeVita and Hortobagi, 2001)

Muscle forces were calculated using the model of (Devita & Hortobagyi, 2001), where static optimization was used to find a set of muscle forces that generated ankle, knee and hip torques from the inverse dynamics modeling in Study 1. Muscle moment arms and orientations were defined as quadratic functions of the knee flexion angle using average values for women from (Ward et al., 2009; Wretenberg, 1996). The patellar tendon moment arm was from (Herzog & Read, 1993)Agonist forces in the hamstring and gastrocnemius muscles were determined from the ankle plantar flexion moment and hip extension moment. These agonist forces were subtracted from the knee extension moment so that the patellar tendon force could be determined by dividing the remaining antagonist moment by the patellar tendon arm. Individual hamstring muscles (biceps femoris, semimembranosus, semitendinosus) and the two gastrocnemius heads distributed by ratios of their physiological cross-sectional areas from (Arnold et al. 2010).

The validity of biceps femoris, patellar tendon, force was supported by visual comparison to experimentally collected group mean muscle activations represented by EMG linear envelopes computed in visual3D software. Linear envelopes were computed from raw analog data obtained from wireless surface sensors which were placed according to Seniam recommendations for placement (Hermens, 1999) on the right side of participants for the vastus medialis, biceps femoris, gastrocnemius medius and tibialis anterior muscles. Signals were filtered, rectified, and processed into linear envelopes then displayed over the normalized gait cycle using a custom code in visual3D software (*EMG Linear Envelope*, 2008). Experimental linear envelopes and of muscle activations and estimates of muscle forces were plotted side by side over the normalized stance cycle for visual comparison. The patellar tendon force pattern was compared to the linear envelope of the vastus lateralis.

Static optimization modeling is a technique that will predict the minimum amount of antagonistic co-contraction (Herzog, 1993). As such, this approach may not account for increased muscular co-contraction which may occur in pregnancy to counteract increased joint laxity or perceived instability. Instead, static optimization will produce conservative estimates of how internal forces may be affected with pregnancy. To compare this conservative modeling approach to co-contraction seen experimentally assumptions were investigated by computing co-contraction areas between the linear envelopes (*EMG Linear Envelope*, 2008) of experimentally obtained muscle activations of the biceps femoris muscle (agonist) and vastus lateralis (antagonist) muscles over the first 33% of stance (Seyedali et al., 2012). Generally, static optimization underestimates total knee contact force throughout the stance phase of the gait cycle (Imani Nejad et al., 2020) and will allow us to generate conservative estimates the mechanical effect of pregnancy on knee joint loading. Co-contraction area (CCA) calculations (Seyedali et al., 2012)were performed to compare co-contraction between the hamstring and quadriceps during early stance:

$$CCA = \frac{\int Antagonist}{\int Agonist} \qquad \text{[EQ 5.1]}$$

Once muscle forces were estimated joint contact force was estimated using a reduction approach. Cruciate and collateral ligament forces were included in the contact force calculation using the model described by Morrison (1968). The distance between the medial and lateral tibiofemoral contact points in the frontal plane was assumed to be 5.0cm on average and scaled linearly for each subject by the distance between the medial and lateral femoral condyle markers during the standing calibration trial. Baseline model parameters were identical to what was used in walking analysis by Miller and Krupenevich., 2020.

Medial knee contact forces were calculated by balancing internal and external moments of force about the lateral tibiofemoral contact point (Miller et al., 2015). Lateral knee contact forces were determined by subtracting medial contact forces from total joint contact force. Errors reported with this method seem to be low, with errors of 0.3-0.9 x body weight (Miller et al., 2015; Dumas et al., 2019), resulting in accurate estimates that are comparable to measures from instrumented joint replacements.

To evaluate the mediolateral distribution of forces between groups a ratio of the medial joint contact force divided by the total "compressive" joint contact force was figured throughout the stance phase of walking (Equation 5.2.2):

$$distribution\ (\%) = \frac{medial\ joint\ contact\ force}{axial\ joint\ contact\ force} \qquad \text{[Eq. 5.2]}$$

5.2.3 Cartilage Mechanics

A phenomenological model of the knee was used to estimate the effect of medial knee joint loading on medial knee joint cartilage and address the last hypothesis, that contact mechanics will cause peak strains on cartilage to be increased during late pregnancy. The distribution of Peak knee contact forces from an average of five strides per subject was input into a model of medial knee contact mechanics, established in Miller & Krupenevich (2020), based on Nuño and Ahmed (2001) was used to determine the strain distribution on the tibiofemoral cartilage (Figure 5.5).

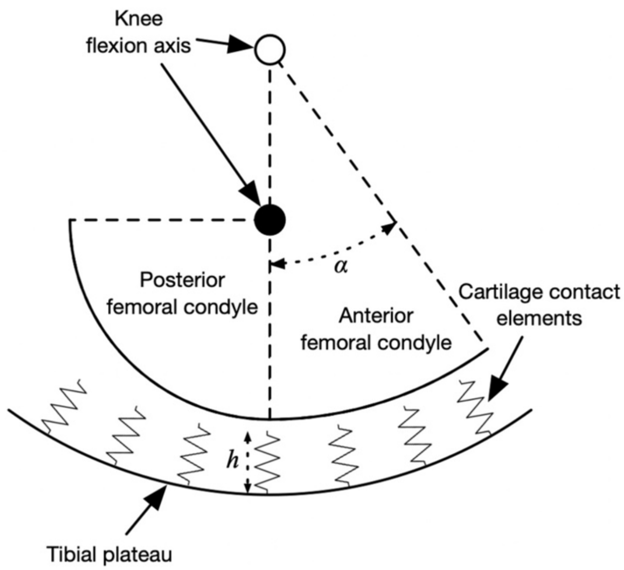

Figure 5.5 Tibiofemoral model of cartilage from Miller and Krupenevich (2020)

Within this tibiofemoral model the tibia was fixed, and the femur had two degrees of freedom (flexion axis height and flexion angle). An array of contact elements represented the tibiofemoral cartilage on the tibial plateau with separation distance (d = 0.05 mm). The nonlinear elastic stress-strain relationship of each element (σ_i) was:

$\sigma_i = -E_i \cdot \ln(1 - \epsilon_i)$ or $\sigma_i = E_i \cdot \epsilon_i$ [Eq. 5.5]

where ϵ_i and $\epsilon_i$were the cartilage/meniscus modulus and strain for each element, respectively. Within this model the moduli for the femoral cartilage, uncovered tibial cartilage, and covered tibial cartilage will be 8.6, 4.0, and 10.1 MPa, respectively (Shepard and Seedhom, 1999/Miller and Krupenevich 2020). The modulus of the medial meniscus was 1.3 MPa and the meniscus covered the outer 46% of the tibia plateau (Danso et al., 2015; Bloecker et al., 2013). The discrete-element model used to represent distributions of cartilage (black) and meniscus (gray) is shown on the right of Figure 5.6, published in Miller and Krupenevich (2020).

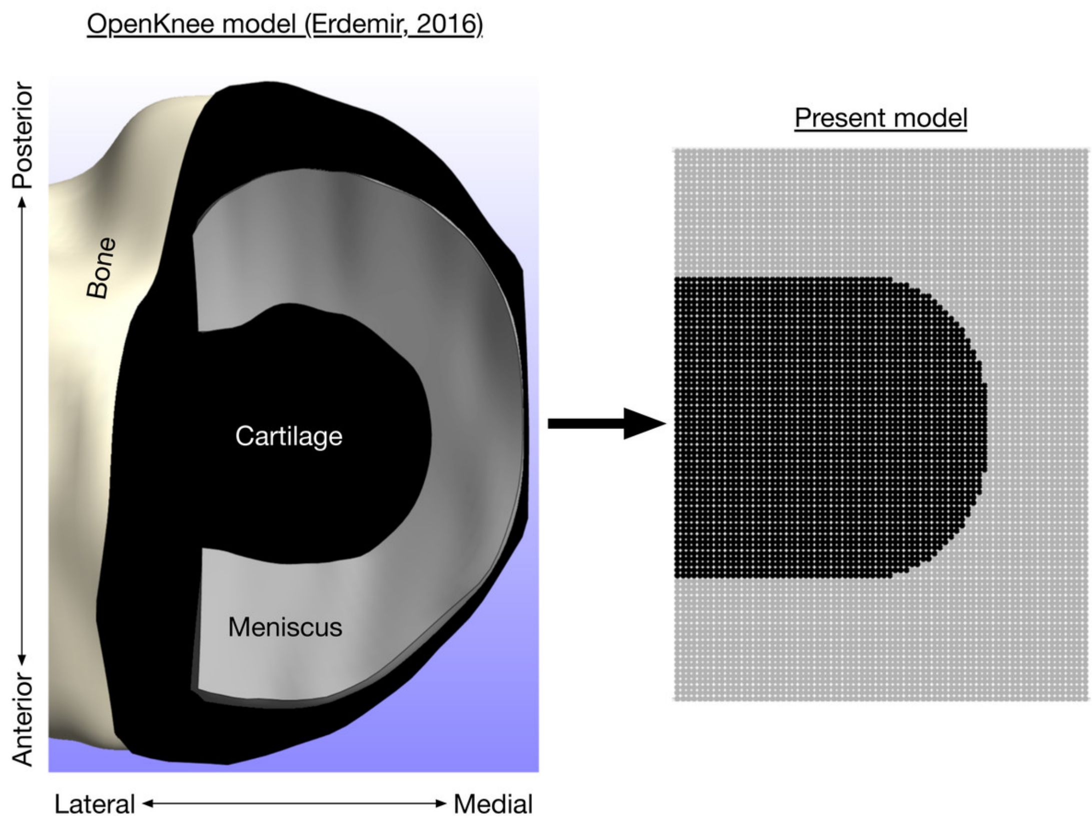

Figure 5.6 Open knee model used in the discrete-element model used to represent cartilage and meniscus. Figure from Miller and Krupenevich (2020)

The strain for each modeled element, ϵ_i :

$$\epsilon_i = y_i/h \quad \text{[Eq. 5.6]}$$

was dependent on spring compression of each element, y_i and flexion axis height, h. Within the model knee flexion angle was set to the angle from the gait analysis dataset (study 1) at which peak medial knee contact force occurred and the flexion axis height was calculated such that the contact force equals the participants average value from the gait analysis data. Knee contact force, F, was the sum of the contact stresses for all the elements multiplied by the element area:

$$F = d^2 \sum_{i=1}^{N} \sigma_i \qquad \text{[Eq. 5.7]}$$

Where N is the number of contact elements (7,326 with d = 0.05mm), d^2 = 0.25 mm^2 and σ_i was the contact stress experienced by element i.

This model of cartilage mechanics was used to estimate the greatest cartilage strains for pregnant and non-pregnant walking at each speed. Visualizations of the average group strain distributions were generated for each group at each walking speed condition. The location of max strain was recorded. Greatest strain was compared between pregnant and non-pregnant groups across three different walking speeds (self-selected, 1.0m/s, 1.5m/s).

5.2.4 Statistical Analysis

Independent t-tests were performed to test the null hypotheses of equal CCA. If the null hypothesis could not be rejected ($p > 0.05$), two-sided tests of equivalence were performed. The equivalence test was accepted if $p < 0.05$). This comparison between pregnant and non-pregnant co-contraction areas was performed for each of the three-walking speed conditions.

SPM analysis using a two-factor (Group: pregnant, non-pregnant) repeated measures (Speed: preferred, 1.0 m/s, 1.5 m/s) ANOVA model was used to determine the extent to which pregnancy and walking speed influence estimates of axial “compressive” joint contact forces and medial joint forces over the stance phase of walking. To avoid problems of heteroscedasticity the same number of trials, three steps, were pulled for each participant at each walking speed. A significant ($p < 0.05$) group-by-speed interaction is expected with Bonferroni corrected post hoc indications of insignificant differences in joint loading at self-selected speeds and increased pregnant joint loading in pregnancy within trials that are speed controlled. Since the hypothesis was directional, a one-way independent t-test was used to compare the distribution of mediolateral as a percentage of total compressive force between pregnant and non-pregnant groups. All tests used an alpha equal to 0.05 with Bonferroni corrected planned to investigate within-speed differences using1D SPM t-tests as post hoc tests.

To address the expectation that peak cartilage strains would be increased in pregnant walking the greatest cartilage strains in walking were compared between groups and walking speeds. The peak medial knee contact forces were used as input to the contact mechanics model and the resulting distributions of strains across the elements in the model were determined and compared between groups at each walking speed. A repeated measures mixed ANOVA model was used to determine how group and speed effects influence peak estimates of cartilage strain. Group-by-speed interactions were investigated with planned, post hoc analysis of between group differences at each walking speed with Tukey HSD correction for family-wise error rates.

5.3 Results

5.3.1 Muscular Force Estimates

The forces estimated by static optimization for the biceps femoris, patellar tendon, and medial gastrocnemius (Figure 5.7a) had visually similar activation regions (% Stance) to the biceps femoris, vastus lateralis, and medial gastrocnemius linear envelopes computed from muscle activations obtained during experimental gait analysis (Figure 5.7b).

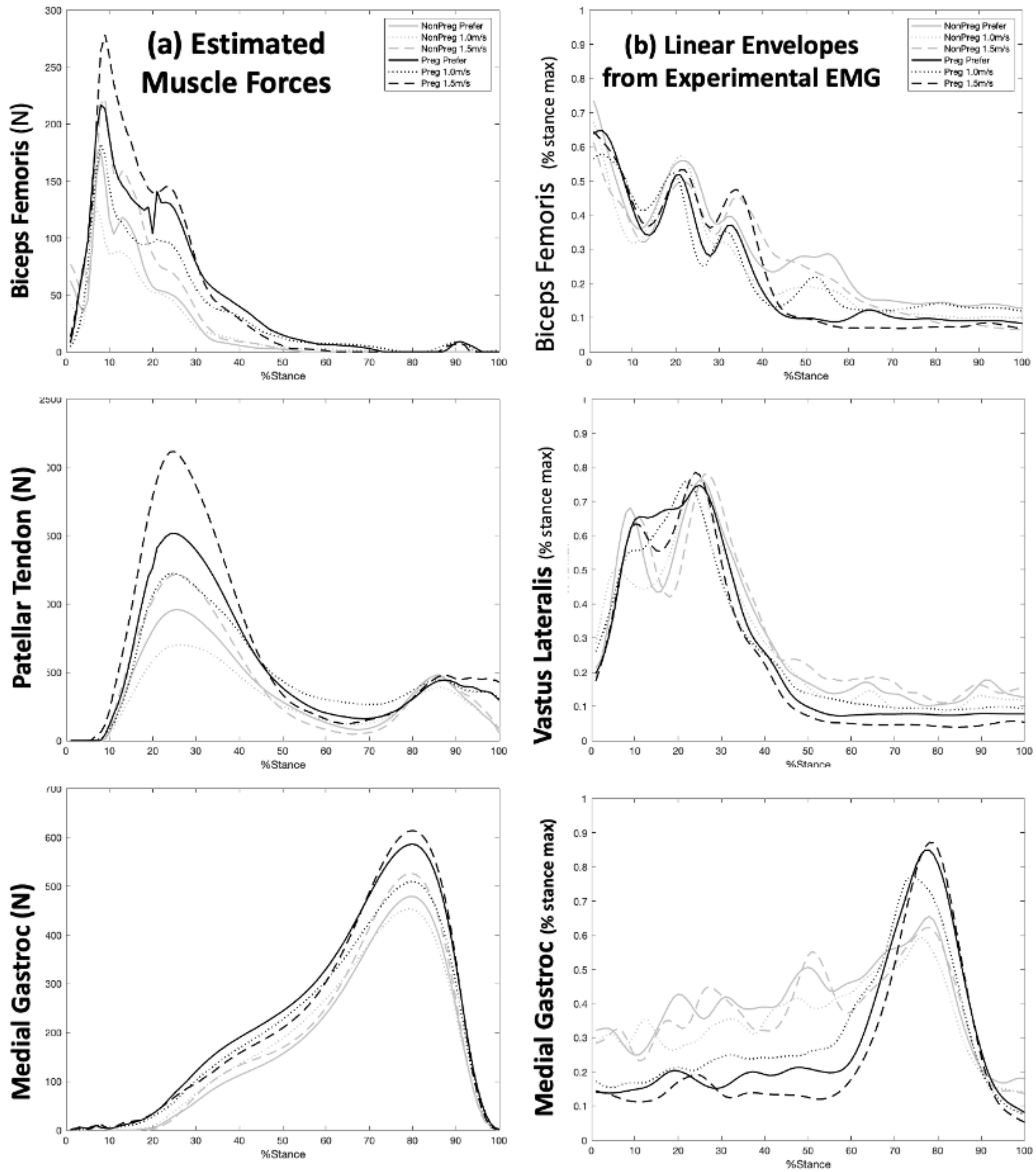

Figure 5.7 Muscle force estimations were compared with experimentally collected EMG patterns which were processed into linear envelopes normalized to the max value during stance.

Co-contraction of the knee was quantified by computing co-contraction areas between the linear envelopes of the experimentally obtained vastus lateralis (VF) activation and bicep femoris (BF) muscle activation during the first 33% of stance for Pregnant and Non-Pregnant groups walking at self-selected "comfortable" speeds and controlled speeds of 1.0 m/s and 1.5 m/s. Table 5.3 indicates group mean (SD) CCA for each walking speed. Co-contraction areas between groups were not significantly different from one another and (Figure 5.8 all $p \geq 0.712$) but not equivalent (Table # all $p \geq 0.299$).

Table 5.3 Group (Pregnant/Non-Pregnant) mean (SD) co-contraction areas for the biceps femoris (Hamstring muscle, agonist) and vastus lateralis (antagonist) during loading response (0-33% stance).

	Pregnant		Non-Pregnant		*t-test*	*Equivalence*
	Mean	(SD)	Mean	(SD)	*p value*	*p value*
Self-Selected	38.3	(11.4)	36.3	(13.5)	*0.8015*	*0.299*
1.0m/s	30.6	(8.0)	33.6	(15.8)	*0.7117*	*0.934*
1.5m/s	39.2	(31.5)	34.0	(10.6)	*0.7518*	*0.507*

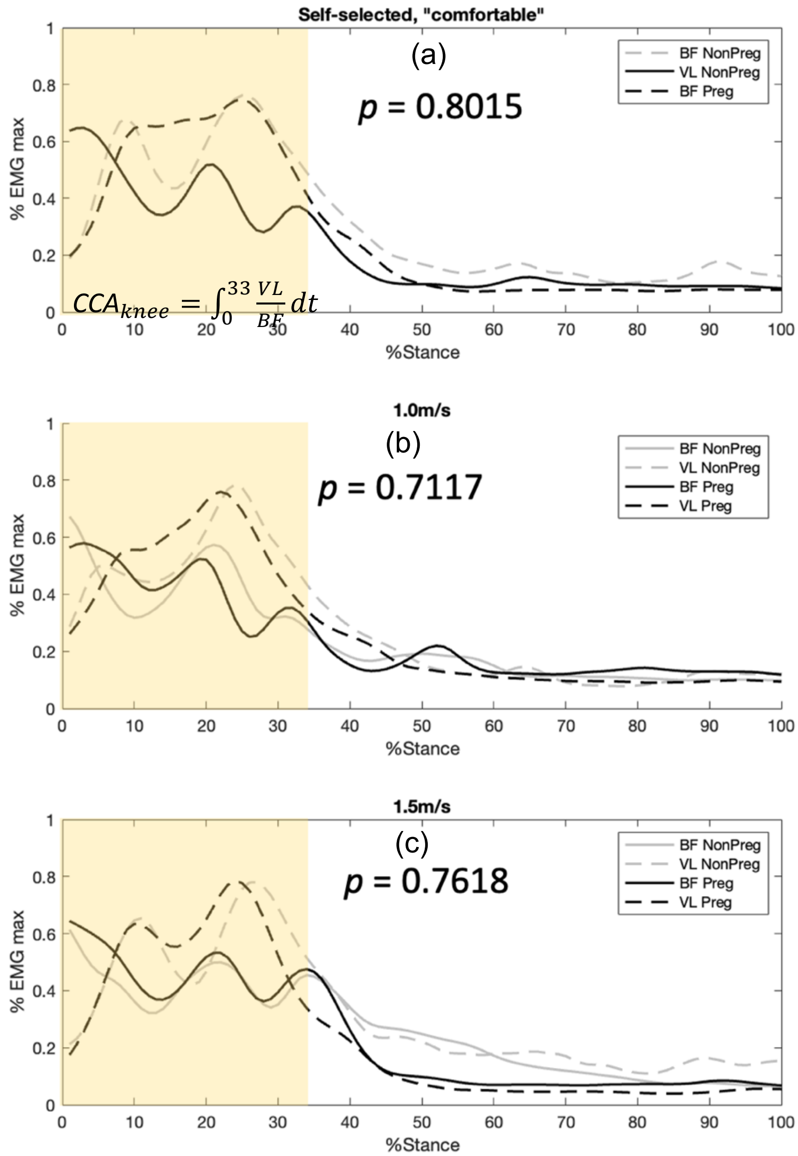

Figure 5.8. Co-contraction of the knee was quantified by computing co-contraction areas between the linear envelopes of the experimentally obtained vastus lateralis (VF solid lines) activation and bicep femoris (BF) muscle activation during the first 33% of stance (yellow highlighted region) for Pregnant (Black lines) and Non-Pregnant (Gray lines) groups walking at (a) self-selected "comfortable" speeds and (b) controlled speeds of 1.0 m/s and (c) 1.5 m/s.

5.3.2 Knee Joint Contact Forces

Analysis of knee joint contact force indicated significant speed effects (F* = 7.009, all $p \leq 0.001$) at limb loading, midstance and at toe off and significant group effects (F* = 12.135, all $p \leq 0.027$) during limb loading in early stance and at push-off in late stance (Figure 5.9). Post hoc analysis revealed increased limb loading in early stance (all $p \leq 0.002$) and at toe off (all $p \leq 0.017$) while walking at controlled speeds (1.0m/s, 1.5m/s).

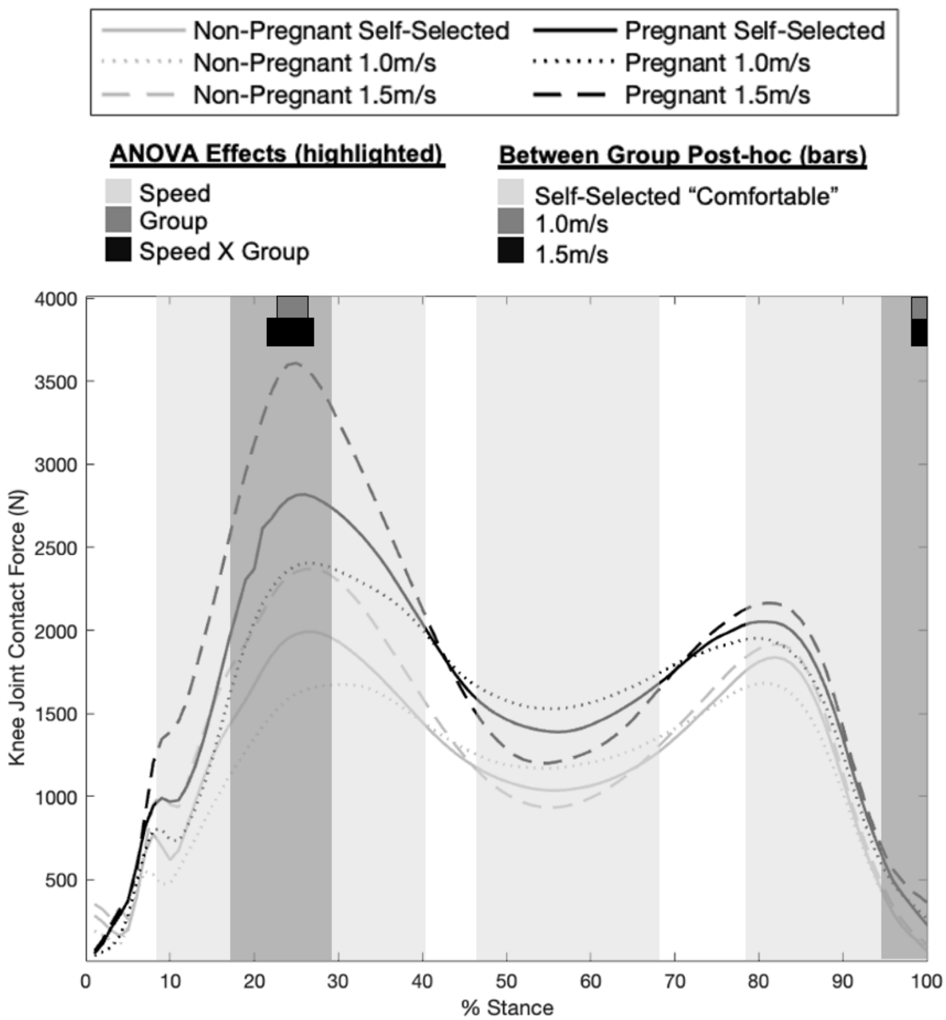

Figure 5.9. Average total compressive knee contact forces for pregnant (black lines) and non-pregnant controls (gray lines) during the stance phase of walking at self-selected "comfortable" (solid lines) and controlled (1.0m/s (dashed lines) or 1.5m/s (dotted lines)) speeds in Newtons. The plots begin at heel-strike and end at toe off.

Main ANOVA effects of Speed (F* = 7.009, all $p \leq 0.001$ light gray) and Group F* = 12.135, all $p \leq 0.027$, dark gray) effects are highlighted over the stance region of significance. Significant Bonferroni corrected post-hoc between group differences within each walking speed are indicated by bars across the top of the graph with (self-selected, 1.0m/s, 1.5m/s represented by light gray, dark gray, black bars, respectively).

Similarly, analysis of medial knee joint contact force indicated significant speed effects (F* = 7.009, all $p \leq 0.001$) at limb loading, midstance and at toe off along with group effects (F* = 12.135, all $p \leq 0.027$) during limb loading and toe off (Figure 5.10). Post hoc analysis revealed increased limb loading at heel strike while walking at 1.5m/s ($p = 0.017$) and greater loading in all walking speeds during pregnancy at toe off (all $p \leq 0.014$).

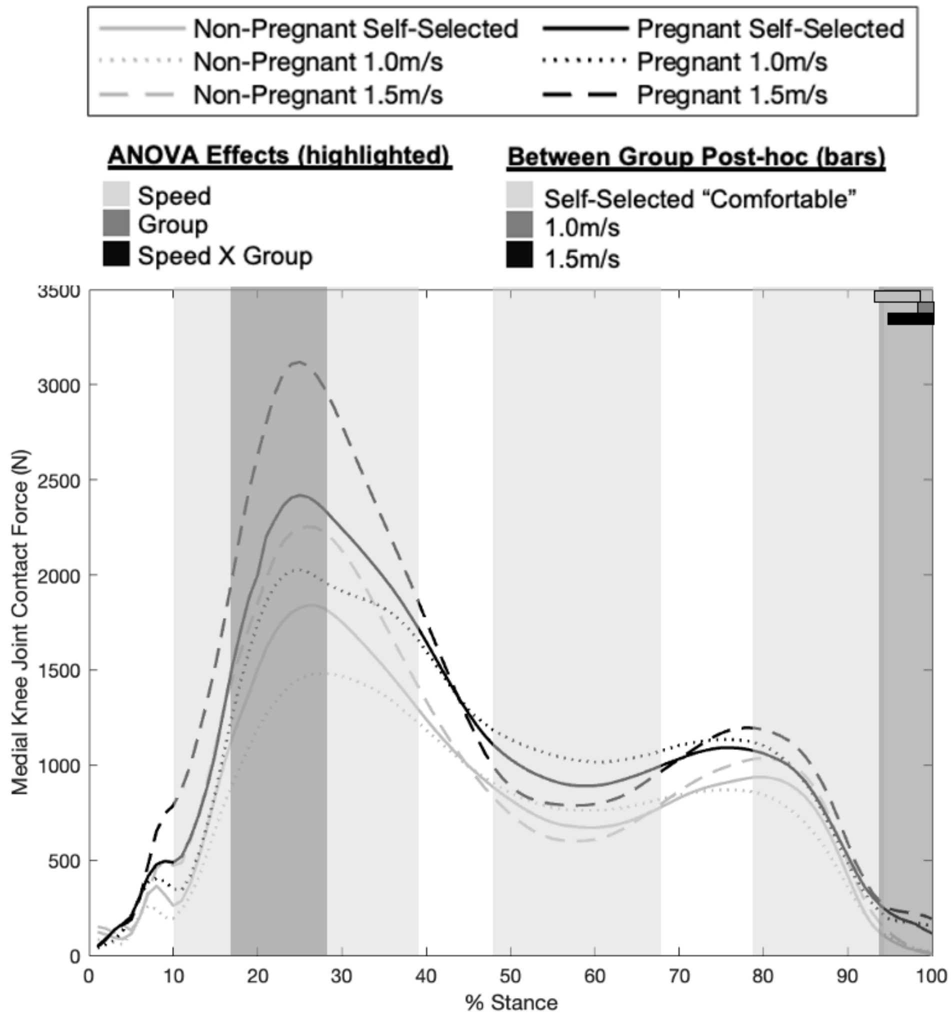

Figure 5.10 Average medial knee contact forces for pregnant (black lines) and non-pregnant controls (gray lines) during the stance phase of walking at self-selected "comfortable" (solid lines) and controlled (1.0m/s (dashed lines) or 1.5m/s (dotted lines)) speeds in Newtons. The plots begin at heel-strike and end at toe off. Main ANOVA effects of Speed ($F^* = 7.009$, all $p \leq 0.001$ light gray) and Group $F^* = 12.135$, all $p \leq 0.027$, dark gray) effects are highlighted over the stance region of significance. Significant Bonferroni corrected post-hoc between group differences within each walking speed are indicated by bars across the top of the graph with (self-selected, 1.0m/s, 1.5m/s represented by light gray, dark gray, black bars, respectively).

The percentage of total joint contact force distribution was not significantly greater for pregnant women walking at any of the speed conditions (Figure 5.11; all $p > 0.4016$).

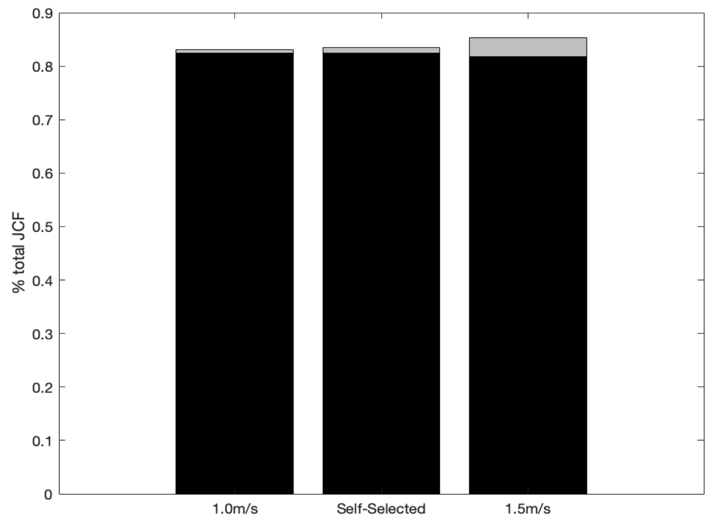

Figure 5.11 Average distribution percentage (average medial joint contact force/ average total axial joint contact force) for pregnant (black bars) and non-pregnant groups.

5.3.3 Knee Cartilage Mechanics

Group mean distributions of cartilage strain from the discrete-element model (Figure 5.12), modeled at the knee angle at which peak medial knee joint contact force occurred and visual inspection of 2D results indicate greater experienced strain during pregnancy at all walking speeds.

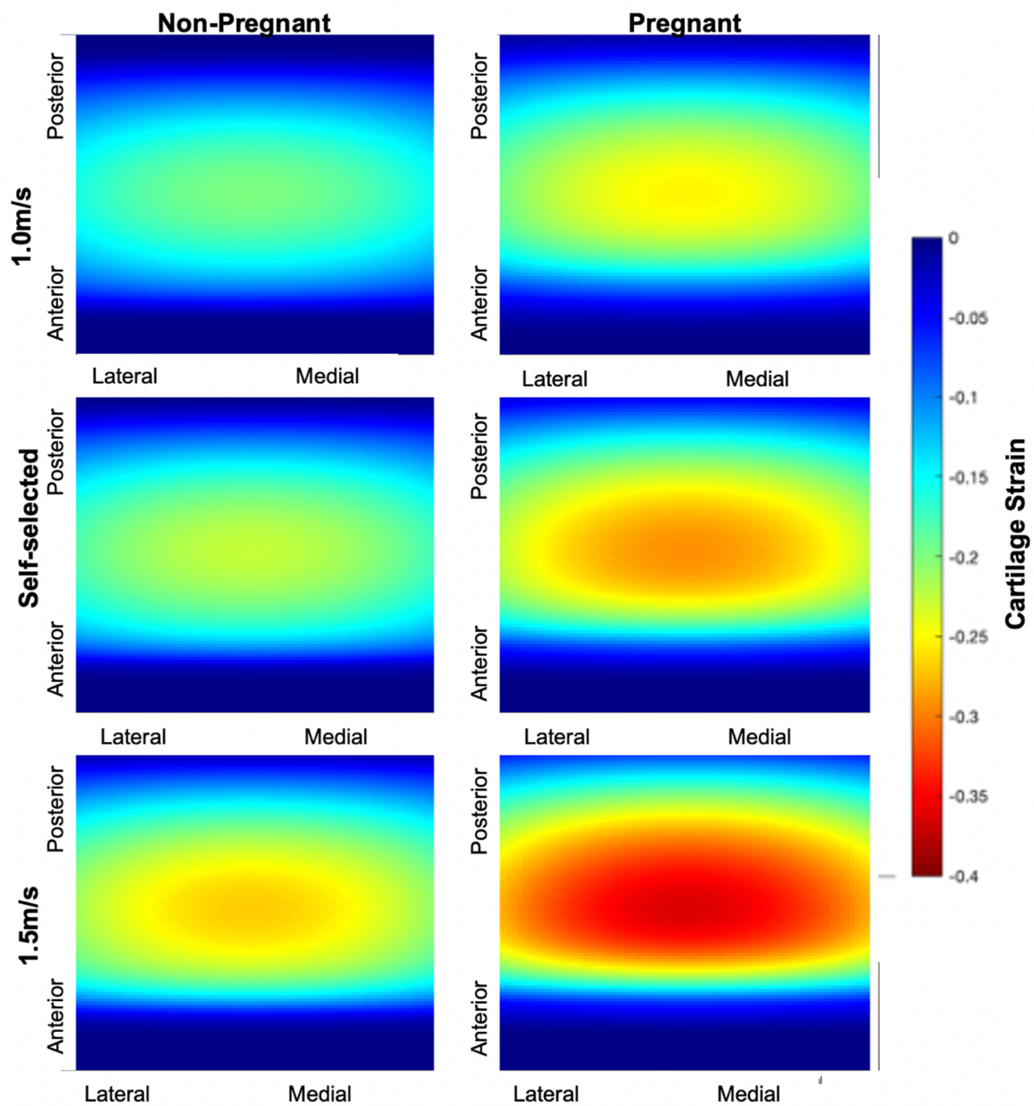

Figure 5.12 Two-dimensional view of group mean strain distribution at the instance of peak medial joint loading for pregnant and non-pregnant groups at self-selected and controlled (1.0m/s, 1.5m/s) walking speeds.

All maximum strain values occurred in the middle cell of the discrete-element model. A two-way mixed ANOVA was conducted to investigate the impact of group and speed on strain. There was a significant speed ($F(2,17) = 80.172$, $p^* < 0.001$, $\eta 2= 0.897$) with faster speeds resulting in greater magnitudes of strain. There was a group effect ($F(1,18) = 11.192$, $p^* = 0.004$ $\eta 2= 0.383$), with pregnant women experiencing more strain. There was a significant interaction between group and speed (F (2,17) = 7.667, p = 0.013, η2= 0.299) indicating that strain increased in a different way as pregnant women walked at faster speeds. Post hoc, one-sided, independent t-tests indicated significantly greater strain for pregnant women walking at self-selected velocities (p = 0.004), 1.0m/s (p = 0.004), and 1.5m/s (p = 0.002).

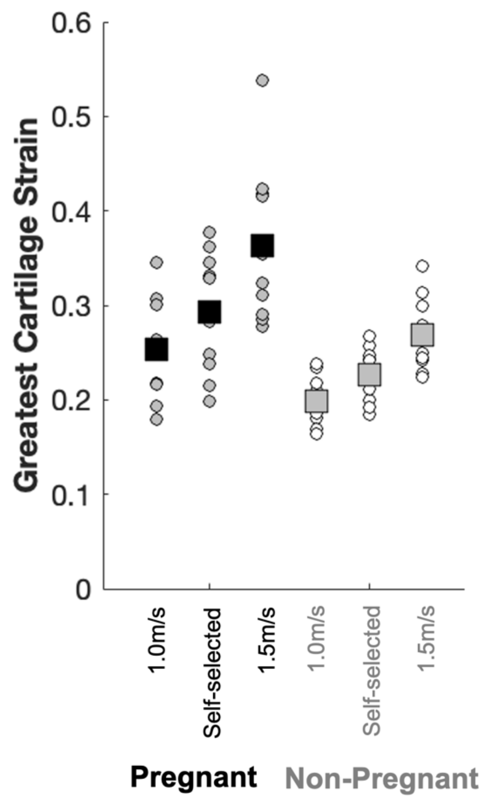

Figure 5.13. Peak cartilage strains (individual data = circles, group mean = square) between pregnant and non-pregnant groups at all walking speeds.

5.4 Discussion

This current study assessed the effect of pregnancy and walking speed on tibiofemoral joint contact forces and estimate how increased or altered loading would change the deformation of medial tibiofemoral cartilage. Present results suggest that pregnant participants experienced increased total and medial compartment knee loading as compared to non-pregnant controls over a range of walking speeds. In line with our hypotheses, over all walking conditions greater knee joint loading was experienced in pregnancy and resulted in greater peak cartilage strain. To our knowledge this is the first study to explore tibiofemoral contact forces and cartilage strain during pregnant walking. The present findings suggest that the mechanical factors associated with pregnancy and shifts in walking mechanics experienced during pregnancy influence internal loading at the knee and may increase and alter the load experienced on cartilage withing the medial tibiofemoral compartment of the knee.

In agreement with the first hypotheses total tibiofemoral joint contact forces were influenced by pregnancy and walking speeds. When walking speed increased loading increased across stance. Pregnant participants experienced greater loading in early stance and at toe off while walking at controlled speeds. Although internal distribution of force was not changed while walking in pregnancy, medial knee joint contact force magnitudes were influenced by speed and pregnancy. Pregnant women experienced greater medial loading at heel strike when walking at 1.5m/s and over all speeds at toe off. These results agree with previous research which demonstrated that tibiofemoral contact forces during weight acceptance are sensitive to changes in walking speed (Knarr. et al., n.d.). Although no previous estimates of medial tibiofemoral contact forces during pregnant walking is available, these results are in line with previous research which found that knee joint contact forces increased with carried load (15 or 30kg of body armor) and walking speed which report that tibiofemoral contact forces increased in response to carried load and increasing walking speed increased the first peak of medial compartment tibiofemoral contact forces (Lenton et al., 2018). The current study suggests that, compared to non-pregnant walking, carrying the load of pregnancy causes increased external loads that muscle forces must counteract to prevent the lower-limb joints from collapsing and increase tibiofemoral contact forces. If, over the relatively short timeline of pregnancy, the body doesn't physiologically adapt to the increased loading during walking then these forces could explain the increased risk of degenerative joint diseases following motherhood.

The third hypothesis, that contact mechanics will cause peak strains to be increased during late pregnancy at all walking speeds is accepted. Contact mechanics between the femoral condyle and tibial plateau resulted in greater peak strains during pregnant walking at all speed conditions with faster walking speeds causing larger magnitudes of peak strain. Current results indicated that peak cartilage strain may increase differently as pregnant women increase walking speed which may indicate that changes in gait mechanics at different speeds influence cartilage deformation.

The current study estimated magnitudes of peak medial compartment contact deformation with a scale that was comparable to *in vivo* fluoroscopic analysis of tibiofemoral cartilage deformation during the stance phase of gait (F. Liu et al., 2010). For example, the healthy non-pregnant women in our study walking at 1.0m/s had peak cartilage strains of 18.5-26.8% which is similar to results from Liu et al. (2010) who had healthy adults (8 male, 2 female) walking at a slower speed (0.67m/s) and experiencing deformation ranges of 7-23% of cartilage thickness. Beyond analysis of peak magnitude of deformation, a future analysis into the location and differences in contact force across the medial tibiofemoral compartment throughout stance may help identify how loading changes and where future injury or disease progression may occur.

A relatively simple 2D musculoskeletal model was used in this study for static optimization (Devita & Hortobagyi, 2001; Miller et al., 2017), which may be considered a limitation. However, this approach is able to produce similar muscle forces to more mathematically complex and computationally costly static optimization methods (Kernozek et al., 2017). Although static optimization may under estimate antagonist measures (Kian et al., 2019) these modeling issues may affect the numerical values of the results but would be unlikely to change the conclusions (Miller et al., 2017). Future studies could utilize EMG informed static optimization methods if greater accuracy is necessary. Such methods may further exacerbate group differences in muscular force estimates because physiological changes associated with pregnancy, such as greater joint laxity / perceived instability may result in greater co-contraction for stability. Within this study a preliminary analysis of muscular co-contraction at the knee was performed with average linear envelopes from five pregnant women and five non-pregnant controls. Traditional independent t-tests and tests of equivalences these co-contraction areas were not different from another and not equivalent between groups in the current study. With average data from only five participants this analysis is significantly underpowered and future work investigating muscular co-contraction would be necessary to identify if healthy pregnant women walking at a range of speeds in the third trimester experience greater co-contraction than non-pregnant controls. Results from the current model are enough to address the current aim, which is focused on how mechanical changes not physiological changes like knee joint laxity affect knee joint loading and cartilage response. Muscular force estimates from the current model were visually like muscle activation patterns computed from experimental gait analysis which strengthens the argument for the validity of this modeling technique. Total magnitudes of hamstring, quadriceps (PAT), and gastrocnemius forces were similar in pattern and force (BW) to previously reported data from healthy adults (Devita & Hortobagyi, 2001; Miller et al., 2017).

Another possible limitation is that this modeling approach did use generic parameters to define muscle arms and cross-sectional areas. Subject-specific parameters or individual musculoskeletal model scaling would likely change the numerical values of the estimates, however, since these groups were similar in height and pre-pregnancy weight the conclusions would not be drastically different. The model did take subject specific experimentally obtained kinematics and kinetics into account.

Physiological consequences of pregnancy are likely associated with pregnancy including tissue changes which were not modeled in this analysis. Still this approach aims to determine the effect of just mechanical changes on knee joint loading to see if the mechanical effect of pregnancy can, at least in part, explain the known risk of knee osteoarthritis for women who experience pregnancies.

Overall, the results from this current study provide a snapshot of how loading is changed over several months in pregnancy. The overall conclusion suggested by these results is that contact mechanics are affected by walking speed and by pregnancy with increases in joint contact forces that result in altered cartilage strain compared to non-pregnant walking.

5.5 Conclusion

Overall, the present results suggest that total, compressive joint contact force is greater over a range of walking speeds are greater in pregnant vs. non-pregnant individuals. Similarly medial joint contact force is greater over a range of walking speeds are greater in pregnant vs. non-pregnant individuals. Further, contact mechanics between the femoral condyle and tibial plateau resulted in greater peak strains on medial tibiofemoral cartilage during pregnant walking at all speed conditions. This analysis indicated that peak cartilage strain may increase differently as pregnant women increase walking speed indicating that changes in gait mechanics at different speeds result in greater cartilage deformation and greater increases in cartilage deformation for pregnant women. If, over the relatively short timeline of pregnancy, the body doesn't physiologically adapt to the increased loading during walking then these forces could explain the increased risk of degenerative joint diseases following motherhood. Still, this analysis provides only a snapshot of how gait mechanics affect knee joint loading and cartilage deformation in late pregnancy.

Chapter 6: The Mechanical Load Associated with Walking in Pregnancy may Contribute to the Lifetime Risk of Knee Osteoarthritis

6.1 Introduction

The previous studies in this dissertation aim to uncover how the mechanical effect of pregnancy may be associated with the known increase in risk of knee osteoarthritis for women that experience pregnancies (Wise et al., 2013; Zhou et al., 2018). These studies examined how pregnancy impacts joint loading by analyzing the differences in knee joint mechanics and internal joint loads between late pregnancy and non-pregnant walking but provide only a glimpse into how pregnancy changes joint loading. To fully understand the impact of pregnant walking on knee joint health we must investigate how that additional or altered loading, which is experienced over a certain number of months in pregnancy or pregnancies, may contribute to the risk for osteoarthritis in the long-term. Traditionally, evaluating such questions required expensive longitudinal observational studies that spanned many decades. But methods established by Edwards (2018) and Miller & Krupenevich (2020) use mechanical models of medial knee contact mechanics and probabilistic models of tissue damage, repair, and adaptation to estimate cartilage's failure probability over the lifetime without the need for costly, time-consuming, and difficult-to-control longitudinal studies. Providing an objective estimate of the mechanical effect of pregnancy or pregnancies on knee joint health over the lifetime may help establish how the mechanical loading experienced throughout pregnancy may contribute to the known risk of knee osteoarthritis for mothers.

Previous findings from the studies in this dissertation indicate that walking in late pregnancy may result in altered and excessive local mechanical loading at the knee. Walking is important in pregnancy for activities of daily living and for exercise (American College of Obstetricians and Gynecologists' Committee on Obstetric Practice, 2015). Experiencing increased or altered knee loading during walking may relate to the known increased risk of knee osteoarthritis for women who are mothers. Experimental measures of cartilage fatigue and failure suggest that even small increases in the peak stress per cycle can exhaust the stress life of cartilage within the human lifespan (Weightman et al., 1978; Riemenschneider et al., 2019). If pregnancy increases the wear and tear on knee joint cartilage it may affect many women over their lifetime as over 80% of females in the United States will experience at least one pregnancy by the end of their childbearing years (Pew Research Center, 2018). Accordingly, understanding the mechanical consequences of pregnant walking on knee joint health is important knowledge for women's health - even if contribution over the time course of one pregnancy is insignificant.

The greatest benefit of using probabilistic models to estimate the mechanical effect of pregnancy on lifetime knee health is that an estimate of risk related to the current generation of mothers can be generated without costly and time-consuming longitudinal experiments. Such a method is uniquely beneficial as the way women experience motherhood has changed. U.S. women are more likely to become mothers. In 2016 86% of U.S. women ages 40 to 44 were mothers compared to 80% in 2006

(Pew). However, these women are having fewer babies at later ages (Ely, 2018; Hamilton, 2021; Martin et al., 2018). On average U.S. women experience fewer births compared to measures from the last two decades (2.042 in 2003; 1.875 in 2013; 1.784 in 2023). The average age of U.S mothers has increased over the last two decades with measures of a mother's age at first birth up from 24.9 years in 2000 to 27.1 years in 2020 (Ely, 2018; Pew Research Center, 2018). While age at which women have their first child has generally risen, a clear gap emerges when socioeconomic factors such as education(Pew Research Center, 2018) or marital status(*National Vital Statistics Reports Volume 70, Number 17, February 7, 2022*, n.d.), possibly reflective widening racial/ethnic, socioeconomic and geographic inequities within the United States (Bui & Miller, 2018). For example, the average age of a mother at her first birth is 23.8 years for women without a college degree and 23.1 years for unmarried women, but 30.3 years for women who have a college degree and 28.8 for married women. The American shift to a bimodal distribution of age at first birth in more recent years (Figure 6.1b) is a trend that extends to other developed countries such as Switzerland, Japan, Spain, Italy, and South Korea (Bui & Miller, 2018). The physical consequences of pregnancies later their lifetime, when tissue is more susceptible to degenerative changes is unknown.

Therefore, this study aims to estimate the lifetime effect of pregnant walking on knee joint health and determine if cumulative damage experienced over the lifetime is increased with experiencing one or more pregnancies or when experiencing pregnancy at an older age. It was hypothesized that increased or altered contact mechanics and greater medial knee cartilage strains (study 2) would increase the damage accumulated on cartilage per distance traveled and result (H3.1) in more damage accumulated from walking in one or more pregnancies which, over the lifespan will contribute to a significant increase of cartilage failure suggesting a greater risk of knee osteoarthritis due to mechanical wear and tear. A secondary investigation focused on the effect of the mothers age at first birth was planned where it was anticipated that (H3.2) experiencing pregnancy later in life, when tissue is more susceptible to degenerative changes, will result in a greater risk of knee osteoarthritis. To test these hypotheses, cumulative damage over a lifetime and failure probabilities for were compared at age 55, a typical age of knee osteoarthritis diagnosis (Losina et al., 2013). By taking a mechanical approach to assess the long-term impact of modified or heightened loading during pregnancy on knee health we aim to determine whether the augmented risk of knee osteoarthritis can be attributed, to some extent, to the mechanical stress encountered while walking during pregnancy.

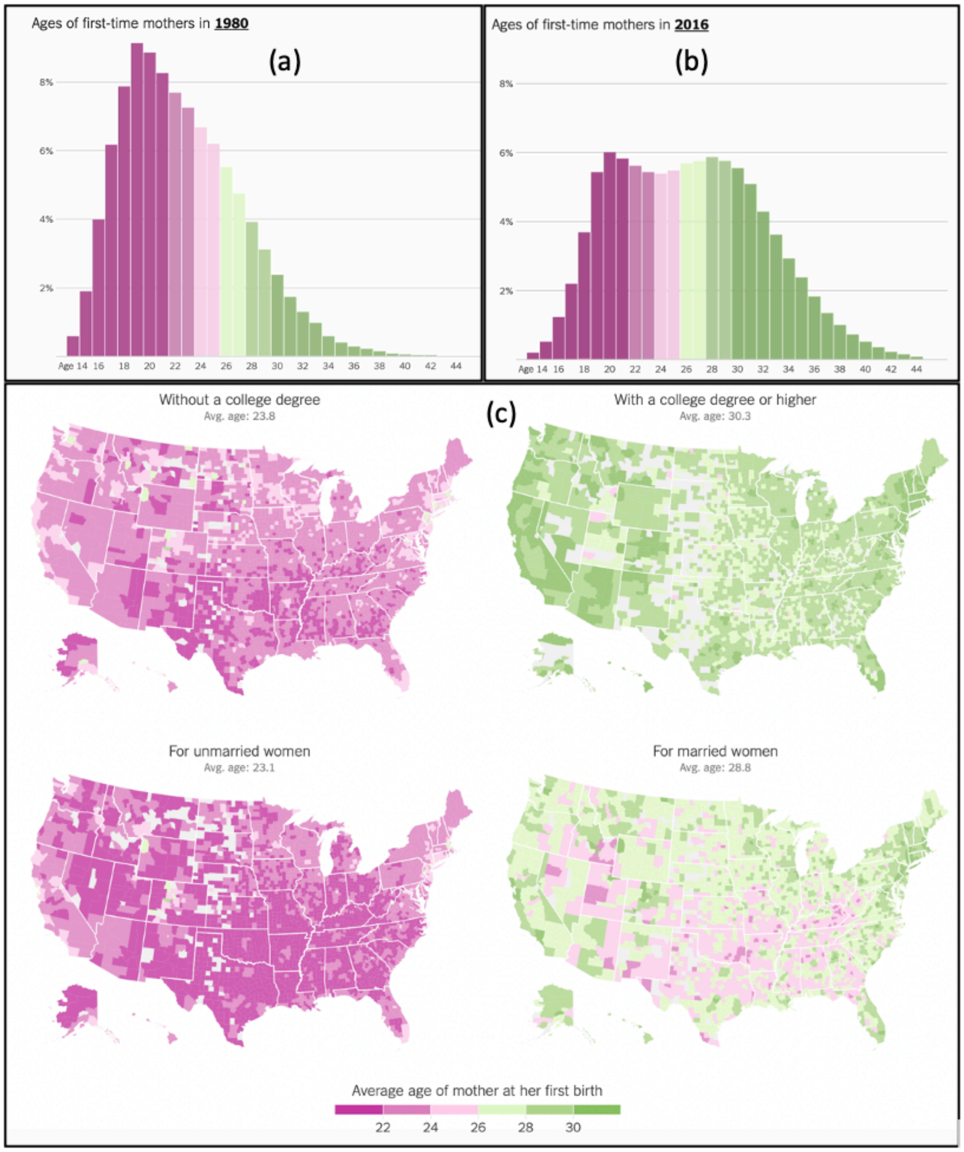

Figure 6.1 Compared to (a) first time mothers in 1980, the (b) ages at which the recent generation of American mothers has a bimodal population distribution where "two America's" emerge where a gap divides women who have children earlier in

their life (pink) and women who have children later (green) are separated by (c) marriage and education status (from (Bui & Miller, 2018).

6.2 Methods

Over the last forty years biomechanists have adapted mathematical models of cumulative failure from engineering methods to evaluate human tissue. Such models were originally adapted in biomechanics to estimate the risk of bone fracture (e.g.,(Carter & Caler, 1985) and have been adjusted investigate clinically relevant variables in the exercise regime such as distance run/walked per day or the effect of improved footwear (Taylor & Kuiper, 2001) or predict stress fractures during periods of intense exercise while considering living processes of bone repair and adaptation (Taylor et al., 2004). Recently, similar phenomenological models have been implemented to provide predictions of failure probability of medial knee cartilage over an adult lifespan (age 23-83 years) for individuals of different activity levels (Miller & Krupenevich, 2020) or for obese individuals (Sinclair et al., 2023) where "failure" defined as macroscopic plastic deformation, like the superficial fibrillation seen in early-stage ''structural'' osteoarthritis (Weightman, B. O., Freeman, M. A. R., & Swanson, S. A. V., 1973) and produce reasonable estimates on average, with medial knee cartilage failure probabilities like estimates of lifetime incidence rates of medial knee osteoarthritis in adults (Losina et al., 2013; Murphy et al., 2008). This dissertation aimed to extend current methods to estimate medial knee cartilage failure probabilities when facing a time-varying stress due to experiencing pregnancy or pregnancies at different maternal ages.

6.2.1 Cartilage Failure Probability

The overall probability of cartilage failure was computed using a custom Matlab script similar to previously published analyses (Brent Edwards et al., 2010; Miller & Krupenevich, 2020) where the long-term failure probability of the medial knee cartilage (Taylor & Kuiper, 2001; Wasser et al., 2020) was computed for 60 years of self-selected "comfortable" pace walking (1.28 (0.13) m/s while not pregnant and 1.19 (0.19) m/s while pregnant) at a recommended daily duration.

This cartilage failure model predicts the percentage risk of failures over time by assuming the underlying life distribution is the Weibull distribution and assuming there is an inverse power law relationship between the Weibull scale parameter and the applied stress. This assumption is necessary since there is considerable scatter in experimental data such as fracture and fatigue data from cartilage testing. In this approach the probability of failure, P_f, of a volume of material V_s, loaded by a stress σ is given by:

$$P_f = 1 - exp\left[-\left(\frac{V_s}{V_{so}}\right)\left(\frac{\sigma}{\sigma^*}\right)^m\right] \qquad \text{[EQ 6.1]}$$

where σ^*, a reference stress representing material strength, V_{so} is a reference volume and m is a constant that expresses the degree of scatter in experimental data. The resulting probability P_f ranges from 0 to 1, representing 0-100% chance of failure.

This approach assumes that failure occurs in the most stressed place in the sample. Taylor & Kuiper (2001) adapted this Weibull approach for use in fatigue by replacing stress by the fatigue strength or range of stress in a cycle that causes a fatigue failure after a given number of cycles. The effect of different constant stress levels can be evaluated by using the standard fatigue equation for the number of cycles to failure, N_f:

$$N_f = (C/\Delta\sigma_o)^n \qquad \text{[EQ 6.2]}$$

Where C and n are constants. Taylor et al., (2004) rearranged these equations so that instead of determining how many cycles a material could withstand before failure the cumulative probability of failure at certain time points can be estimated.

An equation which allows for the estimation of time of failure, t_f, can prove valuable in assessing the fatigue levels of biological tissues (i.e., bone, cartilage) due to repetitive, cyclic movements like walking. To estimate this probability the scatter in experimental cycles to failure data from a range of constant stresses (fixed value of $\Delta\sigma_o$) is used and cycles are converted to time to failure, t, by dividing by the frequency of cycling or number of cycles per day. Then, the cumulative probability of failure, P_f, at a time, t, for a tissue undergoing constant $\Delta\sigma_o$ and sustaining $\dot{D}/L$ loading cycles per unit time can be determined:

$$P_f(t) = 1 - exp\left[-\left(\frac{V}{V_{ref}}\right)\left(\frac{t}{t_f}\right)^{m/n}\right] \qquad \text{[EQ 6.3]}$$

where $\dot{D}$ is the distance traveled per unit time, e.g., meters per day, and L is the stride length. The ratio $\frac{V}{V_{ref}}$ represents the volume of the material over which failure rate is being calculated and is due to the assumption that failure will occur at the weakest point of a material. Within equation 6.3, the "strain-life" or "fatigue-life" relationship, t_f is assumed to be a power law relationship between the time until failure, t_f, and element strain, ϵ_i:

$$t_f = \left(\frac{CL}{\dot{D}}\right)(b\epsilon_i)^{-n}$$ [EQ 6.4]

Where m, C, n and b are constants, V is the volume of material stressed by σ_i and V_{ref} is the referenced stressed volume in the data from which the other parameters are determined. This damage model takes peak strain as an input since strain causes plastic deformation which is like actual structural "damage" experienced by cartilage tissue. This dissertation uses failure probability model parameters which are also listed in Miller and Krupenevich (2020). These constants were derived by fitting a power law to cycles, N_f.

Models in this study used one of the only published accounts of cartilage fatigue life data (Riemenschneider et al., 2019; Figure 6.2) to estimate a failure strain distribution for about 64 years of walking 10,000 steps (10^7 total loading cycles) where 63.2% of cases loaded with strain $b\epsilon_i$ over $\dot{D}/L$ cycles per day would be expected to fail, with a Weibull cumulative distribution function fit to these estimates to defined failure probability model parameters (Figures 6.2).

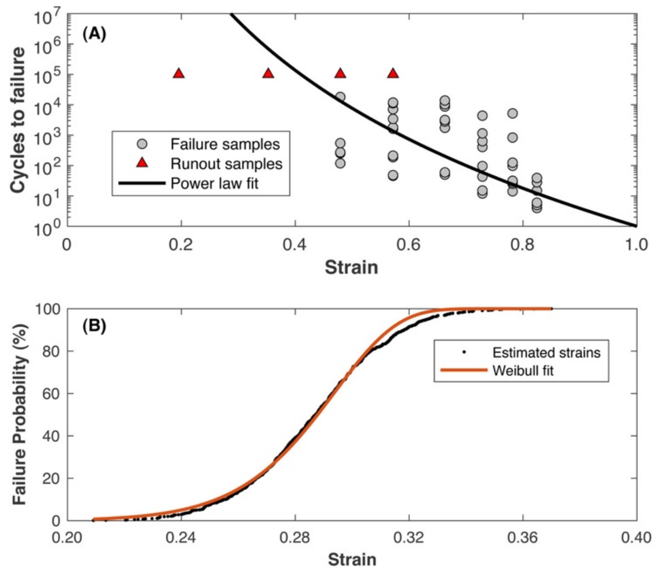

Figure 6.2 Fatigue life model from Miller and Krupenevich, 2020. (A) Strain vs. cycles to failure using data from Riemenschneider et al., 2019. Triangle symbols indicate runout samples that survived 100,000 cycles of the indicated strain without failure and were not included in the model fitting. (B) Estimated failure strain distributions for $1 \cdot 10^7$ loading cycles (symbols), fit with a Weibull cumulative distribution function (red line).

6.2.2 Cartilage Repair

Despite cartilage's limited natural capacity to heal damage that hasn't reached the underlying bone(Heinemeier et al., 2016), evidence suggests that young adults' living cartilage exhibits some inherent ability to partially recover from such damage over the span of several years (Nakamura et al., 2008). Therefore, the inclusion of cartilage repair was factored into the equation as a secondary Weibull function:

$$P_r = 1 - exp\left[-\left(\frac{t}{t_r}\right)^v\right] \quad \text{[EQ 6.5]}$$

Where t_r and v are the scale and shape parameters. t_r is the time after which repair would be expected in 63.2% of cases of damage and v depends on the scatter of repair times between subjects and effects the rate at which P_r increases with increasing t. Repair included by first taking the derivative of the probability density function which gave the instantaneous probability at a given time:

$$Q_f = \left(\frac{V_m}{nV_{ref}t_f}\right)\left(\frac{t}{t_f}\right)^{m/n-1} exp\left[\left(\frac{V}{V_{ref}}\right)\left(\frac{t}{t_f}\right)^{m/n}\right] \quad \text{[EQ 6.6]}$$

The instantaneous probability of failure is multiplied by the cumulative probability that repair has not occurred yet $(1 - P_r)$, then this product is integrated over time to determine the probability of failure with repair, P_{fr}:

$$P_{fr} = \int_0^t \left[Q_f \cdot (1 - P_r)\right] dt \quad \text{[EQ 6.7]}$$

6.2.3 Damage from Time-varying Stresses

Previous applications of the cartilage failure probability model rely on, non-interactive damage accumulation theory, commonly used for engineering materials (Nelson, 1990), to account for variable-amplitude loading or loading in which the stress ranges varies from cycle to cycle (Taylor & Kuiper, 2001). This theory assumes that the order in which the cycles are applied has no effect on the outcome and allows for the definition of an equivalent constant-amplitude cycle which would do the same amount of damage as the variable-amplitude cycle.

This equivalent stress, $\Delta\sigma_{eq}$, is determined by taking a weighted average of the stress levels based on the number of lifetime steps N_T at that stress level N_i:

$$\Delta\sigma_{eq} = \left(\frac{1}{N_T}\sum_{i=0}^{j} N_i \Delta\sigma_i^n\right)^{1/n} \quad \text{[EQ 6.8]}$$

Likewise, an equivalent strain can be calculated as

$$\Delta\varepsilon_{eq} = \left(\frac{1}{N_T}\sum_{i=0}^{j} N_i \Delta\varepsilon_i^n\right)^{1/n} \qquad \text{[EQ 6.9]}$$

where N_t is the total number of load cycles, N_i is the number of load cycles at which the strain $\Delta\varepsilon$ is applied, and n is the constant from Equation 1. With time-varying stresses, $\sigma(t)$, the life-stress relationship must consider the cumulative effect of the applied stresses, calculated using a cumulative damage model, sometimes called a cumulative exposure model, $\varepsilon(t)$, visualized in Figure 6.3 (*Accelerated Life Testing Reference*, 2015; Nelson, 1990):

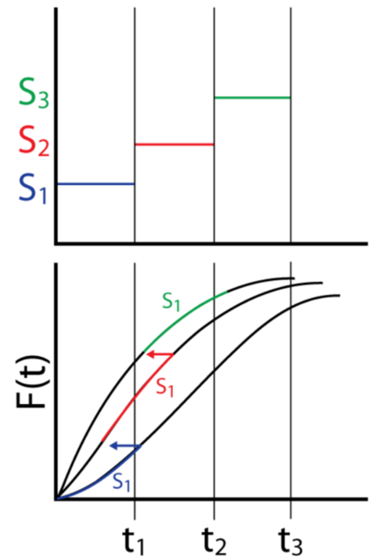

Figure 6.3 Example of cumulative damage model relating time varying stresses to the life-stress relationship.

$$\varepsilon(t) = \int_0^t dt/\alpha[\sigma(t), x] \qquad \text{[EQ 6.10]}$$

Where the distribution scale parameter $\alpha[\sigma(t), x]$ is a function of time, $\alpha(\text{t}) = \alpha[\sigma(t), x]$. For simplicity it was assumed that the stress experienced in the third trimester of pregnancy can be approximated using a step function where the cumulative probability of failure for each stress level (Nelson, 1990) is:

$$P_{fi}(t_i, \sigma_i) = 1 - exp\left[-\frac{1}{C}\sigma_i{}^n(t_i - t_{i-1}) + \varepsilon_{i-1}\right]^{\beta} \qquad \text{[EQ 6.11]}$$

where:

$$\varepsilon_{i-1} = (t_{i-1} - t_{i-2} + t_{i-1} + \varepsilon_{i-2})\left(\frac{\sigma_{i-1}}{\sigma_i}\right)^n \qquad \text{[EQ 6.12]}$$

and:

$$\varepsilon_i = t_i(\frac{\sigma_{i-1}}{\sigma_i}) \quad \text{[EQ 6.13]}$$

Within these equations β is the Weibull shape parameter and ε_i represents the equivalent time to account for exposure cartilage has undergone during pregnancy. $Q_f(t_i, \sigma_i)$ was then determined using:

$$Q_f(t_i, \sigma_i) = -\frac{d}{dt}\left[P_{fi}(t_i, \sigma_i)\right] \quad \text{[EQ 6.14]}$$

Once $Q_f(t_i, \sigma_i)$ is known, repair can be added into the model as usual:

$$P_{fr}(t_i, \sigma_i) = \int_0^t \left[Q_f(t_i, \sigma_i) \cdot (1 - P_r(t_i, \sigma_i)\right] dt \quad \text{[EQ 6.15]}$$

For the current study the cumulative exposure model can be explained graphically (Figure 6.4 as an adaptation to the current model that steps between equivalent failure probability points for virtual subjects that never experience pregnancy or always experience pregnancy.

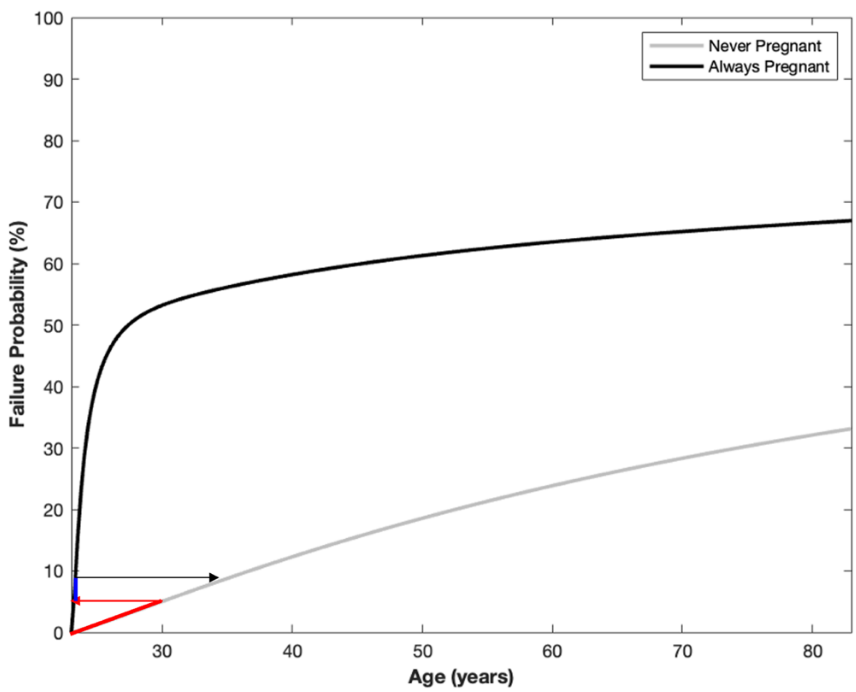

Figure 6.4 Mean failure probabilities for virtual subjects that never experienced pregnancy (gray) or always experienced pregnancy (black). The red lines indicate how the cumulative exposure allows for a shift in failure probability functions (*Pf*) at equivalent failure probability points. The blue lines indicate how the cumulate failure probability function would shift back to the never pregnant condition after one duration of pregnancy.

6.2.5 Simulations of Time-varying Stress

The current study aimed to model the effect of any abnormal loading on future knee joint health and determine if increased knee joint loading over certain number of months in pregnancy helps to explain the increased risk for knee osteoarthritis in the long term. To address the first hypothesis, that experiencing multiple pregnancies over the lifetime would increase knee osteoarthritis risk, the cumulative damage model was used to evaluate the effect of virtual subjects as they experienced either pregnant $\Delta\sigma_1$ or non-pregnant cartilage stresses, $\Delta\sigma_i$ while walking at pregnant or non-pregnant step durations with pregnant or non-pregnant stride lengths.

Then, stress step functions for 10 virtual "subjects" were created by matching stress data from pregnant and non-pregnant participants by body mass index (BMI). Pregnant BMI was computed from measured height and self-reported pre-pregnancy mass and pregnant and non-pregnant participants were matched by rank order. Each pregnancy was modeled as an increase in stress that lasted for 0.5 years (two-trimesters). Step functions represented the lifetime loading experienced by each virtual "subject" who experienced 0,1,or 2 pregnancies starting at age 23.8 with births separated by two year periods as is commonly recommended to reduce health risks for the woman and baby (Starbird & Crawford, 2019) or 0-2 pregnancies starting at age 30.3years (Figure 6.5). These stress functions were used for each virtual subject to calculate the failure probability by using the cumulative model of exposure model with repair (see equation 6.15: $P_{fr}(t_i, \sigma_i)$).

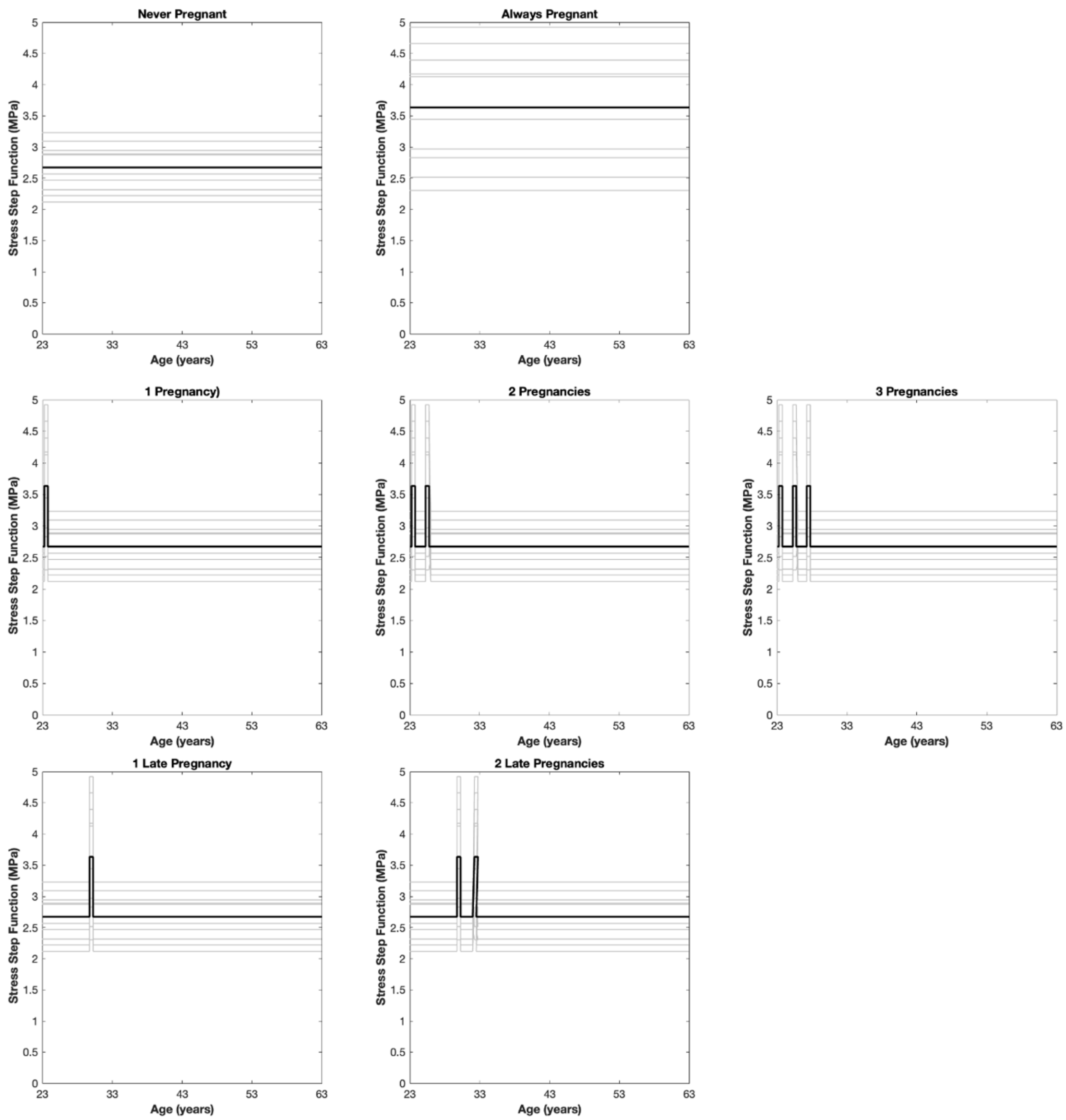

Figure 6.5. Stress over the lifetime was estimated using step functions over the lifetime. Stress functions for each virtual participant (gray) and mean step functions by condition (black) are shown. Each pregnancy was represented by over the last two trimesters (6 months) of pregnancy. 0, 1, and 2 births were modeled for women who were 23.8 years old at first birth (b, c) or 30.3 years old at first birth.

6.2.4 Population Specific Parameters

Experimental data from study 1 indicated that our pregnant and non-pregnant women walked with shorter self-selected, “comfortable” step lengths to Miller and

Krupenevich (2020) so updated estimated step counts were used for our pregnant and non-pregnant women. Daily walking durations of 4000 m per day (~5970 steps per day) were used for non-pregnant women since this number of steps per day was within one standard error of the steps reported for healthy American females (Tudor-Locke et al., 2009). This selected walking duration is shorter than the 6km per day used by Miller & Krupenevich (2020) but yielded similar steps per day because the self-selected, “comfortable” stride lengths taken by our non-pregnant female participants were shorter (1.33 (0.04) m) than the healthy young adults (1.55 (0.15) m) in their study who walked at a faster self-selected pace of 1.52 (0.18) m/s. To allow for a conservative estimate pregnancy walking durations were reduced to 2500 m, which given the step lengths for pregnant women in this study (0.66 (0.09) m) equates to an average of about 3787 steps/day. This step count per day for pregnancy was selected because it was within one standard deviation of available step counts from accelerometer estimates from the third trimester of pregnancy (4489.6 steps per day; Kim & Chung, 2015).

To determine if cumulative damage over a given distance was similar between pregnant and never-pregnant women failure probabilities were calculated for each virtual participant where stress, strain, daily walking distance, and step length were functions of being pregnant or not (Table 6.1). Overall cumulative failure probability was computed for each virtual participant over an assumed adult walking period of 32 years (age 23-55 years for these participants) and estimates of damage accumulated with and without considering cartilage repair across the lifespan were visually compared and discussed with respect to possible relevance and connections with known disparities and risk for knee osteoarthritis across education level, marriage status and race and ethnicity.

Table 6.1
Mean (SD) temporospatial parameters and simulation settings

	Self-Selected "Comfortable"			
Parameter	Pregnant		Non-Pregnant	
	Mean	(SD)	Mean	(SD)
Speed (m/s)	1.19	(0.19)	1.28	(0.13)
Step Length (m)	0.65	(0.09)	0.67	(0.04)
Distance per day (m)	4000		2500	
Steps per day (steps)	5970		3787	

Paired t-tests were planned to compare average risk for cartilage failure at age 55 between virtual subjects who never experienced pregnancy and those who experienced multiple early or late pregnancies. Additionally, paired t-tests were planned to compare risks between 1 or 2 pregnancies experienced early vs. later in life. One-way tests were used because the hypotheses were directional with multiple pregnancies and later pregnancies expected to result in greater risk. Family-wise error rates were controlled using FDR correction for multiple tests.

6.3 Results

6.3.1 Failure Probability Distributions for Never / Always Pregnant Women

Initially, failure probability distributions for women who never experienced pregnancy and always experienced the loading of pregnancy were computed over the lifetime (Figure 6.6).

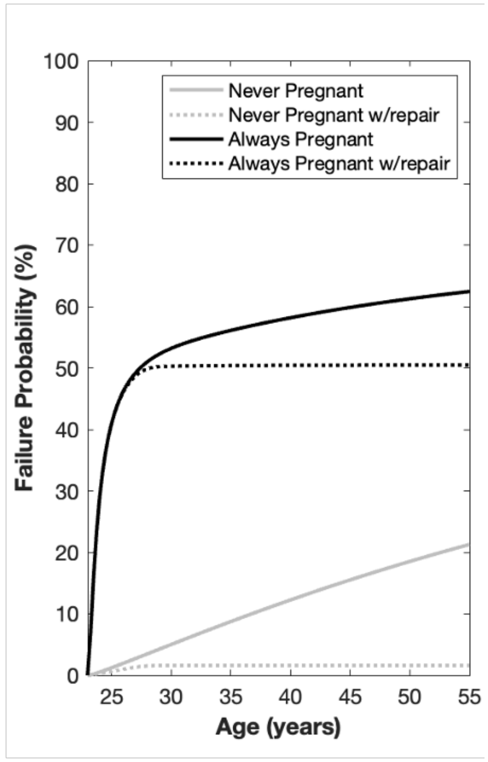

Figure 6.6: Average medial tibiofemoral cartilage failure probabilities over adulthood (age 23 to age 55) years representing healthy women walking for 4000 m/day with no pregnancies (gray lines) or with walking 2500 m/day during the third trimester (black lines) Failure probabilities after including cartilage repair in early adulthood are indicated with dashed lines.

6.3.2 Effect of Multiple Pregnancies

The failure probability for women who experienced pregnancies early in their reproductive timeline is shown in Figure 6.7a. Comparison of the failure probabilities at age 55 indicated greater risk after experiencing 1pregnancy ($t(9) = 2.343$ $p = 0.022$, $d = 0.741$), 2 pregnancies ($t(9) = 2.57$, $p = 0.015$, $d = 0.811$), or 3 pregnancies ($t(9) = 2.684$, $p = 0.013$, $d = 0.849$), with average increases in failure probability at age 55 of 7.69%, 13.43% and 15.45% from the never-pregnant condition, respectively. There were also significant increases between 1 and 2 pregnancies ($t(9)$

= 2.807 p = 0.01024, d = 0.888), and between 2 and 3 pregnancies ($t(9)$ = 2.895 p = 0.009, d = 0.915),

(a) (b)

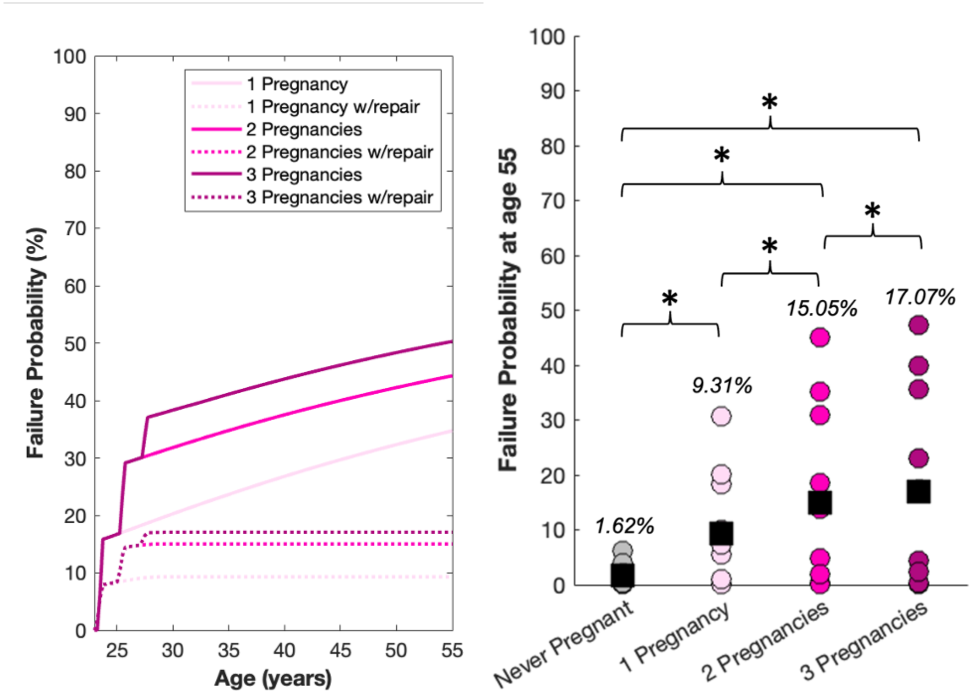

Figure 6.7 (a) Average medial tibiofemoral cartilage failure probabilities (a) over early and mid-adulthood (age 23 to age 55 years) and (b) at age 55, a common age of diagnosis for knee osteoarthritis, for healthy women who experience one (light pink) two (pink) or three pregnancies (dark pink) with births experienced at 23.3years, 25.3years and 27.3 years, respectively. (b) Group mean failure probabilities (black squares) at age 55 for healthy women who experience no pregnancy (gray) one (light pink) two (pink) or three pregnancies (dark pink).

6.3.3 Effect of Age at First Birth

The failure probability for virtual subjects who experienced pregnancies later in life is shown in Figure 6.8a. Compared to never experiencing pregnancy comparison of the failure probabilities at age 55 indicated there was a significant effect for experiencing 1 late pregnancy ($t(9) = 3.667$ $p = 0.003$, $d = 1.160$) or 2 late pregnancies ($t(9) = 3.618$, $p = 0.003$, $d = 1.144$), with average increases in failure probability at age 55 of 6.91% and 20.34% from the never-pregnant condition, respectively. Compared to 1 late pregnancy virtual subjects with 2 late pregnancies had significantly greater (+ 13.43%) failure probability at age 55 ($t(9)$ = 3.573 p = 0.003, d = 1.113). Although there was no significant difference between the failure probabilities at age 55 for women who experienced 1 early or 1 late pregnancy ($t(9)$ = -0.375 p = 0.642, d = 0.118), there was a significant increase between women who experienced 2 early and 2 late pregnancies ($t(9)$ = 2.498 p = 0.0.017, d = 0.790).

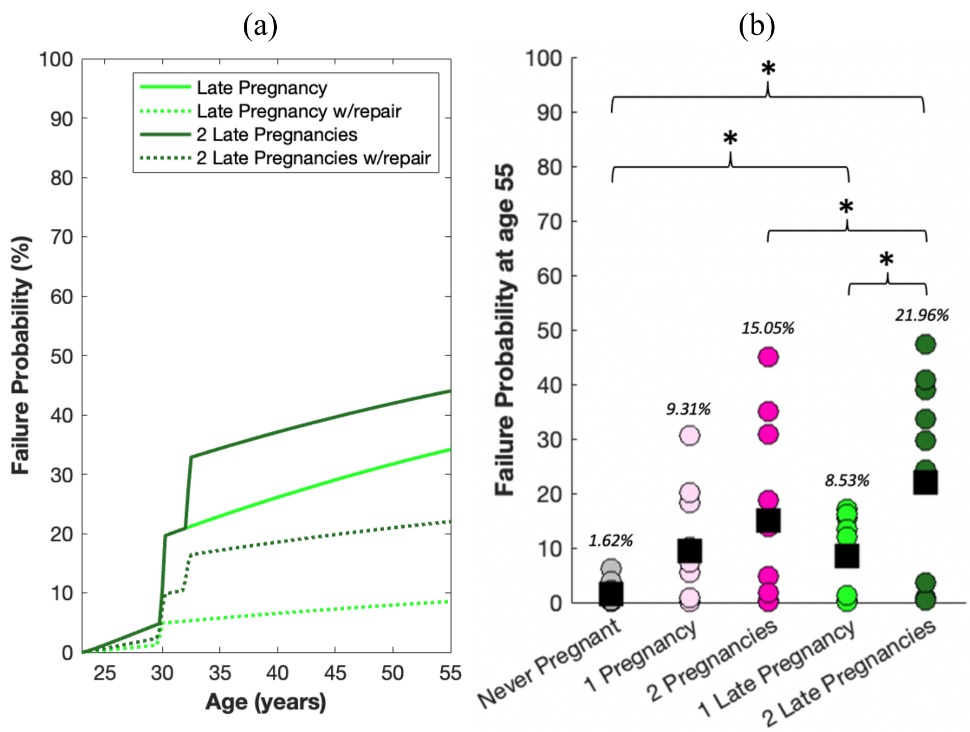

Figure 6.8 (a) Average medial tibiofemoral cartilage failure probabilities over early adulthood (age 23 to age 55) years representing healthy women who experience one late pregnancy at 30.3years (green) or two late pregnancies at 30.3 and 32.3 years (dark green), respectively. (b) Group mean failure probabilities (black squares) for women who experience no pregnancy (gray) one early pregnancy (light pink), two early pregnancies (pink), one late pregnancy (bright green) or two late pregnancies (dark green).

6.4 Discussion

The main purpose of this study was to determine if the additional and altered loading experienced over several months in pregnancy or pregnancies may contribute to greater knee osteoarthritis risk and if the damage accumulated from walking in pregnancy at an older maternal age contributes to the risk for knee osteoarthritis in the long-term. Given the challenges of studying osteoarthritis across the lifespan, a model-based evaluation of cumulative damage and cartilage failure probability was performed. The expectation that the damage accumulated from walking in pregnancy/pregnancies would contribute to the risk for knee osteoarthritis in the long term was supported. The expectation that undergoing pregnancy later in the lifetime, when tissue is more susceptible to degenerative changes would result in additional risk was partially supported with greater risk apparent with multiple pregnancies after age 30. The present findings suggest that mechanical changes experienced while walking in pregnancy result in statistically greater probability of failure so mechanical loading associated with pregnancy may contribute, in part, to the known risk of knee osteoarthritis for this population.

The main limitation that could affect these results is that the approach uses lots of model-based estimation. For example, since the failure model is dependent on stress pattern and duration of increased loading it could be argued that that the step function used was too simple and instead a ramp function should be used. However, the goal of this study was to isolate mechanical effect not replicate reality. Further, the specific the specific percentage failure probabilities estimated in this study indicated a greater average risk of cartilage failure than the risk reported from observational clinical studies. Still the goal of this investigation was to determine effect of time-varying stress on knee joint health not to generate specific risk estimates to be interpreted clinically. Finally, this analysis assumes cartilage properties remain unchanged throughout pregnancy which is likely not representative of pregnancy physiology. Still animal studies focused on the influence of pregnancy on articular cartilage surfaces suggest that cartilage may actually soften, or weaken during pregnancy (Hellio Le Graverand et al., 2000) which would result in greater damage than what has been modeled. The estimates of joint loads, contact mechanics and cartilage failure in this approach used generic model parameters. This analysis performed a within-virtual subject design which reduces the severity of this limitation. Additionally, this approach only considers the loading experienced throughout pregnancy. Likely these estimates are underestimating the effect of any altered locomotion sustained throughout postpartum or effects experienced in pregnancies that do not result in full-term childbirth such as pregnancy losses or even abortions.

The current study extended the ability of probabilistic models of medial tibiofemoral cartilage failure to evaluate the effect of increased loading experienced in pregnancy on knee joint health by age and number of pregnancies experienced. Unlike previous applications of the cartilage failure probability model which considered a constant stress applied over the lifetime, we assessed the impact of stress that changes over the lifetime due to pregnancy/pregnancies experienced early or later in a woman’s reproductive years. Our hypotheses were time dependent and could not assume that the order in which the cycles were applied has no effect on the outcome.

Since this analysis was concerned with the order (time variance) in which the cycles are applied a cumulative exposure model which will relate the life distribution (Weibull distribution) of the units at one stress level to the distribution at the next level was needed (Figure 6.3). To achieve this, we adapted the established model to incorporate a cumulative exposure model (Nelson, 1990) which allowed for time-varying stresses over the lifetime. The cumulative effect of time-varying stress was represented by a step-stress profile representing pregnant and non-pregnant time points over the lifetime (Figure 6.5). A virtual population of BMI-matched participants were generated, and within-virtual subject analyses were performed to investigate changes in cartilage failure probabilities over the lifetime.

Our results are in line with clinical evidence that suggests that experiencing multiple pregnancies influences future knee joint health. For example, experiencing one pregnancy at age 23 resulted in a 7.7 (10.38) % increase in knee cartilage failure probability at age 55. Then experiencing a second pregnancy at age 25 this risk increased by an additional 5.74 (6.46) %. These differences were significant in our model and like previous observational analyses where pregnancy was seen to increases the relative risk for knee replacement, a consequence of knee cartilage failure, by 8% per birth (Liu et al., 2009). Still, this is the first analysis to suggest that even one pregnancy significantly increases the risk for knee osteoarthritis over the lifetime. Parity, or the number of times a female has given birth, significantly increases the risk for osteoarthritis particularly for females who have more than four children (Wise et al., 2013) and being pregnant more than six times has been found to be an independent risk factor for knee osteoarthritis (Zhou et al., 2018). However, having more than two children than is rather extreme for most American females, who average 2.07 children during their lives (Pew Research Center, 2018). Having more than two children is even extreme for the proportion of American females who are mothers - who on average give birth to 2.47 children throughout their lifetime (Pew Research Center, 2018). Possibly we find a significant effect for even one pregnancy since this modeling technique allows us to isolate mechanical effects and not face confounders experienced in real-life longitudinal investigations. Overall, current results suggest that experiencing pregnancy results in greater risk compared to never experiencing pregnancy with increases in risk when experiencing additional pregnancies. An advantage of performing a probabilistic investigation using a virtual subject population is that we were able to isolate the effect of age on the probability of knee cartilage failure. While we found no significant difference between the risk between 1 early (9.31 (10.53) %) or 1 late pregnancy (8.53 (7.27) %) was not significantly different, there is greater risk when mothers experience multiple pregnancies later in their lifetime. This effect may be particularly important as the median age of new mothers continues to rise and having babies after 30 becomes more common.

6.5 Conclusion

In conclusion, these model-based results suggest that experiencing pregnancy increased the probability of cartilage failure and there was additional risk when experiencing multiple pregnancies later in life.

Chapter 7: Contribution of Dissertation

6.1 Summary

Overall, this research aimed to model the isolated, mechanical consequences of pregnancy on knee joint loading and future knee health and results from these three studies suggest that the mechanical consequences of pregnancy on knee joint loading and future knee health are significant. These results may have implications for pregnant physical activity recommendations. Future work could investigate how this loading is changed postpartum. Additional work could also investigate how gait or velocity modifications may be used to noninvasively change knee loading during walking in pregnancy and possibly reduce the risk of knee osteoarthritis.

Although understanding the underlying causes of knee osteoarthritis is complex, pregnancy is associated with abnormal walking mechanics and an increased mechanical load on cartilage over a range of walking speeds. Mechanical changes during pregnancy result in increased and altered loading as pregnant women walk faster and may, in part, contribute to the increased risk of knee osteoarthritis reported for this population.

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