An Exploration of the Influence of Joint Hypermobility in Adolescents with Juvenile Fibromyalgia

Dissertation

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Abstract

Juvenile fibromyalgia (JFM) affects up to six percent of the adolescent population and results in chronic, widespread pain, functional disability, and poor quality of life that often persists for years. Generalized joint hypermobility is common among adolescents with JFM and is also associated with widespread joint pain and many similar symptoms of JFM. Both adolescents with JFM and generalized joint hypermobility demonstrated altered biomechanics which may contribute to pain exacerbation. Despite the association between JFM and generalized joint hypermobility, it is unknown if joint hypermobility exacerbates symptoms and influences response to treatment in this cohort. Preliminary evidence suggests cognitive behavioral therapy (CBT) and neuromuscular training (NMT) are effective in reducing pain and functional disability in this cohort; however, NMT has been shown to be differentially effective to individuals who demonstrate faulty biomechanics. A better understanding of factors, such as joint hypermobility, that influence symptom exacerbation and response to treatment will aid in the development of targeted interventions and hopefully improve outcomes for adolescents with JFM.

Therefore, the purpose of this dissertation was to provide a comprehensive exploration of the influence of generalized joint hypermobility on the clinical symptoms, physical function, and response to intervention in adolescents with JFM. The goals of this study were 1) to compare baseline pain, functional disability, strength, and biomechanics

between hypermobile and non-hypermobile adolescents with JFM, 2) compare baseline pain, functional disability, strength, and biomechanics between hypermobile adolescents with JFM and healthy adolescents with generalized joint hypermobility, and 3) compare response to treatment between hypermobile and non-hypermobile adolescents with JFM.

As part of a secondary analysis of a pilot randomized controlled trial, adolescents with JFM were categorized as hypermobile or non-hypermobile and baseline subjective pain, functional disability, lower extremity strength, and lower extremity gait biomechanics were compared between groups. Baseline subjective pain, functional disability, lower extremity strength, and gait and jump landing biomechanics were then compared between hypermobile adolescents with JFM and healthy adolescents with generalized joint hypermobility. Finally, pre- to post-intervention changes in subjective pain, functional disability, strength, and gait and jump landing biomechanics were compared between hypermobile and non-hypermobile adolescents with JFM, following completion of sixteen combined CBT and NMT sessions.

Although there were no differences in subjective pain, functional disability, or strength between hypermobile and non-hypermobile adolescents with JFM, hypermobile adolescents with JFM did demonstrate greater peak knee extension and lower peak ankle eversion during the stance phase of gait. Hypermobile adolescents with JFM also reported greater pain and functional disability and demonstrated greater lower extremity strength, lower knee extension moments during gait, and greater knee abduction angles during jump landing than healthy adolescents with generalized joint hypermobility. Comparison of response to treatment between hypermobile and non-hypermobile adolescents with JFM indicated there was no difference in change in pain, functional disability, strength, or biomechanics between groups. This information adds to our understanding of the presentation of JFM and the influence of generalized joint hypermobility in this cohort. While joint hypermobility may not influence subjective pain and functional disability, it does appear to influence movement patterns in adolescents with JFM, establishing groundwork for future research to explore the correlation between these movement variations and symptoms in adolescents with JFM.

Dedication

This dissertation is dedicated to my husband Joe and daughters, Alexis and Addison. This would not have been possible without your love, support, encouragement, and sacrifice. This work is also dedicated to my parents, Richard and Linda, who have supported me unconditionally and who taught me the value of hard work and persistence.

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Fields of Study

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Chapter 1. Introduction

1.1: Dissertation Overview

The purpose of this dissertation was to gain a better understanding of the role of joint hypermobility among adolescents with juvenile fibromyalgia (JFM) to aid in the long-term goal of developing targeted interventions in order to improve quality of life and decrease limitations in adolescents with JFM. The introductory chapter provides a review of JFM and generalized joint hypermobility syndrome, including the relationship between the two conditions. During the course of this study, it became clear that despite a high prevalence of joint hypermobility in adolescents with JFM and many similarities between the two conditions, it is unknown whether joint hypermobility exacerbates the symptoms of JFM and diminishes responsiveness to treatment. Chapters two through four describe studies that explored the influence of joint hypermobility on the clinical and functional presentation of JFM and response to treatment in this cohort.

Chapter 2, the first primary research chapter of this dissertation, was a cross-sectional study that compared baseline pain, functional disability, strength, and gait biomechanics between hypermobile and non-hypermobile adolescents with JFM. The goal of this study was to aid to the knowledge of whether or not generalized joint hypermobility plays a significant role in the presentation of adolescents with JFM. Chapter 3 was also a cross-sectional study that compared baseline pain, functional disability, strength, and gait and jump landing biomechanics between hypermobile adolescents with JFM and healthy adolescents with generalized joint hypermobility. The goal of this study was to help determine if pain, functional disability, weakness, and movement patterns are unique to adolescents with JFM or if adolescents with generalized joint hypermobility demonstrate similar deficits in functional disability, strength, and movement patterns. Chapter 4 compared the response to neuromuscular training and cognitive behavior therapy between hypermobile and non-hypermobile adolescents with JFM. Pain, functional disability, strength, and biomechanics were measured pre- and post-intervention. Changes in scores following intervention were compared between hypermobile and non-hypermobile adolescents with JFM. The goal of this chapter was to identify if hypermobile adolescents with JFM respond differently to intervention than non-hypermobile adolescents with JFM in order to determine if targeted interventions are warranted in this population. Finally, chapter 5 summarizes the findings of each research chapter, discusses the potential impact of these findings, and proposes future research in order to reach our long-term goal of decreasing the impact of JFM and improving quality of life for these individuals.

1.2: The Clinical Presentation of Juvenile Fibromyalgia

JFM is a non-articular rheumatic condition, characterized by diffuse musculoskeletal pain and tender points. In 1985, Yunus and Masi[1] established diagnostic criteria for primary juvenile fibromyalgia syndrome that are unique from the diagnostic criteria for adult fibromyalgia. The current diagnostic criteria for JFM includes (1) generalized musculoskeletal pain in three or more sites for at least three months in the absence of an underlying condition, (2) the presence of five or more tender points, and (3) the presence of at least three minor criteria including: anxiety, depression, fatigue, poor sleep, chronic headaches, irritable bowel syndrome, subjective soft tissue swelling, numbness, pain modulation by physical activity, pain modulation by weather, and pain modulation by anxiety or stress.[1–5] JFM disproportionately affects females with over ninety percent of JFM patients being female.[6–9] Age at onset of JFM symptoms ranges from three to seventeen years, with the most common age of onset ranging from thirteen to fifteen years old.[1,6,8,10,11] Adolescents diagnosed with JFM report significant limitations in daily functioning and quality of life and symptoms frequently persist for years, often into adulthood, for the majority of adolescents diagnosed with JFM, indicating the need for a better understanding of the pathological processes of JFM, and factors that influence symptoms and response to treatment in this cohort.[2,7,11–14]

Although the exact pathophysiological mechanism of JFM is still unknown, there are multiple theories to explain increased pain in adolescents with this syndrome including abnormal pain processing and neurochemical imbalances.[15–22] Under normal physiological conditions, pain sensation is initiated by the activation of free nerve endings of primary Aδ or C afferent fibers via a noxious stimuli.[23,24] The pain signal then travels through Rexed's laminae I, II, and V in the dorsal horn of the spinal cord to the thalamus. Localized fast pain is perceived by Aδ fibers that terminate and release glutamate and neuropeptides such as substance P to activate second order neurons in Rexed's laminae I, II, and V of the dorsal horn.[24,25] These fibers relay pain sensation to the lateral thalamus via the spinothalamic pathway. Poorly localized slow pain is perceived by C fibers that terminate and release glutamate and substance P to activate second order neurons in Rexed's laminae I and II.[24,25] These fibers relay pain sensation to the medial thalamus via the spinothalamic pathway. From the thalamus, tertiary neurons send pain signals to the postcentral gyrus or primary somatosensory cortex and other regions of the brain including the secondary sensory cortex in the parietal operculum, anterior cingulate cortex, insula, amygdala and prefrontal cortex.[24–28] Pain is also relayed to the periaqueductal gray of the midbrain via the spinomesencephalic pathway, which is believed to contribute to the affective component of pain, and to the reticular formation in the brainstem via the spinoreticular pathway.[24,25] In addition, axons from Rexed's laminae I and V project to hypothalamic nuclei via the spinohypothalamic tract, which is responsible for the autonomic response to pain.[24] Under normal conditions, ascending pain pathways are modulated by descending, inhibitory neurons that originate from various regions of the brainstem including the raphe nuclei in the medulla, periaqueductal gray in the midbrain, and locus ceruleus in the pons.[25] These descending inhibitory neurons terminate in the substancia gelatinosa of Rexed lamina II. Raphe nuclei release serotonin in the dorsal horn of the spinal cord which inhibits ascending pain signals.[29] Stimulation of the periaqueductal gray activates the raphe nuclei.[29] The locus ceruleus inhibits spinothalamic activity by releasing norepinephrine in the dorsal horn which binds to the primary afferent neuron to suppress the release of nociceptive neurotransmitters.[30] In individuals with fibromyalgia, it is believe that the normal pain processing pathways are dysfunctional. There are two prevalent theories, the gate control theory and central sensitization, for abnormal and heightened pain responses in this population.[22]

The gate control theory suggests that the substantia gelatinosa of the dorsal horn serves as a gate control and modulates ascending pain pathways as they enter the spinal cord. The substantia gelatinosa is modulated by descending inhibitory neurons.[31] In healthy individuals, these descending inhibitory neurons limit pain signals from reaching the central nervous system and therefore down-regulate pain. It has been theorized that these inhibitory neurons do not down-regulate pain signals in individuals with fibromyalgia, resulting in increased pain.[22] Central sensitization is the result of activity-dependent synaptic plasticity resulting in increases in membrane excitability of neurons in the central nervous system. Synaptic strength can increase by temporal summation once a synapse has been activated repeatedly via an excitatory neurotransmitter or reduced inhibition at the synapse, causing increased activation of an action potential in these neurons.[17,32] It is through this process that hyperalgesia, an increased response to a painful stimulus, or allodynia, a pain response from a stimulus that is not normally painful, can result. Both hyperalgesia and allodynia are observed in adolescents with JFM. For example, the tender points specific to JFM are points that result in pain when pressure is applied; however, these points are not typically painful to pressure for those without this condition. In addition, evidence from adults with fibromyalgia suggests that neurochemical imbalances may also play a role in pain exacerbation in this cohort. Adults with fibromyalgia present with increased levels of substance P and glutamate and decreased levels of inhibitory neurotransmitters including serotonin, norepinephrine, and dopamine.[15,18,20,21,33] Although the pathophysiological process of JFM are not yet understood, insight into the physiological processes underlying JFM and physical and environmental factors that influence these processes will aid in the development of effective interventions for this cohort.

The majority of adolescents with JFM report significant functional disability and decreased physical activity level. Adolescents with JFM demonstrate significant dysfunction in academic, home, recreational, and social functioning.[2,34–36] Many adolescents with JFM are homeschooled due to difficulty attending school and those who attend school miss on average three days of school a month as a result of their pain.[35] Compared with other pediatric rheumatology patients and pediatric cancer patients, adolescents with JFM report lower physical and psychosocial functioning.[37] Adolescents with JFM spend the majority of their time performing sedentary activities despite recommendations to increase exercise and physical activity levels, which may be partially due to reports of physical activity increasing pain in as many as 88% of adolescents with JFM.[1] Physical activity monitoring of over one hundred adolescents with JFM revealed that these individuals participated in minimal, moderate or vigorous physical activity and less than one percent met national guidelines for daily vigorous physical activity.[38] Therefore, decreasing pain with physical activity may improve compliance with exercise recommendations and improve the overall health and function of these patients.

Pain and associated JFM symptoms often persist for years in adolescents with JFM despite a multifaceted approach to treatment. It is reported that more than 90% of patients still reported diffuse pain and fatigue at an average of 2.6 years following initial diagnosis.[7] Another study that followed up at approximately 4 years after initial diagnosis discovered that 62.5% of patients still reported pain and 60.4% of patients noted related symptoms such as chronic fatigue.[13] When long-term outcomes were examined at approximately six years following diagnosis, more than 80% of patients reported symptoms of fibromyalgia as young adults.[39] This same study found that compared with healthy adolescents, adolescents with JFM reported significantly higher pain, greater disability, greater anxiety and depression, and more frequent medical visits.[39] This suggests that although patients may be able to cope with their symptoms, their symptoms often persist into young adulthood and continue to lead to disability in this population. Therefore, a better understanding of factors that moderate pain and functional disability in this cohort is warranted in order to assist in the development of more comprehensive treatment options.

1.3: Physical Performance of Individuals with Fibromyalgia

Physical performance deficits including weakness, decreased endurance, balance deficits and altered movement patterns have been observed in both adults and adolescents with fibromyalgia.[40–44] Although more evidence exists to support physical performance deficits in adults with fibromyalgia, in recent years physical performance deficits have also been identified in adolescents with JFM. Adolescents with JFM demonstrate lower extremity weakness when compared with healthy adolescents.[45,46] Adolescents with JFM also demonstrate deficient functional stability and balance on the Star Excursion Balance Test compared with healthy adolescents.[46] In addition, a preliminary study of adolescents with JFM demonstrated biomechanical alterations during gait including shorter stride length, increased ankle dorsiflexion and eversion, and greater knee internal rotation compared with healthy adolescents.[45] Adolescents with JFM also demonstrated increased knee abduction, decreased ankle dorsiflexion, and decreased trunk flexion during drop vertical jump landing compared with healthy adolescents.[45] The knee biomechanics demonstrated by JFM patients are associated with increased injury risk in healthy adolescents and may contribute to pain exacerbation with physical activity in this cohort.[45,47,48] Based on this evidence, it is likely that deficient balance and stability, weakness, and altered lower extremity biomechanics contribute to pain and functional disability in this cohort. However, it is unknown if these observed biomechanical alterations are a result of JFM or if these changes are the result of moderating factors such as joint hypermobility.

1.4: Generalized Joint Hypermobility Syndrome and its Relationship to Juvenile Fibromyalgia

Generalized joint hypermobility, the ability of joints to perform multiple joint movements with greater than normal amplitude due to ligamentous laxity, is common among adolescents with JFM.[49,50] The prevalence of joint hypermobility among individuals with JFM ranges from 48% to 81%.[49,50] In comparison, the prevalence of joint hypermobility ranges from 4.6% to 35.4% among healthy adolescents,[49,51–53] 18.3% to 28.8% among healthy adults,[54–56] 27.3% to 64.2% among adults with fibromyalgia[55–60] and 11.4% to 13.2% among patients with other rheumatologic conditions.[58,60] Many individuals with generalized joint hypermobility, without an underlying inflammatory or rheumatological condition, also report many similar symptoms to JFM.

Many hypermobile individuals, without an underlying inflammatory or rheumatological condition, report chronic musculoskeletal pain.[57,61,62] The presence of joint hypermobility is associated with up to a 40% increased risk of experiencing severe pain.[51,57] In addition, joint hypermobility is associated with a significantly lower pressure pain threshold.[63] While the association between joint hypermobility and pain has been frequently reported, one study found no association between joint hypermobility and pain in children; however, this group used a more conservative measure for the Beighton-Horan laxity score and may have not adequately differentiated between hypermobile and non-hypermobile children.[52] Overall, the presence of joint hypermobility is associated with increased risk of musculoskeletal pain and increased pain sensitivity. In addition to an increased risk of pain, generalized joint hypermobility is also associated with other symptoms of JFM including fatigue, sleep disturbances, irritable bowel syndrome, anxiety, and depression.[54,64–68] Figure 1 depicts the relationship between JFM and joint hypermobility syndrome.

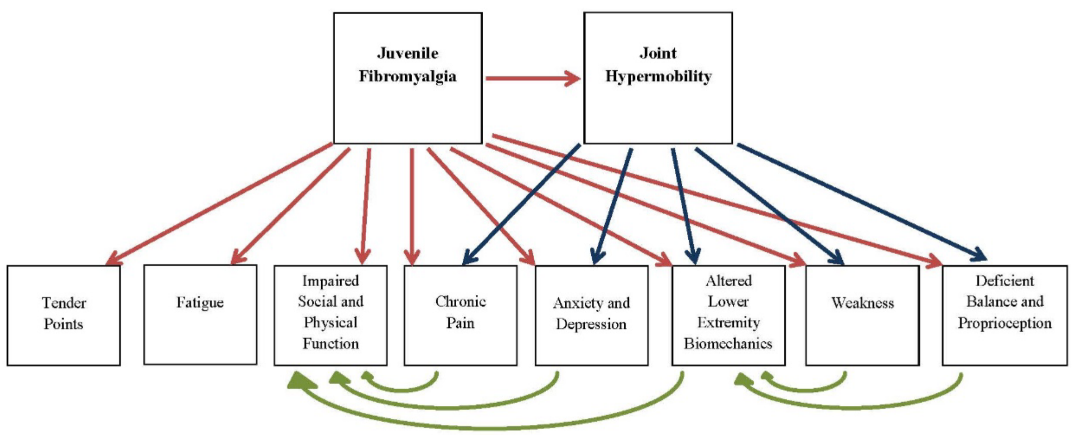


Figure 1. The relationship between JFM and joint hypermobility syndrome

1.5: Physical Performance of Individuals with Joint Hypermobility Syndrome

Joint hypermobility is also associated with numerous physical performance deficits. Many hypermobile children are considered clumsy or described as having poor coordination.[69] Compared to non-hypermobile individuals, hypermobile individuals demonstrate reduced lower extremity strength, diminished muscle endurance, and poorer functional performance as measured by the chair rise test, walking distance and jumping capacity.[68,70,71] Compared with non-hypermobile adolescents, hypermobile children are often deconditioned as measured by $VO_{2Max.}$[72] Furthermore, individuals with joint hypermobility also display neuromuscular deficits including deficient balance, diminished reflex function, deficient joint proprioception and a higher frequency of falls than non-hypermobile individuals.[73–78] Symptomatic adolescents with generalized joint hypermobility also demonstrate deficient joint proprioception and balance compared to non-hypermobile adolescents; however, these deficits were not observed in asymptomatic adolescents with generalized joint hypermobility.[53,74,78–80] Muscle activation strategies are also altered in hypermobile children compared with non-hypermobile children.[81] Similar to adolescents with JFM, hypermobile adolescents exhibit limited physical activity, compared with non-hypermobile adolescents.[69,78]

In addition to deficient coordination, weakness, and physical deconditioning, biomechanical alterations have also been observed in hypermobile individuals. Multiple studies have reported variations in gait and stair climbing mechanics in hypermobile individuals.[76,82–85] Hypermobile adolescents exhibit deficient head and trunk stability during gait.[82] In addition, hypermobile adolescents demonstrate greater knee extension during mid stance of the gait cycle than non-hypermobile adolescents.[86] These results suggest that joint hypermobility is associated with altered biomechanics during multiple activities of daily living.

Because many individuals with joint hypermobility demonstrate weakness, decreased endurance, deficient proprioception, deficient balance, and altered biomechanics, it is possible that joint hypermobility further exacerbates these physical performance deficits in adolescents with JFM. It is also possible that these physical performance deficits may further exacerbate pain in hypermobile adolescents with JFM. Soft tissue and joint microtrauma due to excessive joint motion is believed to be one potential mechanism of pain in hypermobile adolescents.[87,88] It has been suggested that soft tissue and joint damage occurs as hypermobile individuals repetitively move though excessive range of motion during daily tasks.[87,88] Damaged soft tissue and cartilage cells release potassium ions, hydrogen ions, adenosine triphosphate, glutamate, proteases, cytokines, serotonin and histamine which activate and sensitize free nerve ending attached to Aδ and C pain fibers.[24,26,27,89] Repeated activation of these fibers over time, can result in central sensitization which is one proposed mechanism of pain exacerbation in adolescents with JFM.[17,90,91] Figure 2 depicts the proposed mechanism for pain exacerbation among hypermobile adolescents with JFM. While JFM is a multifaceted syndrome, the purpose of this study was to determine if the presence of joint hypermobility is one mechanism contributing to exacerbation of pain, functional disability, and physical performance deficits associated with JFM.

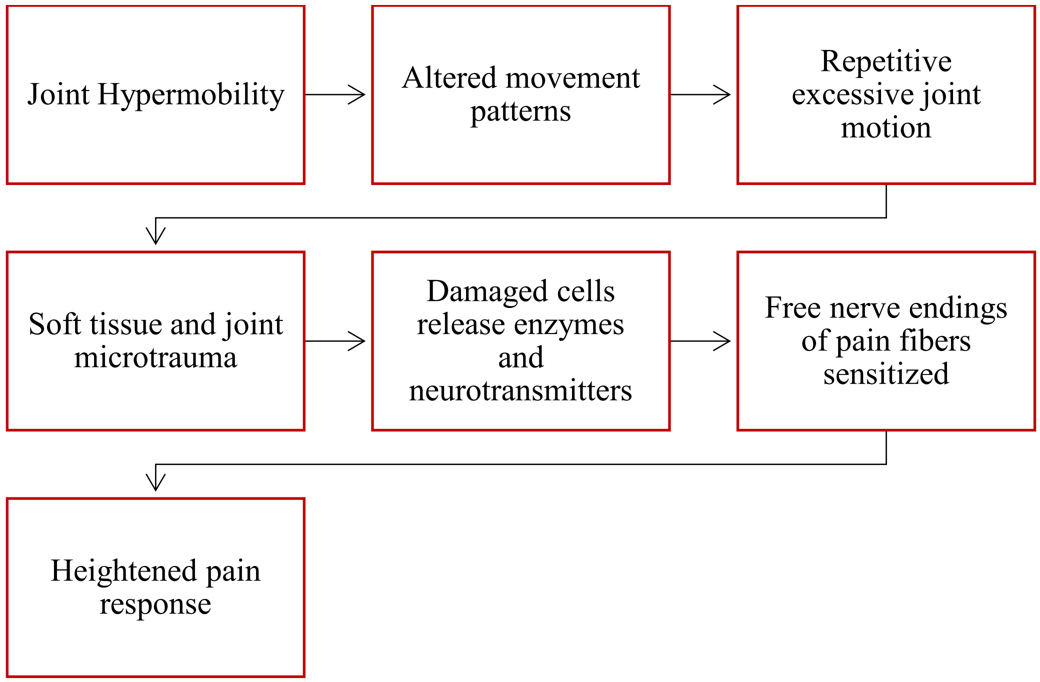


Figure 2. Proposed mechanism of pain exacerbation in hypermobile adolescents with JFM

1.6: Current Treatment of Juvenile Fibromyalgia

Current treatment for JFM includes pharmacological management, cognitive behavior therapy, and exercise. There are currently no US Food and Drug Administration (FDA) approved medications for treatment of JFM. However, studies are ongoing for the use of the three medications approved for management of fibromyalgia in adults in adolescents with JFM. There is limited evidence to suggest that Milnacipran may improve pain and quality of life for adolescents with JFM.[92] Similarly, a randomized controlled trial evaluating the effect of Pregabalin in adolescents with JFM found no significant change in pain scores compared to a placebo treatment.[93] Due to limited evidence of the efficacy of pharmacological management in adolescents with JFM, non-pharmacological treatment approaches, such as cognitive-behavioral therapy and exercise, are frequently utilized.

CBT is commonly used for the treatment of JFM. It is effective at reducing functional disability, pain, fatigue, anxiety, and depressive symptoms in this cohort.[14,94–96] Coping skill training, when included as part of the CBT, leads to greater reduction in symptoms and better ability to cope with pain.[95] CBT is well tolerated by adolescents with JFM and studies indicate good compliance with this intervention as the majority of adolescents complete the course of treatment.[14] Adolescents with JFM who have greater disability and enhanced coping efficacy are more likely to achieve a clinically significant improvement in function.[97] CBT has been shown to be effective at decreasing disability and depressive symptoms; however it does not result in a clinically significant reduction in pain.[14] Therefore, while cognitive-behavioral therapy is beneficial for adolescents with JFM, additional interventions are necessary in order to reduce pain for these individuals.

Exercise is a common intervention used to improve physical and emotional function for individuals with fibromyalgia and has been shown to reduce pain in adults with fibromyalgia. Both aerobic exercise and strengthening programs are beneficial for reducing pain severity, improving mood, and improving functional capacity in adults with fibromyalgia.[98–103] These benefits can be maintained over time when patients continue to participate in regular exercise.[103] Compared to relaxation therapy, resistance exercise results in significantly greater improvements in strength, pain, and reported quality of life for adults with fibromyalgia.[104] Balance exercises and flexibility training also reduce pain and improve reported quality of life in adults with fibromyalgia but are not as effective as aerobic and strengthening exercises.[105,106] Limited evidence supports the use of exercise programs for the management of JFM symptoms. A small sample of adolescents with JFM demonstrated significant improvements in functional capacity, quality of life, fatigue, pain, and symptom severity following twelve weeks of aerobic exercise.[107] Despite evidence of symptom reduction with exercise, many JFM patient remain non-compliant with exercise recommendations. Non-compliance with exercise is likely due to increased fear of movement and frequent pain exacerbation following exercise in this cohort.[1,108,109] Therefore it is important to develop exercise interventions that will limit pain exacerbation and emphasize exercise compliance.

The majority of adolescents with JFM reported pain exacerbation with exercise which may be the result of altered biomechanics and increased stress on joints during movement.[1,45] Adolescents with JFM demonstrated altered gait patterns, increased knee abduction with jump landing and poorer trunk control compared with healthy adolescents.[45] It is also interesting that JFM preferentially affects females and increased knee abduction during jump landing is frequently observed in adolescent females.[110,111] These biomechanical alterations are associated with increased injury risk in athletes and likely increased joint stress during exercise and functional activities in this cohort.[48,112] Because adolescents with JFM demonstrate altered biomechanics during functional tasks, it has been suggested that neuromuscular training will be beneficial in this cohort to restore biomechanics, decrease joint stress, and decrease pain with functional activities.[45,109] Neuromuscular training improves biomechanics and reduces injury risk in healthy adolescents[113–115] and may be beneficial for improving biomechanics and reducing pain with exercise in adolescents with JFM. Preliminary evidence from a pilot randomized controlled trial indicates that combination treatment of cognitive behavioral therapy and neuromuscular training decreases pain, increases motivation to exercise, and increases energy levels in patients with JFM.[116–118] However, physical activity levels of JFM patients decreased significantly when cognitive behavioral therapy was used as treatment in the absence of exercise interventions.[119] These data indicate that exercise is an essential component of a comprehensive treatment approach for this population. While initial evidence suggests that neuromuscular training will be beneficial in reducing disability in adolescents with JFM, the effect of neuromuscular training on pain, strength, biomechanical and functional limitations in this cohort is currently unknown.

1.7: Current Treatment for Joint Hypermobility Syndrome

Just as physical activity has been shown to be beneficial for adolescents with JFM, exercise is also helpful for hypermobile individuals and has been reported to decrease pain and disability in this cohort.[62,120,121] An eight-week home exercise program consisting of closed kinetic chain exercises significantly improved proprioception, balance, strength, and quality of life measurements in hypermobile adults.[122] A similar eight-week strengthening program restored an absent non-monosynaptic quadriceps reflex in hypermobile individuals.[74] These results suggest that the musculoskeletal deficits associated with joint hypermobility may be modifiable with exercise interventions. While it is not possible to ameliorate joint hypermobility, it may be feasible to compensate for joint instability by increasing strength and neuromuscular control. Therefore, neuromuscular training emphasizing joint protection, stability, and proprioception will likely decrease pain and limitations in these hypermobile individuals. It has been suggested that exercise interventions for adolescents with JFM and individuals with joint hypermobility should emphasize joint protection, proprioception, and strengthening, with the goal of decreasing mechanical stress on joints and pain sensitivity.[50,120,123] Neuromuscular training interventions differentially affect "high-risk" individuals or those who demonstrate greater biomechanical alterations.[124] Since hypermobile individuals demonstrate deficient strength, proprioception, and altered biomechanics compared with non-hypermobile individuals, it is likely that neuromuscular training will differentially affect hypermobile and non-hypermobile adolescents with JFM. Therefore it will be beneficial to identify individuals most likely to benefit from neuromuscular training and to develop targeted interventions in order to optimize the efficacy of neuromuscular training interventions. As a result, another purpose of this study is to examine the differential effect of neuromuscular training in hypermobile and non-hypermobile adolescents with JFM.

1.8: Summary

Despite the increased prevalence of joint hypermobility among adolescents with JFM, the clinical significance of this correlation remains unclear. The only known correlation between joint hypermobility and clinical symptoms in JFM patients is increased objective pain sensitivity.[13] Hypermobile adolescents with JFM reported lower tender point thresholds and greater tender point counts than non-hypermobile JFM patients.[50,56] Although healthy individuals with generalized joint hypermobility demonstrate many of the same symptoms as adolescents with JFM, the clinical significance of joint hypermobility among adolescents with JFM remains unclear. Current treatment of JFM includes pharmacological interventions, cognitive behavioral therapy, and exercise recommendations. Exercise is a beneficial component of a multifaceted treatment approach; however, compliance with exercise recommendations is poor. It is important to fully understand all factors contributing to pain and disability in this population in order to implement appropriate exercises and limit pain exacerbation with exercise. A better understanding of how joint hypermobility moderates clinical symptoms and impacts treatment responses in adolescents with JFM, will aid in the understanding of the presentation of this condition and assist in the development of targeted interventions to reduce pain and disability in this cohort. The purpose of this dissertation was to provide a comprehensive exploration of the influence of joint hypermobility on the clinical symptoms, physical function, and response to intervention in adolescents with JFM. This was accomplished through the following specific aims:

Specific Aim 1: To compare pain, functional disability, strength, and biomechanics between hypermobile adolescents with JFM and non-hypermobile adolescents with JFM.

Specific Aim 2: To compare pain, functional disability, strength, and biomechanics between hypermobile adolescents with JFM and healthy adolescents with generalized joint hypermobility.

Specific Aim 3**:** To compare the response of hypermobile adolescents with JFM and non-hypermobile adolescents with JFM to combined neuromuscular training and cognitive behavioral therapy intervention.

Chapter 2. The Influence of Joint Hypermobility on the Clinical and Functional Presentation of Adolescents with Juvenile Fibromyalgia

2.1: Abstract

Background: Generalized joint hypermobility is common among adolescents with juvenile fibromyalgia (JFM). Joint pain is commonly reported in hypermobile adolescents and both adolescents with JFM and adolescents with generalized joint hypermobility demonstrate altered biomechanics during gait compared to healthy non-hypermobile adolescents. Though joint hypermobility is common in adolescents with JFM, and generalized joint hypermobility syndrome is associated with many juvenile fibromyalgia-related symptoms, it is unknown if hypermobility further exacerbates symptoms or alters biomechanics in adolescents with JFM. Purpose/Hypothesis: The primary purpose of this exploratory study was to compare pain, functional disability, strength, and sagittal and frontal plane knee biomechanics during gait between hypermobile and non-hypermobile adolescents with JFM. The secondary purpose was to compare hip and ankle gait sagittal and frontal plane biomechanics between individuals with JFM who did and did not present with hypermobility. The hypotheses tested were that hypermobile adolescents with JFM would report worse pain and greater functional disability, and demonstrate weaker lower extremity strength and greater peak knee extension during gait compared to non-hypermobile adolescents with JFM. Methods: 30 female participants with JFM were categorized as hypermobile (n=13) or non-hypermobile (n =17) based on the Beighton-Horan Laxity Scale. Pain and functional disability were measured via the visual analog scale (VAS) and Functional Disability Inventory (FDI). Seated knee flexion and extension and standing hip abduction isokinetic strength were assess using a Biodex system. 3D motion analysis was used to capture over ground walking at a self-selected speed. Peak sagittal and frontal plane lower extremity kinematics and kinetics during the stance phase of gait were the variables of interest. Mann-Whitney U tests were performed to compare pain, functional disability, and lower extremity biomechanics between participants with and without hypermobility ($p<0.05$). Results: There were no differences in subjective pain rating, FDI scores, knee flexion strength, knee extension strength, or hip abduction strength between groups. Hypermobile adolescents with JFM demonstrated greater peak knee extension angles. Hypermobile adolescents with JFM also demonstrated lower peak ankle eversion angles and moments during gait compared to non-hypermobile adolescents with JFM. There were no other biomechanical differences observed between groups. Conclusions: The presence of joint hypermobility does not appear to exacerbate subjective pain and functional disability ratings in those with JFM. However, the presence of joint hypermobility in adolescents with JFM is associated with gait alterations at the knee and ankle. Future research is needed in order to better understand the role of joint hypermobility in adolescents with JFM.

2.2: Introduction

Juvenile fibromyalgia (JFM), a complex non-articular rheumatic condition, characterized by diffuse musculoskeletal pain, tender points, fatigue, and significant impairments in physical and social function, is also associated with a high prevalence of joint hypermobility, with as many as 48-81% of adolescents with JFM demonstrating generalized joint hypermobility.[1,3,49,50] Healthy adolescents with joint hypermobility syndrome demonstrate many common symptoms to adolescents with JFM, including chronic pain, fatigue, anxiety, depression, and impaired physical function.[51,66,69,71,78,86] Joint hypermobility is associated with an increased risk of developing musculoskeletal pain and it has been theorized that this is due to soft tissue microtrauma resulting from excessive joint mobility. [51,87,125–128] Joint hypermobility has also been linked to physical deficits and biomechanical alterations, which may lead to the increased injury frequency observed in individuals with joint hypermobility.[126,127] Despite the high prevalence of joint hypermobility among adolescents with JFM, the relationship between JFM and joint hypermobility is not well understood and it is unknown if joint hypermobility further exacerbates pain in this cohort.

There is preliminary evidence to suggest that hypermobile adolescents with JFM report greater pain sensitivity than non-hypermobile adolescents with JFM;[50] however, the relationship between join hypermobility and pain and functional disability in adolescents with JFM is not fully understood. Both adolescents with JFM and hypermobile adolescents demonstrate altered biomechanics and physical performance deficits compared to their healthy, non-hypermobile peers. Recently, preliminary evidence suggests that adolescents with JFM are weaker and demonstrate biomechanical alterations compared with their healthy peers.[45] Specifically, adolescents with JFM demonstrate hip and knee weakness, shorter stride lengths during gait, and differences in knee and ankle mechanics during gait and jumping.[45] Although these variances in physical performance have been observed in adolescents with JFM, the clinical significance of these alterations is still unknown.

Similar to adolescents with JFM, hypermobile adolescents demonstrate weakness and altered biomechanics compared to non-hypermobile adolescents. Impaired knee flexor and knee extensor strength has been observed in hypermobile adolescents.[73] In addition, hypermobile adolescents demonstrate deficient lower extremity joint proprioception compared with non-hypermobile adolescents.[73,126] Adolescents with joint hypermobility demonstrate altered movement strategies during gait compared with adolescents without joint hypermobility. Hypermobile adolescents ambulate with deficient head and trunk stability, reduced peak knee flexion, reduced knee excursion, and greater knee extension during midstance.[86,129] In addition, during gait, hypermobile adolescents demonstrate lower hip abduction, knee abduction, lower knee flexion, lower hip extensor and lower ankle plantar flexion moments.[130] Aydin et al found that hypermobile individuals demonstrated higher pressure and force values at the second metatarsal, which has been correlated with development of patellofemoral pain.[131,132] Since it has been suggested that joint hypermobility results in joint pain due to soft tissue damage from excessive joint motion, it is possible that these physical deficits and biomechanical alterations increase stress on joints and exacerbate pain in hypermobile adolescents with JFM. It is unknown if joint hypermobility is one potential moderator of pain and functional disability in this population. It is possible that these biomechanical variances, combined with soft tissue microtrauma from excessive joint mobility may propagate the cascade of pain exacerbation in hypermobile adolescents with JFM. Therefore, it is necessary to better understand movement qualities and factors that may affect these qualities in order to develop a better understanding of pain and function and develop more comprehensive treatment options for this cohort.

The symptomology similarities between joint hypermobility and JFM may be indicative of common pathophysiological processes specific to these conditions;[49] however, it is currently unknown if joint hypermobility further exacerbates symptoms in adolescents with JFM. The primary purpose of this exploratory study was to evaluate JFM as a movement disorder and to determine if pain, functional disability, hip and knee strength, and knee biomechanics during gait differ between hypermobile adolescents with JFM and non-hypermobile adolescents with JFM. Secondary aims of sagittal and frontal plane hip and ankle biomechanics during gait were also examined. Knee biomechanics were the primary biomechanical variables of interest in this study due to Beighton-Horan Laxity Scale specifically assessing knee joint laxity. The hypotheses tested were that hypermobile adolescents with JFM would demonstrate higher subjective pain rating, greater functional disability, muscle weakness, and greater peak knee extension during gait compared to non-hypermobile adolescents with JFM.

2.3: Methods

Female adolescents, 12-17 years old, who were diagnosed with JFM by a licensed pediatric rheumatologist using Yunus and Masi[1] and the American College of Rheumatology[133] criteria, were recruited from clinics at a large Midwestern US Children's Hospital. This study was a secondary analysis of a larger trial and therefore a power analysis was not performed. Participants were excluded if they also had a diagnosis of a comorbid rheumatic disease, untreated major psychiatric diagnosis, or documented developmental delay. Informed written consent was obtained from parents and adolescents provided written assent. Institutional review board approval was obtained prior to study initiation.

After informed consent was obtained, a trained researcher obtained height (cm) and weight (kg). A nine point Beighton-Horan Laxity Scale (BHLS) was performed on each subject to determine joint mobility status (Table 1). Goniometry was used to verify joint range of motion. Adolescents who scored a 4 or greater on the BHLS were considered hypermobile and adolescents who scored a 3 or less on the BHLS were considered non-hypermobile.[134,135]

Table 1. Beighton-Horan Laxity Scale

Parameter	Score
Elbow hyperextension of at least 10º	Left: 1 point Right: 1point
Knee hyperextension of at least 10º	Left: 1 point Right: 1point
Little finger extension to at least 90º	Left: 1 point Right: 1point
Thumb apposition to forearm	Left: 1 point Right: 1point
Forward bend	1 point
Total score (9 points possible)	

Self-Reported Measures. Participants rated their pain severity on a 10cm Visual Analog Scale (VAS) with 0 being labeled as "no pain" and 10 being labeled at "pain as bad as it can be."[136] Functional disability was measured with the Functional Disability Inventory (FDI) questionnaire which has been validated in pediatric populations (Appendix A).[137,138] The FDI is a fifteen item questionnaire with scores ranging from 0 to 60. Higher scores indicate greater functional disability.

Strength. Isokinetic knee flexion and extension was assessed in a seated position at using the Biodex System II. Each subject performed 10 repetitions of maximal effort on each limb at 300º/second. Peak torques (Nm/kg) for each limb were recorded. Isokinetic hip abduction was assessed at using the Biodex System III. Each participant stood facing the dynamometer head with the hip center of their swing limb lined up to the axis of the dynamometer. Each participant performed 5 repetitions of maximal effort hip abduction on each limb at 120°/second. Peak torques for each limb were recorded and normalized to mass (Nm/kg).

Biomechanical Assessment. Study participants were fitted a modified Helen Hayes marker set using forty-seven (47) retro-reflective markers by at trained researcher (Figure 3). Participants were provided a small backpack with three non-collinear markers to track trunk motion. If a participant's anterior superior iliac spine marker could not be placed properly due to soft tissue obstruction, the anterior superior iliac spine were virtually reconstructed during post-processing via digitizing wand pointing captures on this landmark in lieu of anatomical marker placement.[139,140] A ten camera passive optical motion-analysis system (Raptor-E; Motion Analysis Corp., Santa Rosa, CA) was used to capture motion analysis data at 200 frames per second. Ground reaction forces were sampled at 1000Hz via five embedded force plates (AMTI Advanced Medical Technology, Inc., Watertown, MA).

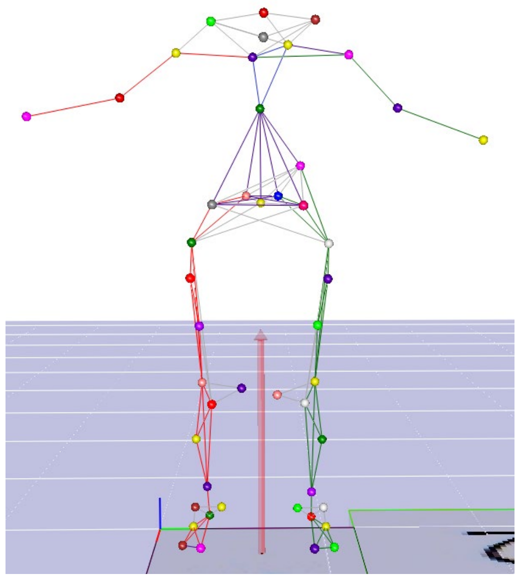


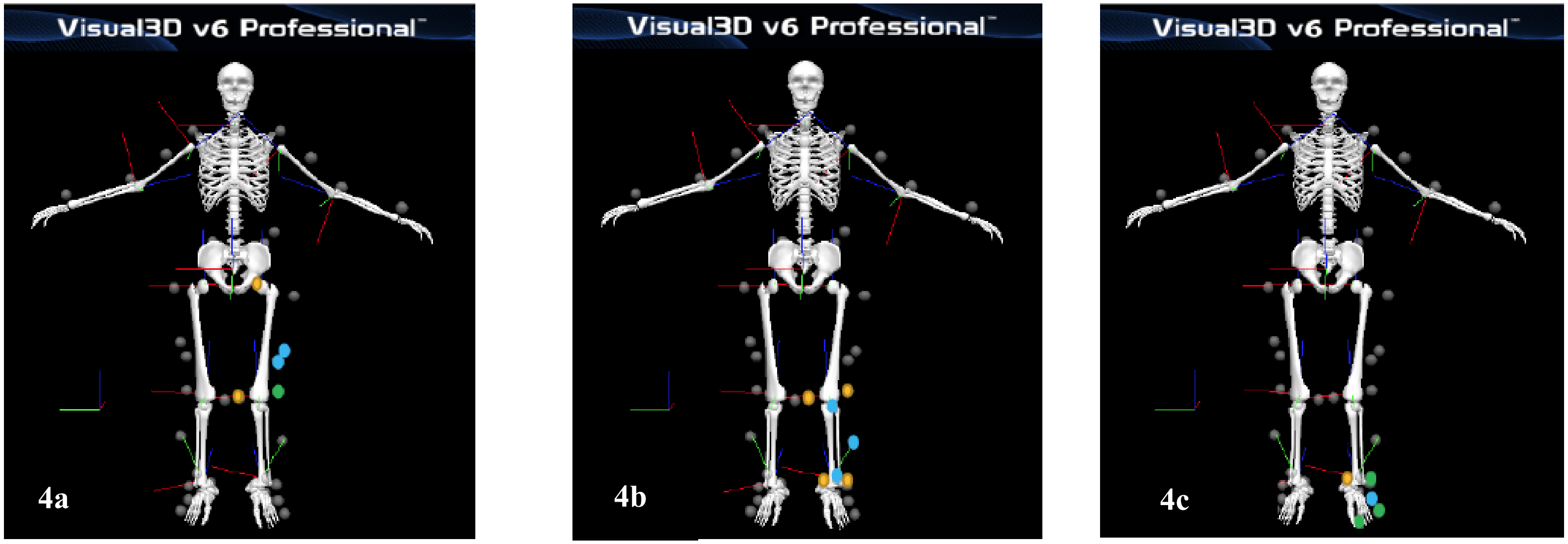
Figure 3. Static calibration pose with 47 retro-reflective markers

Each participant completed a static calibration trial standing in a neutral "T" position (Figure 3). Following the static calibration trial, ten markers used to define segments (medial ankle, medial knee, shoulders, sternum and C7) were removed for dynamic trials for ease of movement. To perform gait trials, participants were instructed to walk across the laboratory floor at their normal, self-selected pace. After a practice trial and participants verbalized feeling comfortable with the task, gait trials were collected until three separate foot strikes on each limb were recorded.

Motion capture software (Cortex version 6.0, Motion Analysis Corp, Santa Rosa, CA) was used to label markers and fill gaps in marker trajectories. Gaps in marker trajectories less than 20 consecutive frames (0.1 seconds) were filled using a cubic spine function. Gaps larger than 20 consecutive frames in markers were filled via the virtual fill function.[141] Once all markers were properly labeled and gaps in marker trajectories were filled, data were imported in Visual3D (C-Motion, Inc., Germantown, MD). Marker trajectory data was filtered at a cutoff frequency of 20 Hz and force data were filtered at a cutoff frequency of 50 Hz using a low-pass fourth order Butterworth filter. A customized model was created for each participant based on their height and mass. A CODA pelvis, based off of each subjects' anterior superior iliac spines and posterior superior iliac spines, was used in the model. Table 2 and Figure 4 depict joint definition markers and tracking markers for each lower extremity segment.

Table 2. Lower extremity segments for motion analysis

Lower Extremity Segment	Proximal Joint & Radius Definition Markers	Distal Joint and Radius Definition Markers	Tracking Markers
Thigh	1. Functional hip joint center	1. Knee 2. Medial knee	1. Knee 2. Mid-thigh 3. Thigh
Shank	1. Knee 2. Medial knee	1. Ankle 2. Medial ankle	1. Tibial tuberosity 2. Mid shank 3. Distal shank
Foot	1. Ankle 2. Medial ankle	1. Lateral foot 2. Toe	1. Ankle 2. Toe 3. Lateral foot 4. Posterior foot



Yellow dots indicate definition markers, blue dots indicate tracking markers, green dots indicate markers used for both definition and tracking purposes.
Figure 4. Lower extremity segment definitions for the thigh (4a), shank (4b), and foot (4c).

Hip joint center was calculated using the CODA pelvis and a regression described by Bell and Brand in 1989 using the inter-ASIS distance (Hip joint center = 0.36*ASIS_Distance, -0.19*ASIS_Distance, -0.3*ASIS_Distance).[142] Joint angles were defined via the Cardan-Euler rotation sequence XYZ as explained by Grood and Suntay.[143] Hip flexion and adduction, knee extension and adduction and ankle dorsiflexion and inversion are represented as positive angles and moments while hip extension and abduction, knee flexion and abduction and ankle plantarflexion and eversion are represented as negative angles and moments.

Lower extremity and trunk Cardan angles and moments were calculated. Custom code in Matlab (Mathworks) was used for biomechanical data reduction. Kinetic data were normalized to mass and height for each subject.[144] Due to unknown limb dominance of each participant, one limb from each participant was randomly selected for analysis using a random number generator. All peak kinematic and kinetic variables were obtained from the stance phase of gait, which was operationally defined as initial contact (vGRF > 10N) to toe off (vGRF < 10N). The mean of the peaks from each subject's three gait trials was used for data analysis.

Statistical Analysis. IBM SPSS Statistics 25 was used for data analysis. Normality testing revealed that the data violated the assumptions of normality and therefore non-parametric tests were used for analysis. Mann-Whitney U tests were performed to assess the effect of joint mobility on pain, functional disability, strength, and discrete measures of peak hip, knee, and ankle frontal and sagittal plane kinetics and kinematics during the stance phase of gait. Because non-parametric tests were used for analysis, medians and interquartile ranges (IQR) are reported. Alpha was set to 0.05, *a priori*.

2.4: Results

Thirty-two (32) female adolescents, diagnosed with JFM, consented to participate in this study. Data collected from two participants were excluded due to the inability to create a model for these subjects due to errors with marker placement during data collection. Of the thirty participants included in analysis, thirteen (13) were categorized as hypermobile (HM) (Beighton-Horan Laxity Scale score greater than or equal to 4) and seventeen (17) were categorized as non-hypermobile (nHM) (Beighton-Horan Laxity Scale score less than or equal to 3). There were no significant differences in age, height, mass, or gait speed between groups ($p \geq 0.39$) (Table 3).

Table 3. Chapter 2 sample demographics.
Median (IQR)

	Age (years)	Height (cm)	Mass (kg)	Gait Speed (m/s)
Hypermobile	16 (14.5, 17.0)	165.0 (158.5, 167.5)	69.6 (55.4, 73.2)	1.24 (1.05, 1.32)
Non-Hypermobile	15 (14.5, 16.5)	162.0 (157.0, 171.0)	63.2 (50.6, 74.2)	1.25 (1.03, 1.32)

2.4.1: Pain and Functional Disability

There were no differences in pain or functional disability scores between hypermobile and non-hypermobile adolescents with JFM (Table 4) (Appendix B).

Table 4. Pain (VAS) and function disability scores (FDI) for hypermobile adolescents with JFM and non-hypermobile adolescents with JFM.
Median (IQR)

	Hypermobile	Non-Hypermobile	p-value
VAS	6.9 (5.5, 7.4)	7.0 (6.3, 7.8)	0.25
FDI	23 (18, 31)	27 (22, 33)	0.20

2.4.2: Strength

Knee flexion, knee extension, and hip abduction strength were not different between hypermobile and non-hypermobile adolescents with JFM (Table 5) (Appendix C).

Table 5. Peak torques for lower extremity strength (Nm/kg) for hypermobile adolescents with JFM and non-hypermobile adolescents with JFM
Median (IQR)

Joint Motion	Hypermobile	Non-Hypermobile	p-value
Knee Flexion	0.69 (0.56, 0.78)	0.59 (0.51, 0.70)	0.18
Knee Extension	0.94 (0.87, 1.04)	0.96 (0.77, 1.14)	0.87
Hip Abduction	0.67 (0.45, 0.92)	0.71 (0.53, 0.82)	0.87

2.4.3 Gait Kinematics

There were no differences in peak knee flexion angles, peak knee abduction angles, or peak knee adduction angles between hypermobile and non-hypermobile adolescents with JFM. However, peak knee extension angles were significantly different between groups (Appendix D), such that hypermobile adolescents demonstrated hyperextension while non-hypermobile adolescents remained in slight flexion. Peak hip and ankle angles were not different between hypermobile and non-hypermobile adolescents with JFM with the exception of peak ankle eversion angle, indicating less eversion in the hypermobile group (Table 6).

Table 6. Peak joint angles (degrees) during stance phase of gait for hypermobile adolescents with JFM and non-hypermobile adolescents with JFM
Median (IQR). Hip flexion and adduction, knee extension and adduction and ankle dorsiflexion and inversion are represented as positive angles while hip extension and abduction, knee flexion and abduction and ankle plantarflexion and eversion are represented as negative angles.

Joint	Motion	Hypermobile	Non-Hypermobile	p-value
Hip	Flexion	34.13 (28.18, 36.37)	38.64 (30.02, 39.81)	0.16
	Extension	-7.21 (-3.22, -13.04)	-6.10 (-3.14, -14.50)	0.85
	Abduction	-2.88 (0.41, -4.41)	-2.12 (-0.10, -4.71)	0.75
	Adduction	8.9 (7.09, 12.13)	11.03 (8.49, 13.99)	0.20
Knee	Flexion	-37.64 (-34.30, -39.69)	-35.06 (-34.19, -44.38)	0.91
	Extension	2.21 (0.58, 3.27)	-2.38 (-4.28, 1.59)	0.03*
	Abduction	-6.97 (-5.91, -9.13)	-6.94 (-5.04, -9.08)	0.85
	Adduction	-1.65 (-4.54, 0.06)	0.96 (-3.65, 1.39)	0.41
Ankle	Plantarflexion	-14.93 (-10.90, -18.79)	-15.04 (-11.88, -19.63)	0.52
	Dorsiflexion	11.90 (8.67, 15.44)	9.91 (8.46, 12.03)	0.25
	Inversion	8.20 (4.68, 11.33)	5.21 (0.71, 9.53)	0.23
	Eversion	-8.89 (-5.90, -15.89)	-13.59 (-10.72, -17.80)	0.04*

2.4.4 Gait Kinetics

Peak knee and hip moments were not different between groups (Appendix E). Peak ankle plantar flexion, dorsiflexion, and inversion moments were not different between hypermobile adolescents and non-hypermobile adolescents with JFM. Hypermobile adolescents with JFM demonstrated lower peak ankle eversion moments than non-hypermobile adolescents with JFM (Table 7).

Table 7. Peak joint moments (Nm/kg*m) during stance phase of gait for hypermobile adolescents with JFM and non-hypermobile adolescents with JFM
Median (IQR). Hip flexion and adduction, knee extension and adduction and ankle dorsiflexion and inversion are represented as positive angles moments while hip extension and abduction, knee flexion and abduction and ankle plantarflexion and eversion are represented as negative moments.

Joint	Motion	Hypermobile	Non-Hypermobile	p-value
Hip	Flexion	0.46 (0.31, 0.61)	0.54 (0.40, 0.62)	0.62
	Extension	-0.33 (-0.26, -0.38)	-0.38 (-0.30, -0.45)	0.23
	Abduction	-0.14 (-0.10, -0.16)	-0.12 (-0.10, -0.16)	0.68
	Adduction	0.55 (0.39, 0.64)	0.59 (0.50, 0.67)	0.20
Knee	Flexion	-0.18 (-0.08, -0.29)	-0.18 (-0.13, -0.26)	1.0
	Extension	0.22 (0.16, 0.30)	0.25 (0.19, 0.28)	0.77
	Abduction	-0.05 (-0.04, -0.07)	-0.06 (-0.04, -0.09)	0.30
	Adduction	0.24 (0.14, 0.28)	0.17 (0.13, 0.27)	0.59
Ankle	Plantarflexion	-0.07 (-0.05, -0.11)	-0.06 (-0.04, -0.12)	0.41
	Dorsiflexion	0.93 (0.86, 1.05)	0.93 (0.88, 1.00)	0.59
	Inversion	0.06 (0.03, 0.09)	0.03 (0.01, 0.06)	0.07
	Eversion	-0.13 (-0.11, -0.17)	-0.19 (-0.15, -0.23)	0.00*

2.5: Discussion

The purpose of this exploratory study was compare pain, functional disability, strength, and gait mechanics between hypermobile and non-hypermobile adolescents with JFM. Despite the high prevalence of joint hypermobility in adolescents with JFM, this is the first study to our knowledge that compared functional disability and gait biomechanics between hypermobile and non-hypermobile adolescents with JFM. We hypothesized that hypermobile adolescents with JFM would demonstrate higher subjective pain rating, greater functional disability, muscle weakness, and greater peak knee extension during gait compared to non-hypermobile adolescents with JFM.

Contrary to our hypotheses, there were no differences in subjective pain rating or functional disability between hypermobile and non-hypermobile adolescents with JFM. Similarly, there were no differences in knee flexion, knee extension, or hip abduction strength between the two groups. Supporting our hypothesis, hypermobile adolescents with JFM demonstrated greater peak knee extension angle during the stance phase of the gait cycle. Hypermobile adolescents with JFM also demonstrated lower peak ankle eversion angles, and lower peak ankle eversion moments than non-hypermobile adolescents with JFM. There was no difference in all other peak joint angles, peak joint moments, or total limb support moment at midstance between groups.

The results of this study suggest that joint hypermobility may not influence self-reported pain or functional disability in adolescents with JFM. This is supported by a previous study by Ting et al. who also found no difference in self-reported pain intensity between hypermobile and non-hypermobile adolescents with JFM; however, this group did find that hypermobile adolescents with JFM presented with a greater number of tender points and had lower tender point thresholds compared to their non-hypermobile peers.[50] This suggests that subjective pain reporting may not be a valid assessment to detect differences between groups; however objective measures of pain may be more sensitive to this cohort.

To our knowledge, this is the first study that provides preliminary evidence that hypermobile and non-hypermobile adolescents with JFM may move differently during a functional, everyday task. Specifically, hypermobile adolescents with JFM demonstrated greater peak knee extension and lower peak ankle eversion during gait. This is similar to a previous study that compared gait kinematics between otherwise healthy adolescents with and without generalized hypermobility. This group found that hypermobile adolescents demonstrated greater knee extension during midstance compared to their non-hypermobile peers.[86] Increased knee extension during gait is often a result of quadriceps weakness; however, there was no difference in quadriceps strength between the two groups in this study. This indicates that the knee hyperextension observed in hypermobile adolescents with JFM may be more likely a result of greater available range of motion or neuromuscular adaptations, such as deficient proprioception, than strength deficits. Proprioceptive deficits have been repeatedly documented in both hypermobile adults and children.[73,77,145] Specifically, children with generalized hypermobility demonstrate deficient proprioception, as measured by joint kinesthesia and joint position sense, compared to children without hypermobility.[73] Although joint proprioception was not measured in the current study, it is possible that this may be contributing to the kinematic variances observed.

Hypermobile adolescents with JFM also demonstrated lower peak ankle eversion ankles and moments compared with non-hypermobile adolescents. Healthy individuals demonstrate a mean peak ankle pronation or eversion angle of 10.5 degrees during gait.[146] In our study hypermobile adolescents demonstrated similar median peak ankle eversion angles (9 degrees) and non-hypermobile adolescents demonstrated a higher median peak eversion angles (14 degrees) compared to what has previously been observed in healthy individuals. Although one may expect hypermobile adolescents to demonstrate greater peak joint angles compared to their non-hypermobile peers, the Beighton-Horan Laxity Scale does not measure ankle mobility and therefore it may be possible that hypermobile adolescents are compensating for proximal joint instability by stiffening and stabilizing at the ankle. Although slight variations in knee and ankle joint angles were statistically significant, it is unknown if these difference are clinically relevant and contribute to pain and dysfunction in this cohort. Future research is need to determine if the observed variation contribute to the symptoms observed in adolescents with JFM.

In addition to neuromuscular adaptations, it is also possible that kinesiophobia may contribute to the observed biomechanical alterations. Compared to their healthy peers, adolescents with JFM report greater fear of movement.[45,108] While hypermobility status did not explain fear of movement in those with musculoskeletal pain,[147] it is interesting that kinesiophobia is correlated with lower peak knee flexion in adults with patellofemoral pain.[148] Although it was not measured in this study, it is possible that pain-related fear of movement may have contributed to some of the observed biomechanical variances in this study.

There are several limitations to the current study that minimize the generalizability of these results. First, this was a secondary analysis of a larger study and as a result we were underpowered which increases our risk of type II error. Although the current sample size is comparable to other biomechanical studies, the number of comparisons in this exploratory study increases the risk of type I error. A second phase of this study is currently ongoing which will allow for a larger sample size, appropriate for multiple comparisons.

This study only included adolescent females with JFM. Although this was intentional due to JFM disproportionately affecting females and known gait variances between sexes, the results are not generalizable to males with this condition.[6–9,149–151] Another potential limitation is the use of the Beighton-Horan Laxity Scale to determine joint hypermobility status. Although the Beighton-Horan Laxity Scale is most commonly used to determine generalized joint hypermobility and is the only tool documented for use in adolescents, there is limited positive to conflicting evidence regarding its reliability.[152] However, when goniometry is used, as it was in this study, the Beighton-Horan Laxity Scale demonstrates good validity.[135] While other test for hypermobility exist such as Carter and Wilkinson, Rotes-Querol, and Hospital del Mar, these tools lack evidence on reliability and validity.[152] In addition while a Beighton-Horan laxity score of four or greater is most commonly used to indicate the presence of joint hypermobility, this score is arbitrary cut off points between four and seven have been reported.[88,135,152,153] It has been suggested that a higher cutoff point of at least six may be necessary for children due to increased joint range of motion that is commonly observed in adolescents but deceases with age.[88,135,154] Although the Beighton-Horan Laxity Scale is the best available clinical test for joint hypermobility, there is further need to establish its reliability and validity and cutoff points for use in the adolescent population.

This study only examined movement variances during one task and did not account for difference in activity levels between participants. The biomechanical gait data obtained in this study demonstrated greater variance than what is typically expected which could be a result of differences in activity levels in participants.[155] Because gait is one of the most common movements performed throughout the day, is it possible that variances in activity levels between groups may have also affected gait biomechanics. Although gait was chosen because it is an essential task of daily life, it may have not been dynamic enough to discern difference between groups. Tasks such as the step down, drop vertical jump, and single leg hop have been frequently used in other populations to examine lower extremity biomechanics.[45,156–158] These more dynamic tasks may be more sensitive to lower extremity biomechanical variances due to the greater moments absorbed by the lower extremity and muscle activation required to control these movements. It will be beneficial to examine the difference in landing mechanics between hypermobile and non-hypermobile adolescents with JFM in the future.

Despite the high prevalence of generalized joint hypermobility in adolescents with JFM, it is unknown if joint hypermobility plays a role in this condition. This preliminary study indicates that joint hypermobility may not influence subjective pain and functional disability measures, but it may contribute to altered movement patterns and strategies during gait, specifically at the knee and ankle. Further research is needed to fully understand the role joint hypermobility may play in this cohort.

Chapter 3. A Comparison of Pain, Functional Disability, and Physical Performance between Adolescents with Generalized Joint Hypermobility and Hypermobile Adolescents with Juvenile Fibromyalgia

3.1: Abstract

Background: There is a high prevalence of generalized joint hypermobility in adolescents with Juvenile Fibromyalgia (JFM). Although not all adolescents with generalized joint hypermobility experience chronic pain, it is associated with an increased risk of developing joint pain. Both adolescents with JFM and healthy adolescents with generalized joint hypermobility demonstrate weakness and altered physical function compared to healthy, non-hypermobile adolescents. It is currently unknown if the presence of generalized joint hypermobility in adolescents with JFM further exacerbates pain and functional disability in this cohort. A better understanding of how adolescents with JFM and joint hypermobility and healthy adolescents with generalized joint hypermobility differ in pain, functional disability, and physical performance will aid in the understanding of the role of joint hypermobility in adolescents with JFM.

Purpose/Hypothesis: The purpose of this study was to compare pain, functional disability, lower extremity strength, and movement strategies during gait and jump landing between hypermobile adolescents with JFM and adolescents with generalized joint hypermobility without an underlying health condition. We hypothesized that hypermobile adolescents with JFM would report worse pain and greater functional disability, and demonstrate weaker lower extremity strength, greater peak knee extension during gait, greater knee abduction during jump landing, and less knee flexion during jump landing compared to hypermobile healthy adolescents. Methods: As part of a secondary analysis of a pilot randomized controlled trial, 12 adolescent females with juvenile fibromyalgia and generalized joint hypermobility and 5 healthy adolescents with generalized joint hypermobility were recruited for this study. Generalized joint hypermobility was determined by a score of four or greater on the Beighton-Horan Laxity Scale. Baseline pain (visual analog scale), functional disability (Functional Disability Inventory), isokinetic lower extremity strength, and biomechanics during gait and drop vertical jump (DVJ) were assessed. Biomechanical variables of interest included peak knee extension angles and moments during gait and peak knee flexion and abduction during DVJ landing. Mann-Whitney U tests were performed to compare pain, functional disability, lower extremity strength, and lower extremity biomechanics between groups ($p<0.05$). Effect sizes were calculated for scores between groups. Results: Adolescents with JFM and hypermobility reported greater pain and functional disability and demonstrated greater thigh strength than healthy adolescents with hypermobility. Adolescents with JFM and hypermobility also demonstrated lower knee extension moments during gait and greater knee abduction angles during DVJ landing compared to healthy adolescents with hypermobility. Hip abduction strength and knee extension angles during gait were not different between groups. There were also no group differences in knee abduction moments, knee flexion angles during DVJ landing, and knee flexion moments during DVJ landing were not different between groups. Conclusions: The results of this study

indicate that hypermobile adolescents with JFM have greater pain and functional disability and move differently during gait and DVJ landing compared to healthy, hypermobile adolescents. The observed biomechanical variances during gait and DVJ may be one mechanism of pain exacerbation in this cohort. Future research is needed to determine if the observed biomechanical variances are correlated to pain and functional disability in this cohort.

3.2: Introduction

Generalized joint hypermobility is the ability to move multiple joints beyond their normal range of motion.[127,152,159] It is estimated that generalized joint hypermobility affects anywhere from 2 to 57% of the population with even higher prevalence rates reported in adolescents.[160] Among adolescents with juvenile fibromyalgia (JFM); however, the prevalence of generalized joint hypermobility is reported to be between 48 to 81%.[49,50] Although many individuals with generalized joint hypermobility are asymptomatic, up to 60% report chronic pain and other systemic symptoms that are similar to those experienced by adolescents with JFM.[57] Generalized joint hypermobility is associated with a two-fold increase in risk of experiencing pain in adolescents, especially at the shoulder, knee, and ankle joints.[51] In a cross-sectional study examining one-hundred and twenty-five adolescents diagnosed with generalized joint hypermobility, exercise related anterior knee pain was the most common reported symptom, which indicates that pain exacerbation may be movement related in this cohort.[69] Despite the increased risk of pain associated with generalized joint hypermobility, the mechanism of pain exacerbation in these individuals is not well understood and it is currently unknown if joint hypermobility worsens pain and functional disability in adolescents with JFM.

Benign generalized joint hypermobility is the asymptomatic presence of joint hypermobility at multiple joints, while joint hypermobility syndrome is characterized by generalized joint hypermobility in the presence of pain and other systemic symptoms. JFM shares many of the same symptoms as joint hypermobility syndrome including widespread pain, fatigue, anxiety, depression, impaired physical function, and lower quality of life.[1–5,161] Deficient strength, balance, joint proprioception, reflex function and altered gait have been observed in both adolescents with benign generalized joint hypermobility and adolescents with joint hypermobility syndrome.[70,83–85,129] Both adolescents with benign generalized joint hypermobility and adolescents with joint hypermobility syndrome demonstrate upper and lower extremity weakness compared to adolescents without joint hypermobility.[73,162] In addition, gait alterations have been noted in adolescents with benign generalized joint hypermobility and adolescents with joint hypermobility syndrome, including increased knee extension or hyperextension during stance and decreased head and trunk stability.[86,129] It is interesting that adolescents with joint hypermobility syndrome demonstrate diminished proprioception and joint position sense compared to adolescents without hypermobility; however, these deficiencies were not observed in asymptomatic adolescents with benign generalized joint hypermobility.[74,79] Similarly, adolescents with joint hypermobility syndrome demonstrate balance deficiencies, while adolescents with benign generalized joint hypermobility demonstrate better balance than adolescents without joint hypermobility.[53,78,80] This may indicate that pain development in symptomatic adolescents with joint hypermobility may be related to neuromuscular control deficiencies such as diminished proprioception and balance. While these physical deficiencies have been observed in hypermobile adolescents, the functional implications and their relationship to chronic pain in adolescent with JFM are unknown.

Similar to hypermobile adolescents, adolescents with JFM also demonstrate physical performance deficits compared to healthy adolescents including weakness, deficient functional stability, and altered gait and jump landing mechanics.[45,46] Adolescents with JFM demonstrate hip abductor and knee flexor and extensor weakness compared to healthy adolescents.[45,46] Adolescents with JFM also demonstrate deficient balance and functional stability as measured by reach distance during the Star Excursion Balance Test.[46] During gait, adolescents with JFM demonstrate shorter stride lengths, increased ankle dorsiflexion and eversion and greater knee internal rotation compared to healthy adolescents.[45] Adolescents with also JFM demonstrate increased knee abduction and decreased trunk flexion and ankle dorsiflexion during jump landing compared to healthy adolescents. Greater knee abduction and decreased knee flexion during jump landing are associated with increased risk of developing knee pain and experiencing a knee injury.[48,157,158,163] Although the exact mechanism of pain for hypermobile adolescents and adolescents with JFM is not understood, it is possible that these observed biomechanical variances caused by joint hypermobility may contribute to pain and functional disability in these cohorts.

Soft tissue microtrauma due to excessive joint motion is believed to be one potential mechanism of pain in hypermobile adolescents.[87,88] It has been suggested that as hypermobile individuals repetitively move though excessive range of motion during daily tasks, soft tissue and cartilage damage occurs.[87,88] Damaged cells release potassium ions, hydrogen ions, adenosine triphosphate, glutamate, proteases, cytokines, serotonin and histamine which activate and sensitize free nerve ending attached to Aδ and C pain fibers.[24,26,27,89] Repeated activation of these fibers over time, can lead to central sensitization which is one proposed mechanism of hyperalgesia in individuals with chronic pain, including adolescents with JFM.[17,90,91] A better understanding of how physical function compares in adolescents with benign joint hypermobility and hypermobile adolescents with JFM will help to determine if altered biomechanics exacerbates pain in hypermobile adolescents.

Despite the similarities between joint hypermobility syndrome and JFM, it is unknown if generalized joint hypermobility and JFM are related and compound to exacerbate symptoms in hypermobile adolescents with JFM. Therefore, the purpose of this cross-sectional study was to compare pain, functional disability, lower extremity strength, and movement strategies during gait and jump landing between hypermobile adolescents with JFM and adolescents with generalized joint hypermobility without an underlying health condition. The knee joint was the focus of this study due to the increased risk of knee pain in hypermobile individuals and knee joint hypermobility being specifically assessed as part of the Beighton-Horan Laxity Scale.[69,88] The hypotheses tested were that hypermobile adolescents with JFM would report worse pain and greater functional disability, and demonstrate weaker lower extremity strength, greater peak knee extension during gait, greater knee abduction during jump landing, and decreased knee flexion during jump landing compared to hypermobile healthy adolescents. A better understanding of how hypermobile adolescents without an underlying health condition and hypermobile adolescents with JFM differ in pain, functional disability, strength, and biomechanics will help us understand the role of joint hypermobility among adolescent with JFM.

3.3: Methods

Hypermobile female adolescents with and without JFM, ages 12-17 years old, were included in this study. Adolescents diagnosed with JFM based on the Yunus and Masi[1] and the American College of Rheumatology[133] criteria were recruited from a large Midwestern US Children's Hospital as part of a larger randomized controlled trial. For this secondary analysis, only female adolescents with JFM who scored greater than or equal to a 4 on the Beighton-Horan Laxity scale were included.[134,135] Participants were also excluded if they had a history of comorbid rheumatic disease, untreated major psychiatric diagnosis, or documented developmental delay. Males were excluded from this secondary analysis due to known sex variances in biomechanics and JFM preferentially affecting females.[149,164]

Healthy female adolescents with generalized joint hypermobility were recruited from the community as a healthy control comparison group. Potential participants who were interested in our study were screened by a researcher over the phone for joint hypermobility using a self-report Beighton Score Questionnaire which has demonstrated excellent reliability (Appendix F).[165] This questionnaire was only used for screening purposes and was not used for data analysis. Participants who answered "yes" to at least four questions on the Beighton Score Questionnaire were included in this study. Informed written consent was obtained from parents and adolescents provided written assent. Institutional review board approval was obtained prior to study initiation. Because the data used in this study was a sub-set of data collected for a larger randomized controlled trial, no power analysis was performed.

Participant height (cm), weight (kg), and joint laxity were obtained by a trained researcher. Joint mobility status was confirmed for all healthy adolescents who reported joint hypermobility on the self-report questionnaire by a using a clinically administered nine point Beighton-Horan Laxity Scale (Table 1). Adolescents who scored greater than or equal to a 4 on the Beighton-Horan Laxity Scale were considered hypermobile and included in this study.[134,135] Variables of interest for this study included pain, functional disability, strength, and knee joint biomechanics during gait and jump landing.

Self-Reported Measures. A Visual Analog Scale (VAS) was used to measure pain. Participants were asked to mark their pain level on a 10cm line labeled with 0 "no pain" and 10 "pain as bad as it can be." Functional disability was measured using the Functional Disability Inventory (FDI) which has been validated for use in adolescent populations (Appendix A).[138,166] Scores on the FDI range from 0-60, with higher scores indicating greater disability.

Strength Assessment. Isokinetic knee flexion and extension strength was measured in a seated position on a Biodex System. After a practice trial, ten repetitions of maximal effort were performed on each limb at 300º/second. Hip abduction strength was measured in a standing position using a Biodex System. After a practice trial, each participant completed five repetitions of maximal effort hip abduction on each limb at 120º/second. Standardized verbal encouragement was provided by the researcher during each task. Peak torques for each limb were recorded and normalized to mass (Nm/kg).

Biomechanical Assessment. Forty-seven (47) retro-reflective markers were applied to each participant based on a modified Helen Hayes marker set (Figure 3). Each participant wore a small non-rigid backpack with three non-collinear markers in order to track trunk motion. If the anterior superior iliac spine could not be easily palpated for proper marker placement, the anterior superior iliac spine was virtually reconstructed during post-processing via a digitizing wand pointing captures on this landmark in lieu of anatomical marker placement.[139,140] For the hypermobile adolescents with JFM, a ten camera passive optical motion-analysis system (Raptor-E; Motion Analysis Corp., Santa Rosa, CA) was used to capture motion analysis data and five embedded force plate (AMTI Advanced Medical Technology, Inc., Watertown, MA) were used to measure ground reaction forces. Motion-analysis data for the healthy hypermobile adolescents were captured using a twelve camera passive optical motion analysis system (Raptor-E; Motion Analysis Corp., Santa Rosa, CA) and ground reaction forces were measured via four embedded force plates (Bertec 6090, Bertec Corp, Columbus, OH). Motion analysis data were collected at 200 frames per second and ground reaction forces were sampled at 1000Hz for all participants.

Each participant completed a static calibration trial as described in Chapter 2 (Figure 3). Following the static calibration trial each participant completed gait trials at a self-selected pace. Participants were instructed to walk across two embedded force plates at a comfortable speed. Once participants completed a practice trial and verbalized feeling comfortable with the task, gait trials were performed until three foot strikes for each limb were recorded.

After completion of gait trials, participants performed the drop vertical jump (DVJ) task. To perform the DVJ, each participant started standing on a 31cm box and dropped forward off of the box onto two embedded force plates. Upon landing the drop, participants were instructed to immediately rebound into a double leg jump. After a practice trial, each participant completed three DVJ trials. Ground reaction forces were collected for each limb.

After completion of collection of each motion analysis session, markers were labeled and gaps in marker trajectories were filled using motion capture software (Cortex version 6.0, Motion Analysis Corp, Santa Rosa, CA). Once markers were labeled and marker trajectory gaps were filled, the data was imported into Visual3D (C-Motion, Inc., Germantown, MD) where a customized model was created for each participant based on their mass and height. A custom code was then used in Matlab (Mathworks) for biomechanical data reduction to determine peak kinematic and kinetic variables during gait and DVJ. Peak knee extension angles and moments were obtained from the stance phase of gait, which was operationally defined as initial contact (vGRF > 10N) to toe off (vGRF < 10N). The entire stance phase of gait was examined due to documented variability of when peak knee extension occurs during gait in adolescents.[167] The frame when each peak knee extension angle and moment occurred during each gait trial was also recorded. Peak knee flexion and abduction values were obtained from the landing phase of the DVJ which was operationally defined as initial contact (vGRF > 10N) to toe off (vGRF < 10N). Kinetic data were normalized to mass and height for each participant.[144] One limb from each participant was randomly selected for analysis using a random number generator.

Statistical Analysis. IBM SPSS Statistics 26 was used for data analysis. Normality testing revealed that the data violated the assumptions of normality and therefore non-parametric tests were used for analysis. Mann-Whitney U tests were performed on pain, functional disability, strength, gait peak knee extension, and DVJ peak knee abduction and flexion values between each group. Because non-parametric tests were used for analysis, medians and interquartile ranges (Q_1, Q_3) are reported. Alpha was set to 0.05, *a priori*. Effect sizes were also calculated for each variable of interest between each group using the equation $r = \frac{Z}{\sqrt{N}}$ for non-parametric data with a small effect size r = 0.1 - < 0.3, medium effect size r = 0.3 - < 0.5, and large effect size $r \geq 0.5$.[168]

3.4: Results

Twelve (12) hypermobile female adolescents diagnosed with JFM and five (5) female adolescents with generalized joint hypermobility participated in this study. There were no significant differences in height, mass, or gait speed between groups ($p \geq 0.13$); however those with JFM were older than the healthy controls ($p=0.03$) (Table 8).

Table 8. Chapter 3 sample demographics
Median (IQR)

Group	Age (years)	Height (cm)	Mass (kg)	Gait Speed (m/s)
hmJFM	16.0 (14.3, 17.0)	164.5 (158.3, 167.8)	68.1 (54.9, 72.8)	1.25 (1.07,1.33)
hmHC	14.0 (12.5, 14.5)	161.5 (156.9, 171.5)	60.2 (44.6, 67.4)	1.11 (1.01,1.21)

3.4.1 Pain and Functional Disability

VAS and FDI scores were significantly different between groups with hypermobile adolescents with JFM reporting greater pain and functional disability than healthy adolescents with generalized joint hypermobility ($p<0.01$) (Table 9) (Appendix G).

Table 9. VAS and FDI scores for hypermobile adolescents with JFM and healthy, hypermobile adolescents
Median (IQR).

	Group	Score	p-value	Effect Size (r)
VAS	hmJFM	6.5 (5.5, 7.3)	<0.001*	0.77
	hmHC	0.2 (0.0, 1.5)		
FDI	hmJFM	24.5 (17.0, 31.5)	<0.001*	0.77
	hmHC	1.0 (0.0, 5.5)		

3.4.2 Strength

Knee flexion and extension strength were different between groups with hypermobile adolescents with JFM demonstrating greater knee flexion and extension strength than healthy, hypermobile adolescents ($p\leq0.04$). Hip abduction isokinetic strength was not different between groups ($p=0.33$) (Table 10) (Appendix H).

Table 10. Knee flexion, knee extension, and hip abduction strength (Nm/kg) for hypermobile adolescents with JFM and healthy, hypermobile adolescents Median (IQR).

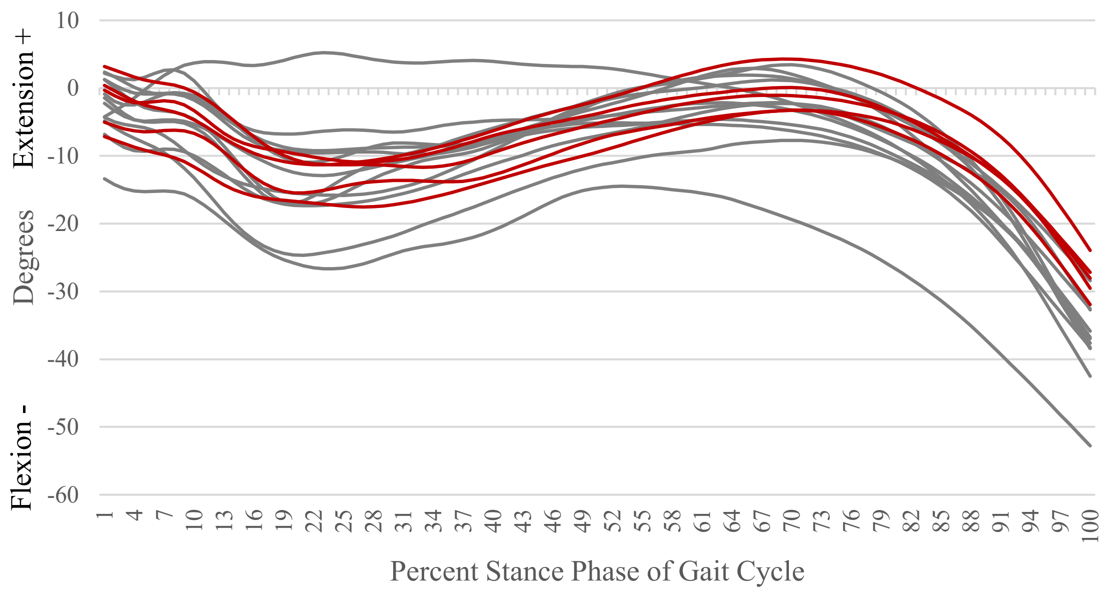
Joint Motion	Group	Strength	p-value	Effect Size (r)
Knee Flexion	hmJFM	0.69 (0.56, 0.78)	0.04*	0.51
	hmHC	0.50 (0.41, 0,67)		
Knee Extension	hmJFM	0.94 (0.87, 1.04)	0.00*	0.74
	hmHC	0.65 (0.58, 0.80)		
Hip Abduction	hmJFM	0.67 (0.45, 0.92)	0.33	0.26
	hmHC	0.73 (0.66, 0.99)		

3.4.3 Biomechanics

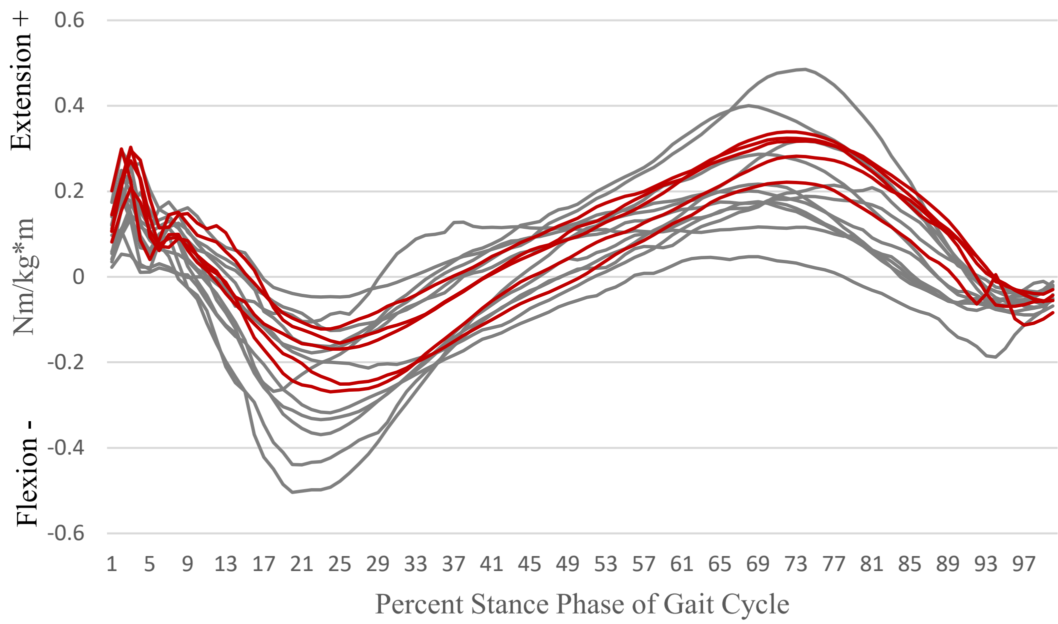
Peak knee extension angle during the stance phase of gait was not different between groups (p=1.00) (Table 11) (Appendix I). Peak knee extension moment during the stance phase of gait was different between groups with healthy, hypermobile adolescents demonstrating greater peak knee extension moments than hypermobile adolescents with JFM (p=0.04) (Table 11) (Appendix J). Within each group, peak knee extension angles occurred either immediately after initial contact or during midstance. Peak knee extension angle occurred after initial contact 51% of the time in hypermobile adolescents with JFM and 31% of the time in healthy hypermobile adolescents. Similar variability was also observed with the timing of peak knee extension moments. Peak knee extension moment occurred after initial contact 49% of the time in hypermobile adolescents with JFM and 60% of the time in healthy hypermobile adolescents. Figure 5 depicts individual time series curves for sagittal plane knee angles during the stance phase of gait. Figure 6 depicts individual time series curves for sagittal plane knee moments during the stance phase of gait.

Table 11. Peak knee extension angle (degrees) and moment (Nm/kg*m) during stance phase of gait for hypermobile adolescents with JFM and healthy, hypermobile adolescents
Median (IQR). Knee extension is represented by positive values while knee flexion is represented by negative values.

	Peak Knee Extension Angle	Peak Knee Extension Moment
hmJFM	2.16 (0.30, 2.98)	0.26 (0.16, 0.31)
hmHC	1.16 (-3.72, 4.54)	0.34 (0.32, 0.38)
p-value	1.00	0.04*
Effect Size (r)	0.00	0.49



Adolescents with JFM and joint hypermobility are depicted in gray. Healthy adolescents with generalized joint hypermobility are depicted in red.
Figure 5. Individual time series curves for sagittal plane knee angles during the stance phase of gait.



Adolescents with JFM and joint hypermobility are depicted in gray. Healthy adolescents with generalized joint hypermobility are depicted in red.
Figure 6. Individual time series curves for sagittal plane knee moments during the stance phase of gait.

Peak knee abduction angle during DVJ landing was different between groups with hypermobile adolescents with JFM demonstrating larger knee abduction angles than healthy hypermobile adolescents (p=0.04). Peak knee flexion angle, peak knee flexion moment, and peak knee abduction moment during DVJ landing were not different between groups (p≥0.28) (Table 12) (Appendices I and J).

Table 12. Peak knee flexion and abduction angle (degrees) and moments (Nm/kg*m) during DVJ landing for hypermobile adolescents with JFM and healthy, hypermobile adolescents

Median (IQR). Knee flexion and abduction are represented by negative values.

	Peak Knee Flexion Angle	Peak Knee Flexion Moment	Peak Knee Abduction Angle	Peak Knee Abduction Moment
hmJFM	-77.16 (-73.49, -89.8)	-1.08 (-0.96, -1.22)	-23.04 (-13.51, -29.66)	-0.42 (-0.25, -0.57)
hmHC	-76.37 (-72.08, -83.50)	-1.08 (-0.88, -1.32)	-12.54 (-8.19, -17.82)	-0.29 (-0.23, -0.39)
p-value	0.51	0.72	0.04*	0.28
Effect Size (r)	0.18	0.10	0.49	0.28

3.5: Discussion

The purpose of this cross-sectional study was to compare pain, functional disability, lower extremity strength, gait, and jump landing mechanics between healthy adolescents with generalized joint hypermobility and hypermobile adolescents with JFM. To our knowledge, this is the first study to compare these variables between asymptomatic adolescents with joint hypermobility and hypermobile adolescents with chronic pain. We hypothesized that hypermobile adolescents with JFM would report worse pain and greater functional disability and demonstrate weaker lower extremity strength, greater peak knee extension during gait, greater knee abduction during jump landing, and decreased knee flexion during jump landing compared to healthy adolescents with generalized joint hypermobility.

As we expected, hypermobile adolescents with JFM reported significantly greater pain and functional disability compared to healthy adolescents with generalized joint hypermobility. The healthy adolescents with generalized joint hypermobility in this study reported minimal to no pain and functional disability. These results are inconsistent with a previous study which found a moderate prevalence of chronic pain in hypermobile individuals.[57] This indicates that while some individuals with generalized joint hypermobility are prone to developing chronic pain, generalized joint hypermobility alone does not lead to widespread pain in all individuals.

Contrary to our hypothesis, hypermobile adolescents with JFM demonstrated stronger knee flexion strength and stronger knee extension strength compared to healthy hypermobile adolescents, while there were no group differences in hip abduction strength. Previous studies have indicated that adolescents with JFM demonstrate weaker hip abduction, knee flexion, and knee extension strength compared to healthy adolescents.[45,46] While the observed differences in this study were unexpected, these could be the result of the healthy adolescents with hypermobility being slightly younger (median age 14 years old) than the adolescents with JFM (median age 16 years old), as strength has been shown to increase with age in adolescent females.[169] In addition, differences in activity level between groups in this study are unknown.

Also contrary to our hypothesis, there were no differences in peak knee extension angles during the stance phase of gait between groups with both groups demonstrating peak knee extension angle that indicated hyperextension. In addition, contrary to our hypothesis, adolescents with JFM and joint hypermobility demonstrated lower peak knee extension moments during the stance phase of gait. Adults with knee osteoarthritis demonstrated lower external knee extension moments in late stance during gait compared to healthy controls.[170] However, it is unknown it this variance contributes to abnormal cartilage loading and the development of knee osteoarthritis or if this observation was compensatory due to knee pain. There was variability of when peak knee extension angles and moments were achieved during the stance phase of gait within each group. The magnitude of peak knee extension angles and moments did not appear to be related to timing during the stance phase of gait in either group. Variations in joint kinematics and kinetics during gait have been shown to be correlated to gait speed in adolescents, with larger knee extension angles and moments being noted during faster gait speeds.[167,171,172] However, in this study gait speed was not different between groups and gait speed did not differ between gait trials when peak knee extension occurred after initial contact and gait trial when peak knee extension occurred during midstance.

Supporting our hypothesis, hypermobile adolescents with JFM demonstrated greater peak knee abduction angles during DVJ landing; however, there was no difference in peak knee abduction moments during jump landing between groups. There were also no differences between peak knee flexion angles or moments between groups. Both knee abduction angles and moments during jump landing have been shown to increase with age in adolescent females.[110] Because healthy adolescents with hypermobility were younger than the adolescents with JFM, the potential influence of age must be considered when interpreting these results. Higher knee abduction angles and moments are associated with an increased risk of patellofemoral pain and knee injury in adolescent females.[47,158,173] Therefore, greater knee abduction angles during jump landing may be one mechanism of pain in hypermobile adolescents with JFM; however further investigation is needed to determine if this variance was a function of group or age.

There are limitations to this study. This was a secondary analysis of a larger study for the purposes of generating hypotheses for future work. As a result we likely were underpowered to fully appreciate potential differences between hypermobile adolescents with JFM and healthy adolescents with generalized joint hypermobility. Another limitation is the cutoff points used on the Beighton-Horan Laxity Scale to determine generalized joint hypermobility status. While a cutoff of four or greater is the gold-standard to determine generalized joint hypermobility status, cutoff points between four and seven have been suggested, especially when classifying adolescents and children.[88,135,152–154] A cutoff of four or greater on the Beighton-Horan Laxity Scale was selected for this study as it has been used previously to classify adolescents with JFM as hypermobile.[50] In addition, while the same methods and parameters were used for each group, the data for the adolescents with JFM were collected in a different laboratory by different researches than the data for the healthy adolescents with generalized joint hypermobility and therefore the interrater reliability may have affected the results of this study.

The results of this study indicate that hypermobile adolescents with JFM present with greater pain and functional disability and greater knee flexion and extension strength compared to healthy adolescents with generalized joint hypermobility. Therefore, generalized joint hypermobility alone does not always result in pain and functional disability. Our results indicated that hypermobile adolescents with JFM move differently than adolescents with generalized joint hypermobility with hypermobile adolescents with JFM demonstrating lower peak knee extension moments during gait and greater knee abduction moments during jump landing compared to healthy, hypermobile adolescents. The biomechanical variances observed in hypermobile adolescents with JFM may be one mechanism of pain exacerbation in this cohort. Further investigation is warranted to determine if the sagittal plane knee mechanics during gait and front plane knee mechanics during jump landing are associated with pain in this cohort.

Chapter 4. The Response to Cognitive Behavior Therapy and Neuromuscular Training in Hypermobile and Non-Hypermobile Adolescents with Juvenile Fibromyalgia

4.1: Abstract

Background: Juvenile Fibromyalgia (JFM) results in chronic widespread pain and decreased physical and social function, which often persists into adulthood. Cognitive behavioral therapy (CBT) reduces pain and functional disability; however these improvements are small and may not be clinically significant. Preliminary evidence suggests that when CBT is combined with neuromuscular training (NMT) adolescents with JFM demonstrate greater reduction in pain; however, there are no greater improvements in functional disability. There is a high prevalence of joint hypermobility in adolescents with JFM. Both adolescents with JFM and hypermobile adolescents demonstrate biomechanical alterations during functional tasks. It is currently unknown if joint hypermobility further exacerbates pain and biomechanical variances and influences response to treatment in adolescents with JFM. A better understanding of how factors such as joint hypermobility influence response to treatment will aid in the development of targeted interventions in order to reduce functional disability in this cohort.

Purpose/Hypothesis: The purpose of this study was to determine if hypermobile and non-hypermobile adolescents with JFM respond differently to combined CBT and NMT. We hypothesized that compared to non-hypermobile adolescents with JFM, hypermobile adolescents with JFM would demonstrate greater improvements in pain, functional disability, and strength, greater increases in knee flexion during jump landing, greater reductions in knee extension during gait and greater reductions in knee abduction during jump landing following CBT and NMT intervention. Methods: As part of a secondary analysis of a pilot randomized controlled trail, 16 female participants with juvenile fibromyalgia were categorized as hypermobile (n=6) or non-hypermobile (n =10) based on the Beighton-Horan Laxity Scale. Participants completed sixteen combined CBT and NMT sessions. Pain and functional disability, lower extremity strength, and biomechanics during gait and drop vertical jump (DVJ) were assessed pre- and post-intervention. Biomechanical variables of interest included peak knee extension angles and moments during gait and peak knee flexion and abduction during DVJ landing. Participants completed sixteen sessions of combined CBT and NMT interventions. The difference in pre- to post-intervention scores were calculated for each variable within each participant. Mann-Whitney U tests were performed to compare pre- to post-intervention change scores in pain, functional disability, lower extremity strength, and lower extremity biomechanics between participants with and without hypermobility ($p<0.05$). Effect sizes were calculated for post-intervention scores between groups. Results: There were no differences in pre- to post-intervention change in pain, functional disability, knee flexion, knee extension, and hip abduction strength, peak knee extension during gait and peak knee flexion and abduction during DVJ between groups. Conclusions: The results of this study indicate that joint hypermobility may not influence response to NMT in adolescents with JFM; however, hypermobile adolescents with JFM may demonstrate altered gait and jump landing mechanics. Future research is needed to

determine the influence of joint hypermobility on response to treatment in adolescents with JFM should focus on sagittal plane knee movement.

4.2: Introduction

Juvenile fibromyalgia (JFM) is a chronic, non-articular rheumatic disease that results in significant pain and functional limitations during adolescent years.[1,2,12] Current treatment options for adolescents with JFM are beneficial, but do not fully eliminate symptoms of this syndrome and often leave those affected with significant impairments in daily and social functioning. Cognitive behavioral therapy (CBT), a common treatment for JFM, is beneficial for improving functional disability, depression, and pain in adolescents with JFM; however, the improvements in pain are smaller than what is thought to be clinically significantly.[14] CBT combined with exercise interventions resulted in reduced pain and functional disability in this cohort[117,174,175] Adolescents with JFM who received combined CBT and exercise intervention reported greater reductions in pain than those who receive CBT alone.[117] The benefits of combined CBT and exercise were also maintained for one year following intervention for many participants.[174] Despite exercise recommendations for the treatment of JFM, the majority of adolescents with JFM remain sedentary.[38] Although the exact reason for persistent sedentary behavior in adolescents with JFM is unknown it may be the result of fear of movement and potential pain exacerbation from faulty biomechanics when exercise is initiated.[45] A better understanding of factors that may influence response to treatment will assist in the development of more targeted interventions with the goal of improving outcomes for individuals with this condition.

There is a high prevalence of joint hypermobility among adolescents with JFM, with up to 81% of adolescents with JFM demonstrating generalized joint hypermobility.[49,50] Despite the high prevalence of generalized joint hypermobility in this population, the influence of joint hypermobility on this condition is not fully understood. Altered biomechanics have been observed in both adolescents with JFM and individuals with generalized joint hypermobility, without an underlying rheumatological condition.[45,46,73,86,129] Although evidence is limited, a preliminary cross-sectional study comparing gait and jump-landing biomechanics between adolescents with JFM and healthy adolescents found differences in both tasks between groups.[45] Specifically, adolescents with JFM walked with shorter strides at a self-selected pace and demonstrated increased ankle dorsiflexion and eversion at a standardized gait speed compared to healthy adolescents.[45] During the drop vertical jump task, adolescents with JFM demonstrated reduced ankle dorsiflexion, increased knee abduction, and decreased trunk flexion during jump landing compared to healthy adolescents.[45] Increased knee abduction and decreased knee flexion during jump landing are associated with increased risk of developing knee pain and experiencing a knee injury.[48,157,158,163] Another study also found that adolescents with JFM demonstrated worse performance on the Star Excursion Balance Test compared to healthy adolescents.[46] It has been suggested that the biomechanical variances and balance deficits observed in adolescents with JFM may contribute to pain exacerbation in this cohort.[45,46]

Similar to adolescents with JFM, adolescents with generalized joint hypermobility demonstrate muscle weakness and neuromuscular deficits including deficient balance, diminished joint proprioception, and altered biomechanics during gait. Multiple studies have reported that hypermobile adolescents are weaker than their non-hypermobile peers.[73,162,176] Adolescents with generalized joint hypermobility demonstrate deficient joint kinesthesia and joint position sense compared to non-hypermobile adolescents, indicating deficient joint proprioception among these individuals.[73] During gait, hypermobile adolescents demonstrate decreased head and trunk stability compared to non-hypermobile adolescents.[82] Hypermobile adolescents also ambulate with lower peak knee flexion angles during loading response and swing phases of gait and greater knee extension angles in mid stance compared to their non-hypermobile peers.[86] It has been proposed that soft tissue microtrauma from excessive joint mobility may be one potential cause of pain in hypermobile individuals.[87,88] The biomechanical alterations observed in hypermobile adolescents and adolescents with JFM may further exacerbate soft tissue and joint microtrauma, especially when both JFM and joint hypermobility are present.

Although, both adolescents with JFM and adolescents with generalized joint hypermobility demonstrate neuromuscular deficits and biomechanical variances compared to healthy, non-hypermobile adolescents, it was previously unknown if the symptoms of JFM compounded with joint hypermobility further exacerbate pain and functional disability in this cohort. In the first aim of this dissertation we found that although hypermobile adolescents with JFM did not demonstrate differences in subjective pain, functional disability or strength compared to non-hypermobile adolescents with JFM, hypermobile adolescents with JFM did demonstrate greater peak knee extension and greater peak ankle eversion during gait compared to non-hypermobile adolescents with JFM. This suggests that although joint hypermobility may not influence baseline subjective pain rating and function in this cohort, joint hypermobility may further exacerbate biomechanical variances in this population. The biomechanical variances observed between hypermobile and non-hypermobile adolescents with JFM may indicate that different exercise interventions are needed to target the different movement patterns for each group.

Neuromuscular training (NMT), which emphasizes strength, balance, and exercise technique, has been used in multiple populations to correct movement deficits and decrease injury risk.[124,177–179] When utilized in adolescents with juvenile rheumatoid arthritis, NMT normalized gait and jump landing mechanics to those comparable to healthy adolescents.[179] Preliminary evidence has shown it to be beneficial in this cohort as well. A pilot study examining the effect of combined CBT and NMT intervention in adolescents with JFM found that this intervention increased trunk and hip flexion angles, increased internal hip extensor moment, decreased ankle eversion during jump landing, improved stride length during gait, and resulted in small to moderate improvement in hip and knee strength.[175] In addition to the biomechanical changes observed with this combined intervention, qualitative analysis also revealed that participants felt the intervention was tolerable and reported feeling stronger and more confident upon completion of the program and adolescents with JFM reported decreased functional disability, depression, and fear of movement.[116,118] This preliminary evidence suggests that combined CBT and NMT may beneficial for management of pain and functional disability in this cohort.

Although NMT improves biomechanics and decreases injury risk, it has been shown to be differentially beneficial among cohorts. Specifically, individuals with "high-risk" movement patterns, or those who have had a previous injury, demonstrated greater improvements in movement patterns following NMT interventions.[124] This suggests that interventions should be targeted to specific cohorts and be tailored to meet the specific needs of each individual. A better understanding of factors affecting movement and response to interventions in adolescents with JFM will assist in the development of targeted interventions for this cohort. Therefore, the purpose of this study was to determine if hypermobile and non-hypermobile adolescents with JFM respond differently to combined CBT and NMT intervention. Variables of interest for this study included pain, functional disability, lower extremity strength, and knee joint kinematics and kinetics during gait and jump landing. Specifically, we examined peak knee extension during gait and peak knee flexion and abduction during jump landing. The knee was selected as the joint of interest due to the Beighton-Horan Laxity Scale assessing hypermobility at this joint. We hypothesized that following CBT and NMT intervention, hypermobile adolescents with JFM would demonstrate greater improvements in pain, functional disability, and strength, greater reductions in knee extension during gait, greater increases in knee flexion during jump landing, and knee reductions in abduction during jump landing than non-hypermobile adolescents with JFM. It is our goal that understanding factors that influence the response to NMT in this population will aid in the development of targeted interventions and improve outcomes.

4.3: Methods

As part of a larger randomized controlled trial, female adolescents, ages 12-17 years old, diagnosed with JFM using Yunus and Masi[1] and the American College of Rheumatology[133] criteria, were recruited from a large Midwestern US Children's Hospital. Exclusion criteria included diagnosis of a comorbid rheumatic disease, untreated major psychiatric diagnosis, or documented developmental delay. While males were included as part of the larger randomized controlled trial, they were excluded from this study due to known sex variances in biomechanics.[149,164] Informed written consent was obtained from parents and adolescents provided written assent. Institutional review board approval was obtained prior to study initiation. Due to this data being a subset of data used for a secondary analysis of a larger pilot study, no power analysis was performed. Only females who completed combined CBT and NMT interventions were included in this study.

Clinical measures including height (cm), weight (kg), and joint laxity were obtained at baseline by a trained researcher. Joint mobility status of each participant was determined using a nine point Beighton-Horan Laxity Scale (BHLS) (Table 1). A trained researcher used a goniometer to verify joint range of motion. For the purpose of this study, joint hypermobility was defined by a score of 4 or more on the BHLS while a score of 3 or less was considered non-hypermobile. Variables of interest including pain, functional disability, strength, and knee joint biomechanics were measured pre- and post-intervention.

Self-Reported Measures. Pain was assessed using a 10cm Visual Analog Scale (VAS) with 0 being labeled as "no pain" and 10 being labeled at "pain as bad as it can be." The Functional Disability Inventory (FDI), a fifteen item questionnaire with scores ranging from 0-60, was utilized to measure functional disability in this adolescent population (Appendix A). Higher scores on the FDI indicate greater functional disability.

Strength Assessment. A Biodex System II was utilized to assess isokinetic knee flexion and extension strength. After a 5 practice repetitions, each participant performed 10 repetitions of maximal effort on each limb in a seated position at 300°/second. Peak torques (Nm/kg) were recorded for each limb. A Biodex System III was utilized to assess isokinetic hip abduction strength. To assess hip abduction strength, each participant was positioned standing facing the dynamometer head with the center of their swing leg aligned with the axis of the dynamometer. After a practice repetitions, 5 repetitions of maximal effort hip abduction were performed on each limb at 120°/second. A researcher provided verbal encouragement during knee and hip trials. Peak torques for each limb were recorded and normalized to mass (Nm/kg).

Biomechanical Assessment. A modified Helen Hayes marker set using forty-seven (47) retro-reflective markers was applied to each participant by a trained researcher (Figure 3). Trunk motion was tracked via a small backpack with three non-collinear markers. If a participant's anterior superior iliac spine marker could not be placed properly due to soft tissue obstruction, the anterior superior iliac spine was virtually reconstructed during post-processing via a digitizing wand pointing captures on this landmark in lieu of anatomical marker placement. A ten camera passive optical motion-analysis system (Raptor-E; Motion Analysis Corp., Santa Rosa, CA) was used to capture motion analysis data at 240 frames per second. Ground reaction forces were sampled at 1200Hz via five embedded force plates (AMTI Advanced Medical Technology, Inc., Watertown, MA).

Following a static calibration trial, as described in Chapter 2, each participant completed gait trials at a self-selected pace. Participants were instructed to walk across two embedded force plates at a self-selected speed. After a practice trial, gait trials were performed until three separate foot strikes for each limb were recorded. After completion of gait trials, participants performed the drop vertical jump (DVJ) task. While standing on a 31cm box with their feet shoulder width apart, participants were asked to drop off the box onto two embedded force plates and immediately rebound into a double leg jump. After 2-3 practice trials, each participant completed three DVJ trials. Ground reaction forces were collected for each limb.

Intervention. Following completion of baseline testing, each participant participated in combined CBT and NMT intervention following the FIT Teen protocol as described by Kashikar-Zuck et al.[117] Participants completed sixteen group-based sessions, twice a week for eight weeks. Each session consisted of approximately forty-five minutes of CBT and forty-five minutes of NMT. The CBT portion of the intervention emphasized education on pain, behavioral strategies, and cognitive strategies. The NMT portion of the intervention followed a protocol as described by Thomas et al.[109] An exercise physiologist led participants through a phasic progression of exercises. The level of difficulty of the exercises increased every two weeks. Level 1 consisted of isometric or holding exercise, level 2 consisted of concentric exercises, level 3 consisted of eccentric exercise, and level 4 combined previous levels for functional movement. Isometric exercises were performed twice for 10 seconds. Two sets of 6-8 repetitions were performed for all other exercise. Figure 7 outlines the NMT interventions. The exercises were modified to each individual participant as needed and instructions were given to protect joints from hyperextension in hypermobile individuals. Verbal feedback was provided throughout the training session in order to encourage proper alignment and form during the exercises. Participants were also given instructions to practice coping skills and exercises at home two additional days a week outside of their group training sessions.

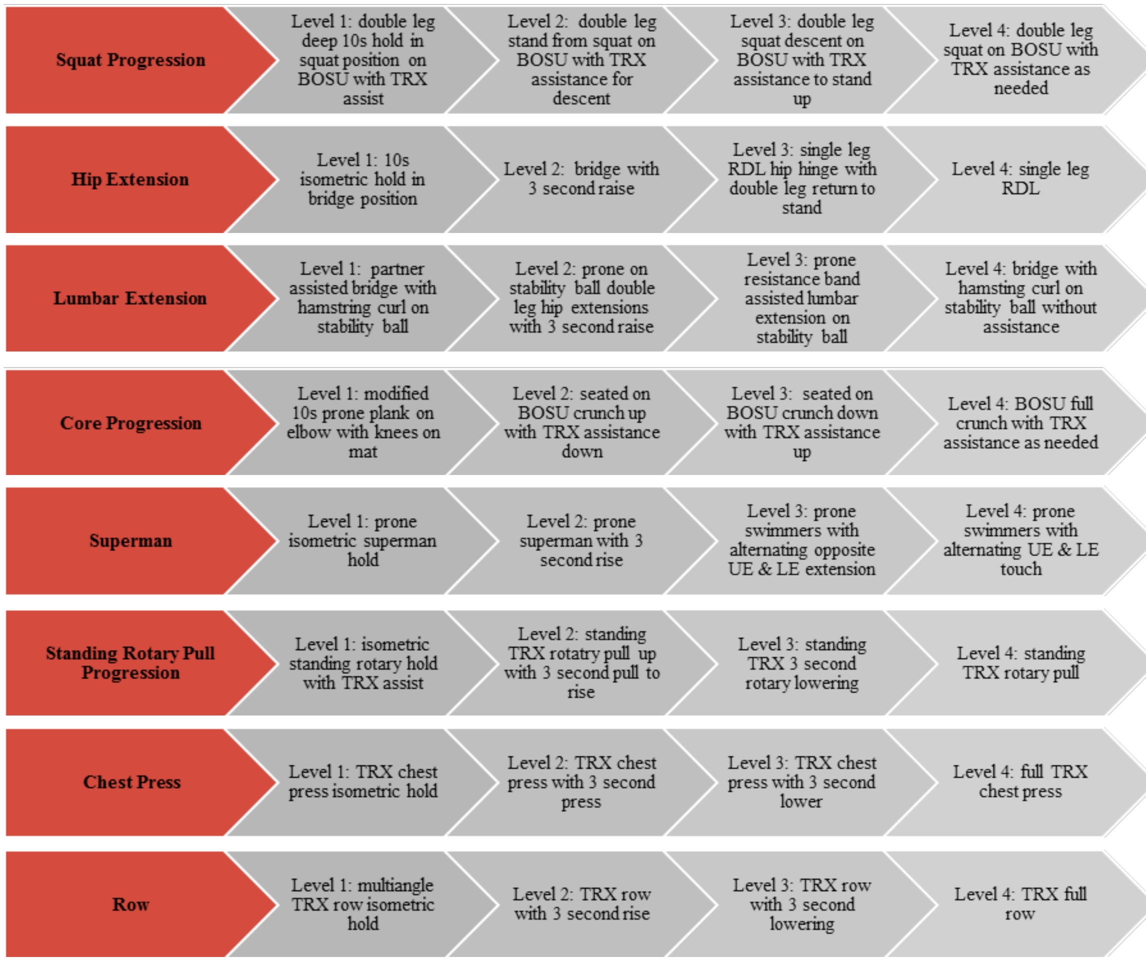


Figure 7. Progression of NMT interventions as described by Thomas et al.[109]

Upon completion of the FIT Teen protocol, pain, functional disability, strength, and knee joint biomechanics were re-assessed using the same procedures described above. Once pre- and post-intervention measures were assessed, Motion capture software (Cortex version 6.0, Motion Analysis Corp, Santa Rosa, CA) was used to label markers and fill gaps in marker trajectories for motion analysis data. Data were then imported into Visual3D (C-Motion, Inc., Germantown, MD) and a customized model was created for each participant based on their mass and height. Custom code in Matlab (Mathworks) was used for biomechanical data reduction to determine peak kinematic and kinetic variables during gait and DVJ. Peak kinematic and kinetic variables were obtained from the stance phase of gait, which was operationally defined as initial contact (vGRF > 10N) to toe off (vGRF < 10N). DVJ peak values were obtained from the landing phase of the drop which was operationally defined as initial contact (vGRF > 10N) to toe off (vGRF < 10N). Kinetic data were normalized to mass and height for each participant.[144] One limb from each participant was randomly selected for analysis using a random number generator because limb dominance was not collected during the original RCT. After means of the peaks from each trial for each participant were calculated, the pre- to post-intervention change was calculated by subtracting the pre-intervention value from the post-intervention value for each participant. Change scores of biomechanical variables that are negative (knee abduction) were multiplied by -1 so that the change score reflects a gain or reduction in that value.

Statistical Analysis. IBM SPSS Statistics 26 was used for data analysis. Normality testing revealed that the data violated the assumptions of normality and therefore non-parametric tests were used for analysis. Mann-Whitney U tests were performed on pre- to post-intervention change scores between each group. Because non-parametric tests were used for analysis, medians and interquartile ranges (Q_1, Q_3) are reported. Alpha was set to 0.05, *a priori*. In order to appreciate a potential effect of group, effect sizes were calculated for post-intervention scores between each group using the equation $r = \frac{Z}{\sqrt{N}}$ for non-parametric data with a small effect size r = 0.1 - < 0.3, medium effect size r = 0.3 - < 0.5, and large effect size $r \geq 0.5$.[168]

4.4: Results

Sixteen (16) adolescent females, diagnosed with JFM, participated in this study. Six (6) participants were categorized as hypermobile (HM) (Beighton-Horan Laxity Scale score greater than or equal to 4) and ten (10) were categorized as non-hypermobile (nHM) (Beighton-Horan Laxity Scale score less than or equal to 3). There were no significant differences in age, height, mass, or gait speed between groups ($p \geq 0.49$) (Table 13).

Table 13. Chapter 4 sample demographics
Median (IQR).

Group	Age (years)	Height (cm)	Mass (kg)	Gait Speed (m/s)
HM	14.5 (13.5, 17.0)	163.5 (158.0, 169.0)	64.6 (54.4, 70.2)	1.28 (1.18, 1.43)
nHM	15.5 (14.8, 17.0)	165.0 (155.0, 172.1)	64.5 (51.9, 72.7)	1.06 (0.92, 1.34)

4.4.1 Pain and Functional Disability

Changes in VAS or FDI scores following treatment were not different between groups ($p \geq 0.31$) (Table 14).

Table 14. Pre-intervention, post-intervention, and change in VAS and FDI scores Median (IQR).

	Group	Pre-Intervention Score	Post-Intervention Score	Pre- to Post-Intervention Change	p-value	Effect Size (r)
VAS	HM	5.8 (5.2, 7.1)	4.4 (2.5, 6.7)	-2.2 (-2.8, 1.1)	0.88	0.03
	nHM	6.9 (6.2, 7.6)	4.7 (3.5, 5.7)	-1.9 (-3.7, -0.9)		
FDI	HM	21.5 (18.5, 26.8)	20.0 (16.5, 22.0)	-3.0 (-5.5, 0.0)	0.31	0.04
	nHM	28.5 (23.5, 35.0)	19.5 (13.8, 23.3)	-7.5 (-20.5, -0.5)		

4.4.2 Strength

Changes in knee extension, knee flexion, and hip abduction isokinetic strength were not different between groups (p≥0.07) (Table 15).

Table 15. Pre-intervention, post-intervention, and change in strength (Nm/kg) Median (IQR).

	Group	Pre-intervention	Post-intervention	Pre- to Post-Intervention Change	p-value	Effect Size (r)
Knee Extension Strength	HM	0.97 (0.89, 1.12)	1.08 (0.96, 1.13)	0.10 (-0.09, 0.17)	0.71	0.00
	nHM	0.92 (0.70, 1.03)	1.10 (0.87, 1.17)	0.07 (0.00, 0.31)		
Knee Flexion Strength	HM	0.69 (0.53, 0.75)	0.65 (0.61, 0.69)	-0.07 (-0.15, 0.16)	0.79	0.11
	nHM	0.57 (0.50, 0.63)	0.65 (0.44, 0.71)	0.06 (-0.16, 0.15)		
Hip Abduction Strength	HM	0.48 (0.43, 0.91)	0.64 (0.49, 0.87)	0.01 (-0.02, 0.13)	0.07	0.13
	nHM	0.60 (0.50, 0.78)	0.80 (0.59, 1.05)	0.19 (0.08, 0.34)		

4.4.3 Biomechanics

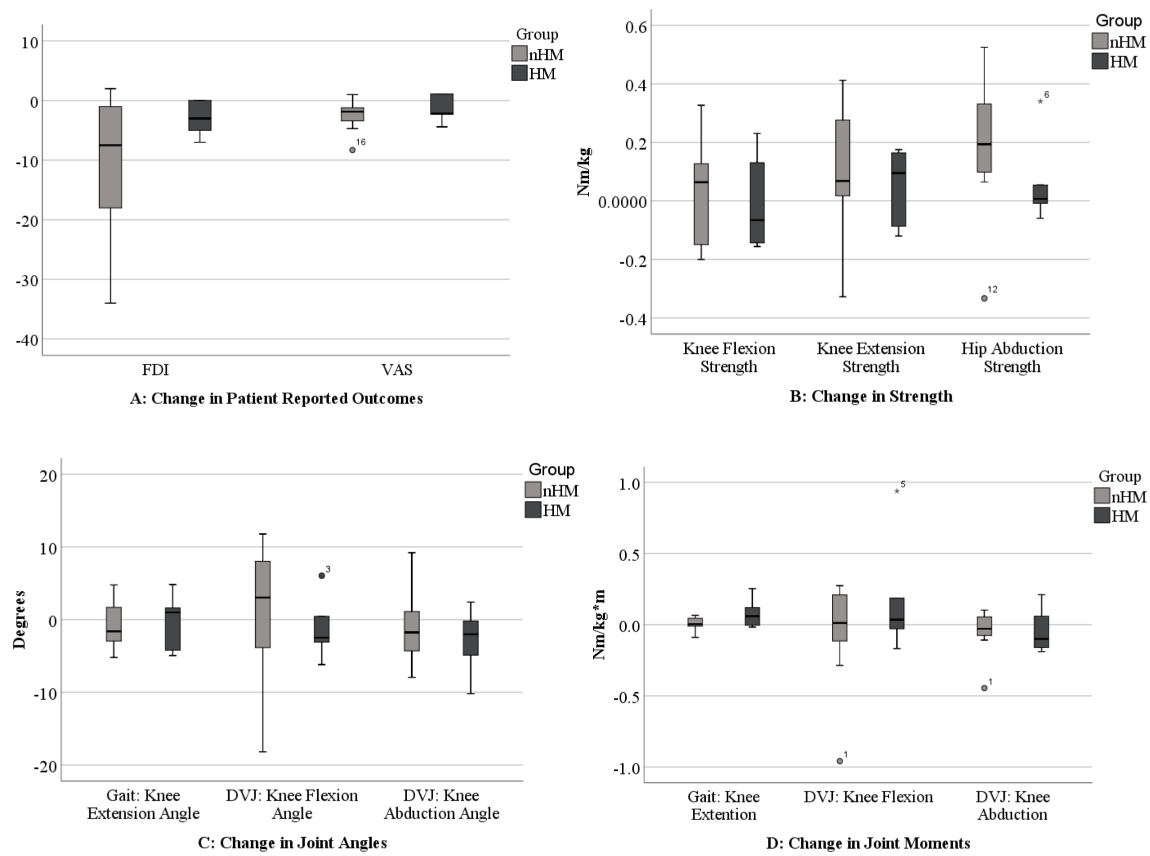
Changes in peak knee extension angle and peak knee extension moment during gait were not different between groups (p≥0.15) (Table 16). Similarly, changes in peak knee flexion angle, peak knee flexion moment, peak knee abduction angle, and peak knee abduction moment during jump landing were not different between hypermobile and non-hypermobile adolescent with JFM (p≥0.56) (Table 17). Figure 8 depicts pre- to post-intervention changes in patient reported outcomes (A), strength (B), joint angles (C), and joint moments (D).

Table 16. Pre-intervention, post-intervention, and change in peak knee extension angles (degrees) and moments (Nm/kg*m) during gait
Median (IQR).

	Group	Pre-intervention	Post-intervention	Pre- to Post-Intervention Change	p-value	Effect Size (r)
Peak Knee Extension Angle	HM	1.73 (-0.35, 3.03)	1.25 (-3.43, 4.49)	1.00 (-4.38, 2.42)	0.79	0.43
	nHM	-3.20 (-4.77, -0.47)	-3.29 (-6.40, -0.54)	-1.61 (-3.08, 2.36)		
Peak Knee Extension Moment	HM	0.21 (0.14, 0.33)	0.28 (0.26, 0.38)	0.06 (-0.01, 0.15)	0.15	0.49
	nHM	0.23 (0.13, 0.27)	0.21 (0.17, 0.29)	0.00 (-0.01, 0.05)		

Table 17. Pre-intervention, post-intervention, and change in peak knee flexion and abduction angles (degrees) and moments (Nm/kg*m) during DVJ landing Median (IQR).

	Group	Pre-intervention	Post-intervention	Pre- to Post-Intervention Change	p-value	Effect Size (r)
Peak Knee Flexion Angle	HM	-75.99 (-73.74, -89.08)	-78.88 (-70.98, -84.16)	-2.49 (-3.89, 1.84)	0.56	0.08
	nHM	-73.47 (-70.43, -103.77)	-81.53 (-72.15, -90.75)	3.04 (-5.11, 8.23)		
Peak Knee Flexion Moment	HM	-1.04 (-0.75, -1.17)	-1.11 (-1.00, -1.17)	0.04 (-0.06, 0.37)	0.64	0.08
	nHM	-1.12 (-1.01, -1.19)	-1.02 (-0.90, -1.02)	0.01 (-0.16, 0.22)		
Peak Knee Abduction Angle	HM	-27.46 (-9.27, -36.08)	-23.58 (-10.69, -31.02)	-2.02 (-6.21, 0.45)	0.64	0.24
	nHM	-18.53 (-14.36, -21.21)	-14.90 (-12.17, -23.29)	-1.76 (-4.71, 2.29)		
Peak Knee Abduction Moment	HM	-0.35 (-0.26, -0.73)	-0.43 (-0.26, -0.56)	-0.10 (-0.17, 0.10)	0.64	0.24
	nHM	-0.35 (-0.30, -0.54)	-0.37 (-0.27, -0.43)	-0.03 (-0.08, 0.06)		



Median change scores are indicated by bold line in box, box ends indicate upper and lower quartiles and whiskers indicate minimum and maximum observations.

Figure 8. Boxplots representing pre- to post-intervention change in patient reported outcomes (A), strength (B), joint angles (C), and joint moments (D)

4.5: Discussion

Because little is known regarding factors that influence the response of adolescents with JFM to exercise interventions and benign joint hypermobility syndrome shares many common symptoms with JFM, the purpose of this study was to determine if hypermobile and non-hypermobile adolescents with juvenile fibromyalgia respond differently to combined CBT and NMT intervention. We hypothesized that hypermobile adolescents with JFM would demonstrate greater improvements in pain, functional disability, and strength, and greater reductions in knee extension during gait, and greater reductions in knee abduction during DVJ landing compared to non-hypermobile adolescents with JFM.

Contrary to our hypotheses pre- to post-intervention changes in pain, functional disability, strength, peak knee extension during gait, and peak knee flexion and abduction during DVJ landing were not different between hypermobile and non-hypermobile adolescents with JFM. Following combined CBT and NMT interventions, both groups reported decreased pain and functional disability. Both groups also demonstrated slight improvements in lower extremity strength following intervention; however, pre- to post-intervention changes were not different between groups. Therefore the results of this study suggest that hypermobile and non-hypermobile adolescents with JFM do not respond differently to combined CBT and NMT interventions.

While there was not a statistically significant difference in pre- to post-intervention change in peak knee extension angles or moments between each group during gait, it is interesting that the hypermobile group demonstrated a slight increase in knee extension angle following intervention while the non-hypermobile group demonstrated a slight reduction in peak knee extension angle. The hypermobile group demonstrated knee hyperextension during gait before and after intervention, while the non-hypermobile group remained in slight knee flexion during the stance phase of gait. These results are consistent with previous work which indicated that hypermobile adolescents demonstrated greater peak knee extension angles during midstance compared with non-hypermobile adolescents.[86] The differences in peak knee extension angles between groups are likely due to neuromuscular adaptations, such as muscular control, stabilization, and proprioception versus pure strength deficits because knee flexion and extension strength was not different between groups. It has been suggested that one potential cause of pain in hypermobile individuals is soft tissue microtrauma due to excessive joint motion.[87,88] It has been suggested that exercise interventions for pain management in hypermobile adolescents be performed in a protected range in order to avoid hyperextension and avoid potential soft tissue trauma.[87] Exercises performed to avoid knee hyperextension are associated with greater improvements in physical health in hypermobile adolescents.[87] Therefore, if may be beneficial for future NMT interventions to emphasize neutral knee alignment and avoidance of knee hyperextension, particularly in hypermobile adolescents with JFM.

Similar to gait, there were no significant differences in change in peak knee flexion and abduction angles and moments between groups during DVJ landing. Although it was not statistically significant, it is interesting that hypermobile adolescents demonstrated a reduction in DVJ peak knee flexion angle while non-hypermobile adolescent demonstrated an increase in peak knee flexion angle after CBT and NMT interventions. Smaller knee joint excursion in the sagittal plane during single-leg jump landing is associated with patella-femoral pain; [180] however, it is unknown if sagittal knee joint excursion during jump landing is associated with pain in adolescents with JFM. Due to the differences in change between each group, it may be worth further investigating the relationship between sagittal plane joint excursion and pain in this cohort.

Both hypermobile and non-hypermobile adolescents with JFM demonstrated reduced DVJ peak knee abduction angle and moments following CBT and NMT interventions. Despite both groups demonstrating a reduction in both knee abduction angles and moments, it is interesting that the hypermobile group landed with greater peak knee abduction angles before and after intervention compared to the non-hypermobile group. Although changes in frontal plane knee mechanics were not different between groups, it is still promising that both groups demonstrated reduced peak knee abduction angles and moments. Greater knee abduction angles and moments are associated with increased injury risk.[47] Since both groups demonstrated decreased knee abduction angles and moments following treatment, NMT may be beneficial in improving frontal plane knee biomechanics, decreasing joint stress, and reducing injury risk in this cohort.

The results of this study indicate that hypermobile and non-hypermobile adolescents with JFM may demonstrate biomechanical differences during gait and DVJ landing; however, it is still unclear if hypermobile and non-hypermobile adolescents respond differently to CBT and NMT interventions. Although, joint hypermobility did not appear to influence response to CBT and NMT training interventions in this study, future investigation of the influence of joint hypermobility on response to exercise interventions in adolescents with JFM is still warranted as we identified biomechanical variances during gait and small differences, but not significant differences in response to treatment between groups. Based on the results of this study, the sagittal plane appears to be most affected by joint hypermobility and as a result future studies should focus on sagittal plane mechanics at the knee.

There are several limitations to this study. The primary limitations is that this is a secondary analysis of a pilot study. Therefore we were underpowered to determine the true effect of joint hypermobility on response to NMT. This comparison also lacked a healthy, hypermobile control group to fully understand the magnitude of response to treatment in this cohort. We also did not control for activity level or fear of movement which may have affected movement strategies, especially during the DVJ. Future studies should focus on knee sagittal plane biomechanics and consider tasks that require balance and control such as the Star Excursion Balance Test or step-downs.

The purpose of this study was to test whether hypermobile and non-hypermobile adolescents with JFM respond differently to combined CBT and NMT interventions in order to aid in the development of targeted interventions and better improve pain and function in these individuals. The results suggest that although hypermobile and non-hypermobile adolescents with JFM do not respond differently to CBT and NMT interventions, hypermobile and non-hypermobile adolescents with JFM move differently and future exploration may be valuable to assist in development of tailored NMT interventions.

Chapter 5. The Role of Generalized Joint Hypermobility in Adolescents with Juvenile Fibromyalgia and Implications for Treatment

5.1: Summary

The goal of this dissertation was to provide a comprehensive exploration of the influence of joint hypermobility on pain, functional disability, physical function, and response to intervention in adolescents with juvenile fibromyalgia (JFM). Joint hypermobility is associated with physical impairments and altered movement strategies and may be one potential mechanism of pain exacerbation in adolescents with JFM. Although joint hypermobility is common among adolescents with JFM, this is the first study, to our knowledge, to compare pain, functional disability, strength, and biomechanics between hypermobile adolescents with JFM and non-hypermobile adolescents with JFM.

Specific Aim 1: To compare pain, functional disability, strength, and biomechanics between hypermobile adolescents with JFM and non-hypermobile adolescents with JFM.

<u>Hypothesis</u>: Hypermobile adolescents with JFM would demonstrate higher subjective pain rating, greater functional disability, muscle weakness, and greater peak knee extension during gait compared to non-hypermobile adolescents with JFM.

This cross-sectional study compared subjective pain (VAS), functional disability (Functional Disability Inventory), lower extremity isokinetic strength and lower extremity gait biomechanics between hypermobile adolescents with JFM and non-hypermobile adolescents with JFM. Pain, functional disability, and lower extremity strength did not differ between hypermobile and non-hypermobile adolescents with JFM. Although there were no differences in pain and functional disability scores between groups in this small pilot analysis, it would be premature to conclude that generalized joint hypermobility does not affect pain and function in adolescents with JFM. Previous work found that while hypermobile adolescents with JFM did not report differences in subjective pain ratings, they did report lower tender point thresholds and a greater number of tender points than non-hypermobile adolescents with JFM.[50] These data were consistent with the results of the current study, and indicate that while hypermobility may not influence subjective pain rating, there may be a difference in objective measures of pain. Similarly, subjective functional disability rating did not vary between hypermobile and non-hypermobile adolescents with JFM, however, we may have been underpowered to detect true differences between groups. Actigraphy has been previously used in adolescents with JFM to track physical activity.[38] An objective measurement of activity level such as actigraphy may be beneficial in future studies to distinguish if differences in activity level and function exist between these groups.

Our findings suggest that hypermobile adolescents with JFM walk differently than non-hypermobile adolescents with JFM. As we hypothesized, hypermobile adolescents with JFM demonstrated greater peak knee extension during the stance phase of gait compared to non-hypermobile adolescents with JFM. While non-hypermobile adolescents remained in slight flexion during the stance phase of gait, hypermobile adolescents with JFM moved into hyperextension. Hypermobile adolescents with JFM also demonstrated lower peak ankle eversion angles and moments during the stance phase of gait, which suggests these adolescents may be stiffening or stabilizing at the ankle to compensate for proximal joint instability. Because differences did not exist in lower extremity strength between groups, the biomechanical variances observed during gait are likely due to differences in neuromuscular control instead of strength variances. Although the clinical significance of these biomechanical variances and whether or not these gait alterations are correlated with pain has not yet been examined in this population, it is reasonable suspect that the observed gait variances may exacerbate pain in hypermobile adolescents with JFM. It has been proposed that joint hypermobility results in altered movement patterns and repetitive excessive joint motion that leads to soft tissue and joint microtrauma.[87,128] These damaged tissues then release enzymes and neurotransmitters that sensitize free nerve endings of pain fibers and result in a heightened pain response.[24,26,27,89] As a result, it is plausible that the dynamic knee hyperextension demonstrated by the hypermobile adolescents with JFM during gait in this study causes repetitive soft tissue and joint microtrauma and damage and is one potential mechanism of pain exacerbation in these adolescents. It will be important to determine if the knee hyperextension demonstrated by adolescents with JFM and joint hypermobility is correlated with greater pain at this joint due to repetitive abnormal tissue loading with ambulation. It is important to continue to evaluate joint hypermobility status among adolescents with JFM and to consider sagittal plane knee motion, particularly knee hyperextension, when developing targeted interventions for these hypermobile individuals. Neuromuscular training interventions should emphasize avoidance of knee hyperextension during gait and weight bearing exercises such as single leg stance and return from squatting in adolescents with JFM and joint hypermobility, as they did in Specific Aim 3 of this thesis.

Specific Aim 2: To compare pain, functional disability, strength, and biomechanics between hypermobile adolescents with JFM and healthy adolescents with generalized joint hypermobility.

Hypothesis: Hypermobile adolescents with JFM would report worse pain and greater functional disability, and demonstrate weaker lower extremity strength, greater peak knee extension during gait, lower peak knee flexion during jump landing, and greater knee abduction during jump landing compared to hypermobile healthy adolescents.

Pain, functional disability, lower extremity isokinetic strength, and gait and drop vertical jump landing mechanics were compared between hypermobile adolescents with JFM and healthy adolescents with generalized joint hypermobility. While many adolescents with generalized joint hypermobility are asymptomatic, many report chronic pain, functional disability, and demonstrate physical impairments. Therefore, by comparing pain and function between adolescents with JFM and hypermobility and asymptomatic adolescents with hypermobility, we hoped to identify variances in physical performance that may be associated with pain exacerbation in hypermobile adolescents with JFM.

As we expected, hypermobile adolescents with JFM reported higher pain and functional disability than healthy hypermobile adolescents. The healthy adolescents with joint hypermobility in this study demonstrated minimal pain and functional disability, which indicates that joint hypermobility alone does not lead to chronic pain in all adolescents. Contrary to our hypotheses, adolescents with JFM and joint hypermobility demonstrated greater knee flexion and extension strength than healthy adolescents with joint hypermobility. Because adolescents with JFM have previously demonstrated lower extremity muscle weakness compared to healthy, adolescents,[45,46] we expected the adolescents with JFM and joint hypermobility to be weaker than the healthy adolescents with joint hypermobility in this study. It is unclear whether this difference is truly a function of group or if it was a result of the adolescents with JFM being older than the healthy control group since strength increases with age in female adolescents.[169]

Both groups demonstrated knee hyperextension during the stance phase of gait. It has been suggested that soft tissue and joint microtrauma resulting from excessive range of motion during daily tasks may be one mechanism of pain exacerbation in hypermobile individuals; however, in our study there was no difference in peak joint angles between groups, indicating that excessive joint range of motion may not lead to pain in all individuals. Hypermobile adolescents with JFM demonstrated lower peak knee extension moments during gait compared to healthy, hypermobile adolescents. Decreased external knee extension moments have also been observed during the late stance phase of the gait cycle in adults with knee osteoarthritis.[170] Although it is unknown if the mechanism is the same between hypermobile adolescents with JFM and adults with osteoarthritis, the lower peak knee extension observed in adolescents with JFM and joint hypermobility may contribute to altered mechanical stress to joint cartilage and potentially lead to pain and dysfunctional in this cohort. In addition, variability of when peak knee extension angles and moments were achieved during the stance phase of gait existed within each group; however, the magnitude of peak knee extension angles and moments did not appear to be related to timing during the stance phase of gait within either group.

Adolescents with JFM and joint hypermobility also demonstrated greater knee abduction angles during jump landing compared to healthy adolescents with hypermobility; however, there were no differences in knee flexion angles or moments during jump landing between groups. Increased knee abduction angles during jump landing are associated with an increased risk of patellofemoral pain, while both increased knee abduction and decrease knee flexion during jump landing are associated with increased injury risk in adolescent females.[47,158,163,173] Therefore, it is possible that the increased knee abduction angles observed during jump landing in adolescents with JFM and joint hypermobility may be associated with the development of pain in this cohort.

Based on the results of this study, not all hypermobile adolescents demonstrate pain and functional disability, however as we have previously suggested, joint hypermobility may be one mechanism to trigger a cascade of heightened pain response in some individuals such as those with JFM. The hypermobile adolescents with JFM demonstrated gait and jump landing mechanics that are associated with increased risk of knee pain and injury[47,158,163,173] and therefore and it likely that these movement patterns contribute to the pain experienced by adolescents with JFM. It will be valuable to determine if the gait and jump landing mechanics observed in this study are correlated with pain in hypermobile adolescents with JFM in order to guide future interventions. If the gait and jump landing mechanics demonstrated by the hypermobile adolescents with JFM in this study are correlated with pain and functional disability, neuromuscular training interventions targeted at reducing knee hyperextension and abduction for these individuals may be beneficial. The results of this chapter further support the results of Chapter 2 that indicate that adolescents with JFM demonstrate biomechanical variances and it is possible that these variances may contribute to pain exacerbation in this cohort. Therefore particular attention should be paid to sagittal plane knee mechanics during gait and frontal plane knee mechanics during jump landing when prescribing exercise interventions for this cohort.

Specific Aim 3: To compare the response of hypermobile adolescents with JFM and non-hypermobile adolescents with JFM to combined NMT and CBT intervention.

Hypothesis: Following CBT and NMT intervention, hypermobile adolescents with JFM would demonstrate greater improvements in pain, functional disability, and strength, greater increases in knee flexion during jump landing, greater reductions in knee extension during gait, and greater reductions in knee abduction during jump landing than non-hypermobile adolescents with JFM.

This was the first study to our knowledge to compare the response to combined neuromuscular training (NMT) and cognitive behavioral therapy (CBT) intervention between hypermobile and non-hypermobile adolescents with JFM. Preliminary evidence suggests that when NMT is combined with CBT adolescents with JFM demonstrate greater reductions in pain; however, there are no greater improvements in functional disability.[117] Factors that influence response to NMT in adolescents with JFM are unknown. NMT elicits different effects for individuals who demonstrate faulty movement strategies[181] and hypermobile adolescents demonstrate weakness, deficient proprioception, and altered movement mechanics. In this study, change in pain, functional disability, strength, or lower extremity biomechanics were not different between groups. The results of this study indicate that hypermobile and non-hypermobile adolescents with JFM do not respond differently to NMT and CBT intervention; however, we may have been underpowered to detect differences between groups. It is promising that both the adolescents with JFM and joint hypermobility and adolescents with JFM without joint hypermobility demonstrated reduced knee abduction during jump landing, suggesting that NTM interventions are beneficial for both cohorts. In addition, because this was a secondary analysis of a larger study, the NMT interventions were directed toward improving core strength, balance, and posture with the goal of improving exercise tolerance and were not targeted toward the specific biomechanical variances demonstrated by adolescents with JFM and joint hypermobility in our first two studies. Targeted NMT to address sagittal plane knee mechanics during gait and knee abduction during jump landing may elicit a different effect in adolescents with JFM and joint hypermobility.

These three studies may have underestimated the influence of joint hypermobility on pain, functional disability, strength and biomechanics in adolescents with JFM due to small sample sizes. We did not find differences in subjective pain, functional disability, strength, and response to treatment between hypermobile adolescents with JFM and non-hypermobile adolescents with JFM. However, hypermobile adolescents with JFM demonstrated different movement patterns than non-hypermobile adolescents with JFM and asymptomatic hypermobile adolescents with generalized joint hypermobility. . While the clinical significance of these differences remains unknown in this cohort, these biomechanics demonstrated by hypermobile adolescents with JFM are associated with increased pain and risk of injury in other populations and likely contribute to pain exacerbation in hypermobile adolescents with JFM.[47,158,173] The results of these studies indicate that joint hypermobility is associated with altered sagittal plane knee mechanics during gait and frontal plane knee mechanics during jump landing, which may disrupt joint and soft tissue loading and contribute to pain exacerbation in this cohort. Just as with adolescents at risk for anterior cruciate ligament injury, NMT interventions should be targeted toward avoiding knee hyperextension in stance and during gait and mitigating knee abduction during jump landing in adolescents with JFM and joint hypermobility. The goal of this thesis was to determine if hypermobile adolescents with JFM should be identified as a subset of the JFM population that is at an increased risk for pain exacerbation and altered movement mechanics that warrant targeted NMT interventions. The results of this study showed that hypermobile adolescents with JFM move differently than non-hypermobile adolescents with JFM. Although this study was small, we infer that these group differences would persist in a larger sample of adolescents with JFM. It is likely that these movement strategies demonstrated by hypermobile adolescents with JFM exacerbate pain in this cohort and should be targeted through NMT interventions. As a result, it is important to continue to assess joint hypermobility in adolescents with JFM in order to identify these adolescents who may present with an increased risk of deleterious movement patterns and to target NMT interventions for these individuals. Prospective studies with larger samples are warranted to determine if and how these movement variances contribute to pain and functional disability in hypermobile adolescents with JFM and to determine if NMT targeting dynamic knee stability results in greater improvements in pain and functional disability in this cohort.

5.2: Future Research

It is important to identify factors that influence symptom exacerbation and response to treatment in individuals with JFM in order to gain a better understanding of this syndrome and improve quality of life for individuals with this condition. Although we identified movement variances between hypermobile and non-hypermobile adolescents with JFM, it is still unknown if these variances contribute to pain and functional disability in this cohort. Future research to determine the interaction between pain, functional disability and altered mechanics will uncover the clinical significance of these variances and may inform precision treatment strategies. If the observed movement patterns are correlated with objective measurements of pain and reported disability, then targeted NMT strategies can be developed and refined to address many patterns of altered movement.

Joint proprioception, though not evaluated in this thesis work, should be included in future studies to examine mechanisms of pain and disability in adolescents with JFM because of its potential association with joint hypermobility. Deficient proprioception is associated with increased knee joint pain and it is believed proprioception has a protective mechanism on joints.[182] Hypermobile individuals demonstrate deficient joint proprioception compared to non-hypermobile individuals,[73,75,77] but it is unknown if joint proprioception is negatively affected by joint hypermobility in the context of JFM, and to what extent it impaired proprioception would affect pain and function Continuing to gain knowledge of how generalized joint hypermobility contributes to pain, functional disability, and biomechanics in adolescents with JFM will assist in the development of individualized NMT interventions in order to improve outcomes and quality of life for these adolescents.

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Appendix A. Functional Disability Inventory

11/2012

ID__________
Date__________

Functional Disability Inventory
Child and Adolescent Form

When people are sick or not feeling well it is sometimes difficult for them to do their regular activities. In the past two weeks, would you have had **any physical trouble or difficulty doing these activities?**

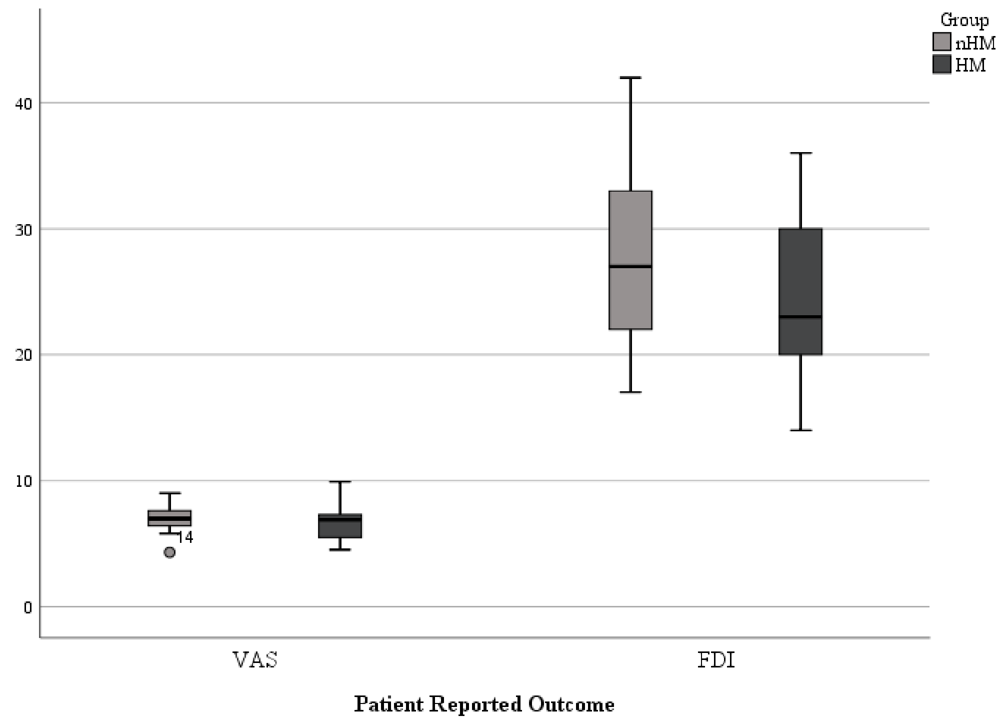
	No Trouble	A Little Trouble	Some Trouble	A Lot of Trouble	Impossible
1. Walking to the bathroom.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Walking up stairs.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Doing something with a friend. (For example, playing a game.)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Doing chores at home.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Eating regular meals.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Being up all day without a nap or rest.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Riding the school bus or traveling in the car.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

Remember, you are being asked about difficulty due to physical health.

	No Trouble	A Little Trouble	Some Trouble	A Lot of Trouble	Impossible
8. Being at school all day.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Doing the activities in gym class (or playing sports).	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Reading or doing homework.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Watching TV.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Walking the length of a football field.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Running the length of a football field.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Going shopping.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Getting to sleep at night and staying asleep.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

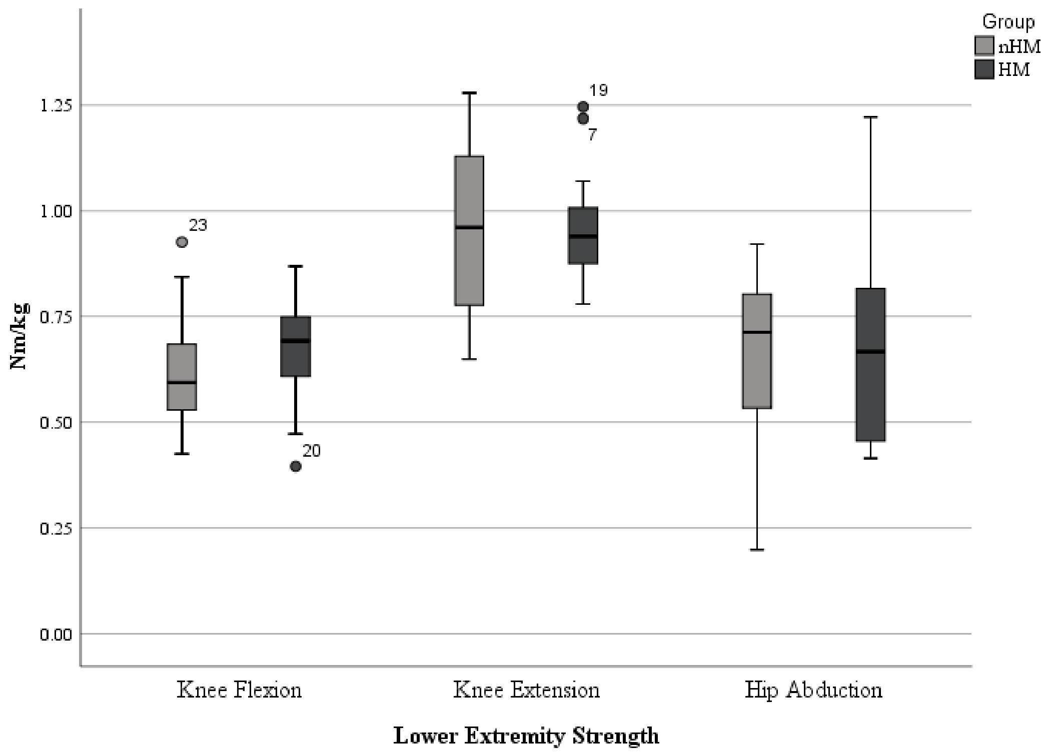
Appendix B. Boxplot representing baseline pain scores (VAS) and functional disability (FDI) for hypermobile and non-hypermobile adolescents with JFM

Median scores are indicated by bold line in box, box ends indicate upper and lower quartiles and whiskers indicate minimum and maximum observations.



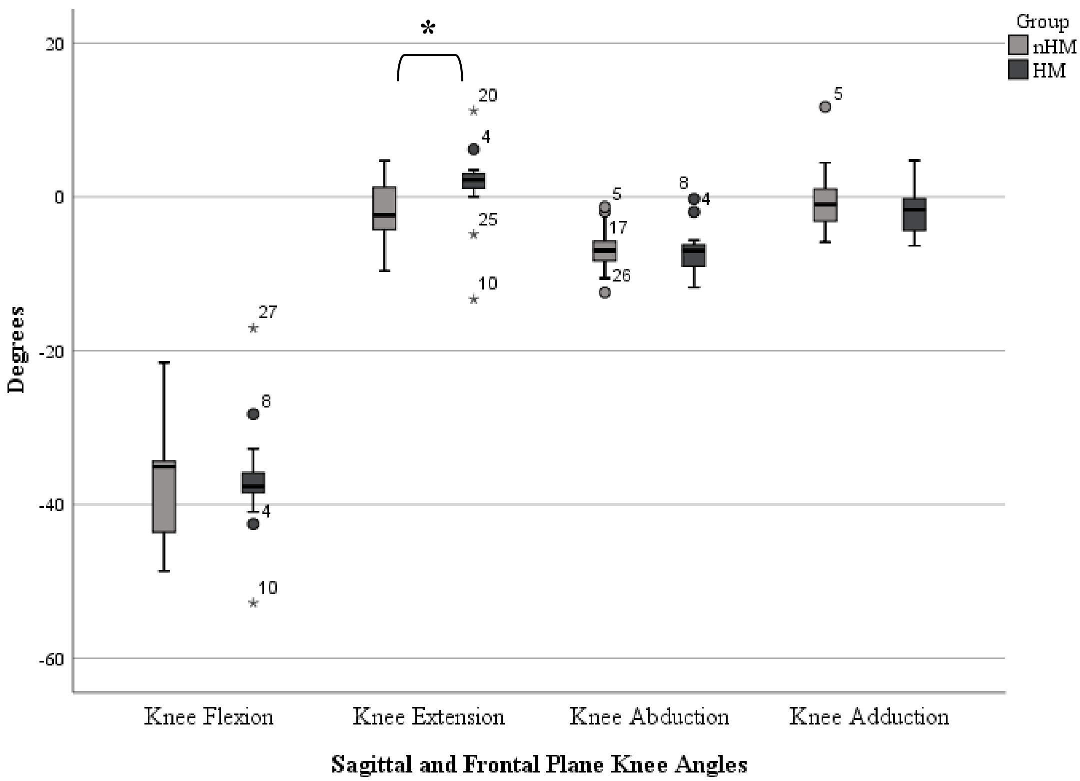
Appendix C. Boxplot representing peak lower extremity isokinetic strength (Nm/kg) for hypermobile and non-hypermobile adolescents with JFM

Median scores are indicated by bold line in box, box ends indicate upper and lower quartiles and whiskers indicate minimum and maximum observations.



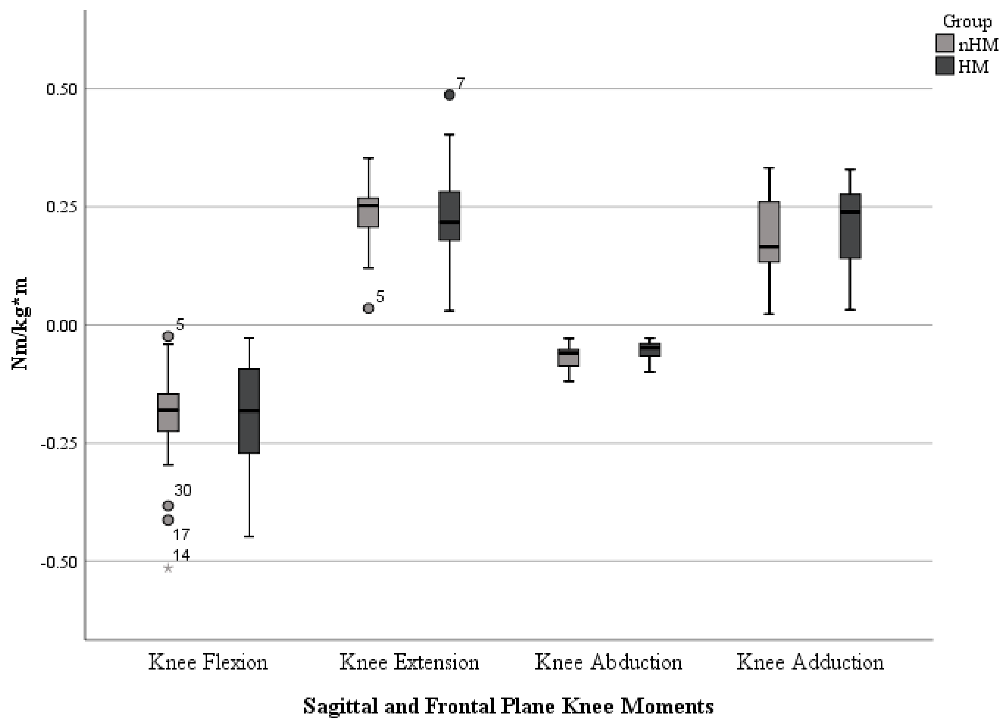
Appendix D. Boxplot representing peak sagittal and frontal plane knee angles (degrees) during the stance phase of gait between hypermobile and non-hypermobile adolescents with JFM

Median scores are indicated by bold line in box, box ends indicate upper and lower quartiles and whiskers indicate minimum and maximum observations. Positive angles indicate knee extension and adduction while negative angles indicate knee flexion and abduction.



Appendix E. Boxplot representing peak sagittal and frontal plane knee moments (Nm/kg*m) during stance phase of gait between hypermobile and non-hypermobile adolescents with JFM

Median scores are indicated by bold line in box, box ends indicate upper and lower quartiles and whiskers indicate minimum and maximum observations. Positive moments indicate knee extension and adduction while negative moments indicate knee flexion and abduction.



Appendix F. Self-reported Beighton-Horan Laxity Scale used to screen healthy participants for generalized joint hypermobility

Beighton score

Please note which of the following movements you can make and mark Yes or No for each side.

1) I can bend my little finger up at 90 degrees (right angles) to the back of my hand

	Right hand	**Left hand**
	yes O no O	yes O no O

2) I can bend my thumb back on the front of my forearm

	Right thumb	**Left thumb**
	yes O no O	yes O no O

3) I can bend my elbow more than 10 degrees

	Right elbow	**Left elbow**
	yes O no O	yes O no O

4) I can bend my knee backwards

	Right knee	**Left knee**
	yes O no O	yes O no O

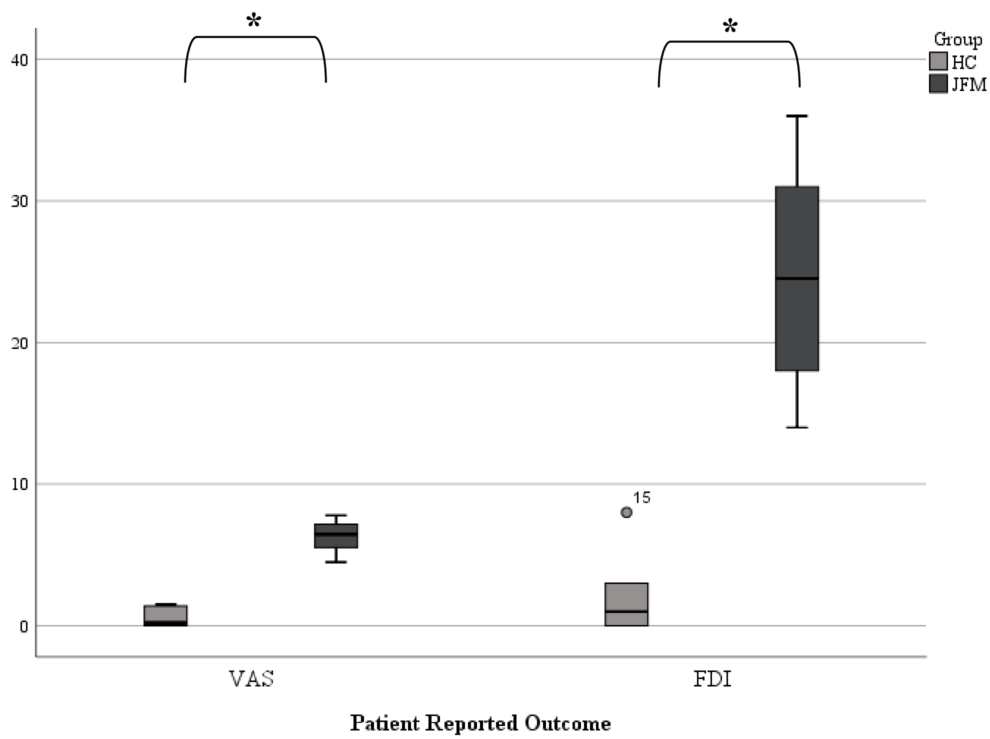
5) I can put my hands flat on the floor with my knees straight

yes O no O

Total Yes (0-9): ____

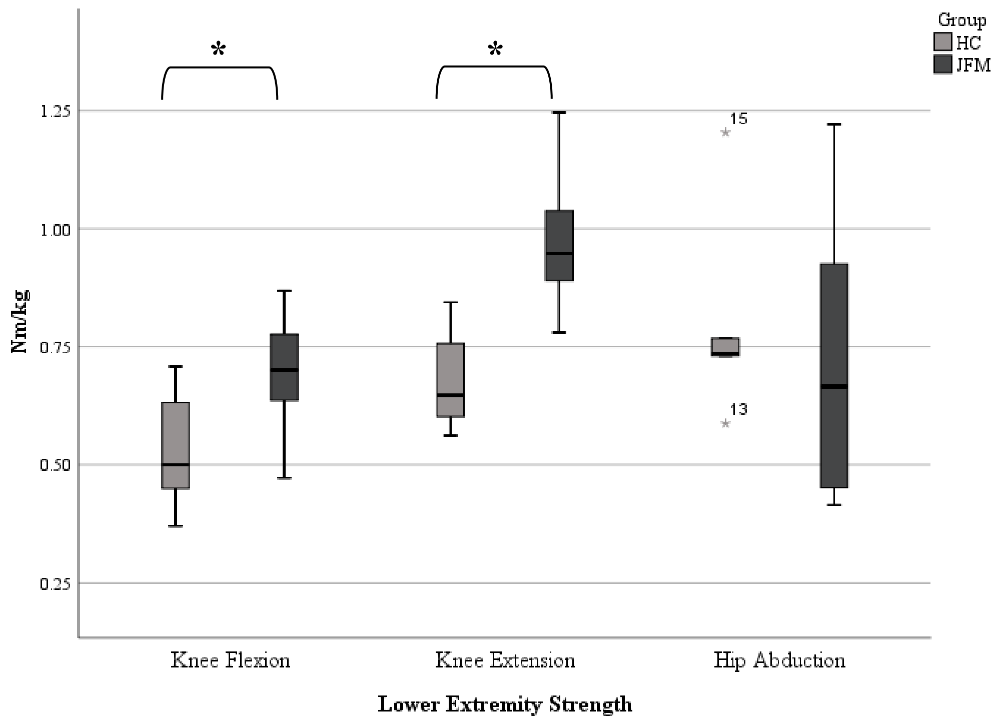
Appendix G. Boxplot representing baseline pain scores (VAS) and functional disability (FDI) for hypermobile adolescents with JFM and healthy adolescents with generalized joint hypermobility

Median scores are indicated by bold line in box, box ends indicate upper and lower quartiles and whiskers indicate minimum and maximum observations.



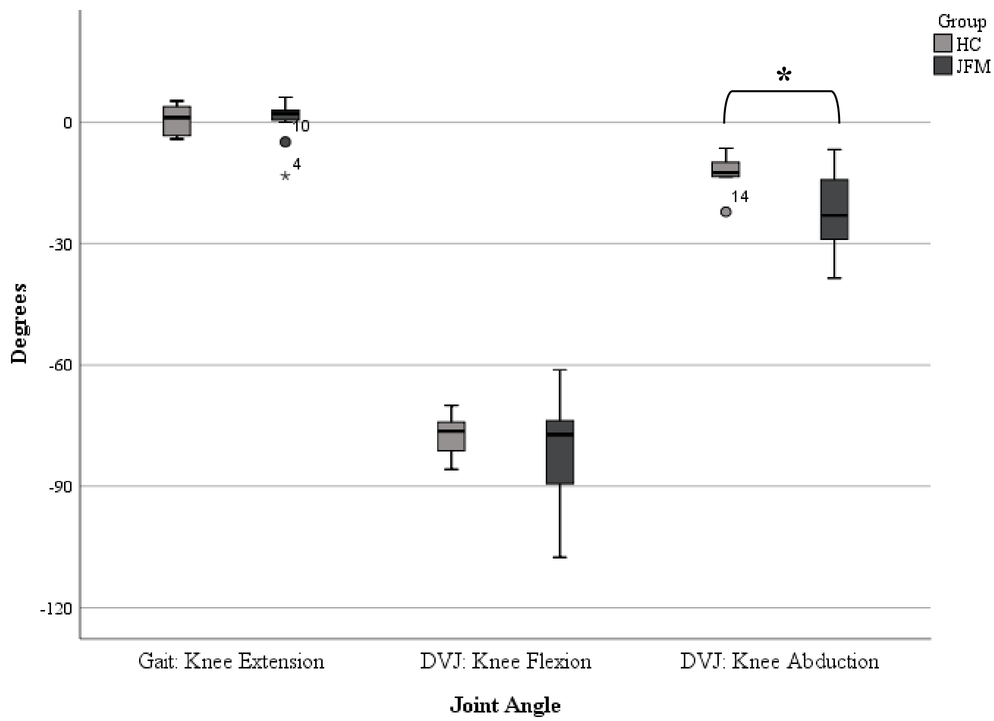
Appendix H. Boxplot representing peak lower extremity isokinetic strength (Nm/kg) for hypermobile adolescents with JFM and healthy adolescents with generalized joint hypermobility

Median change scores are indicated by bold line in box, box ends indicate upper and lower quartiles and whiskers indicate minimum and maximum observations.



Appendix I. Boxplot representing peak knee angles (degrees) during stance phase of gait and DVJ landing between hypermobile adolescents with JFM and healthy adolescents with generalized joint hypermobility

Median scores are indicated by bold line in box, box ends indicate upper and lower quartiles and whiskers indicate minimum and maximum observations. Positive angles indicate knee extension and adduction while negative angles indicate knee flexion and abduction.



Appendix J. Boxplot representing peak knee moments (Nm/kg*m) during stance phase of gait and DVJ landing between hypermobile adolescents with JFM and healthy adolescents with generalized joint hypermobility

Median change scores are indicated by bold line in box, box ends indicate upper and lower quartiles and whiskers indicate minimum and maximum observations. Positive moments indicate knee extension and adduction while negative moments indicate knee flexion and abduction.