PATIENT SUBGROUPS OF ACHILLES TENDINOPATHY: CLINICAL IMPLICATIONS TO INFORM PRECISION TREATMENT STRATEGIES

by

Shawn L. Hanlon

A dissertation submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Biomechanics and Movement Science

Summer 2022

PATIENT SUBGROUPS OF ACHILLES TENDINOPATHY: CLINICAL IMPLICATIONS TO INFORM PRECISION TREATMENT STRATEGIES

by

Shawn L. Hanlon

Approved: _____
Darcy Reisman, Ph.D.
Chair of the Department of Physical Therapy

Approved: _____
Kathleen S. Matt, Ph.D.
Dean of the College of Health Sciences

Approved: _____
Louis F. Rossi, Ph.D.
Vice Provost for Graduate and Professional Education and
Dean of the Graduate College

I certify that I have read this dissertation and that in my opinion it meets the academic and professional standard required by the University as a dissertation for the degree of Doctor of Philosophy.

Signed: _____

Karin Grävare Silbernagel, Ph.D.
Professor in charge of dissertation

I certify that I have read this dissertation and that in my opinion it meets the academic and professional standard required by the University as a dissertation for the degree of Doctor of Philosophy.

Signed: _____

Ryan Pohlig, Ph.D.
Member of dissertation committee

I certify that I have read this dissertation and that in my opinion it meets the academic and professional standard required by the University as a dissertation for the degree of Doctor of Philosophy.

Signed: _____

Tom Kaminski, Ph.D.
Member of dissertation committee

I certify that I have read this dissertation and that in my opinion it meets the academic and professional standard required by the University as a dissertation for the degree of Doctor of Philosophy.

Signed: _____

Dave Ebaugh, Ph.D.
Member of dissertation committee

I certify that I have read this dissertation and that in my opinion it meets the academic and professional standard required by the University as a dissertation for the degree of Doctor of Philosophy.

Signed: _____

Peter Malliaras, Ph.D.
Member of dissertation committee

ACKNOWLEDGMENTS

I am most fortunate to find myself indebted to many friends and colleagues, collaborators, family members, mentors, and students who deserve acknowledgment. Without you, this would not be possible.

To my advisor, Karin Grävare Silbernagel. As a person and a professional, you have changed the trajectory of my life. Your authority as a clinician-scientist is matched only by your compassion, your grace, and limitless optimism. Thank you for leading by example, proving you can have an immensely successful career and still be an amazing parent and spouse, have a fulfilling personal life, and most importantly, have fun doing it all. I am grateful for your leadership, your encouragement, and most of all, your influence.

To my dissertation committee, Ryan Pohlig, Tom Kaminski, Dave Ebaugh, and Peter Malliaras, thank you all for your mentorship and willingness to support my development. Each of you have made a meaningful impact on me and I am grateful for the wisdom you have shared to enhance this dissertation. A special thank you is deserved for Tom. You fostered my interest in research as my Master's Thesis advisor almost 10 years ago and have continually supported my professional development. Your support and encouragement guided me to pursue this terminal degree. Additionally, I would like to express my gratitude to Ryan, without your mentorship this dissertation would not have been possible. I have the utmost respect for your ability to share your unrivaled statistical expertise with humility and patience. Thank you for shaping me as an academic.

To my fellow lab mates, Nabeel Alghamdi, Brian Honick, Kayla Seymour, Hayley Smitheman, Nao Ito, Andy Smith, and Morgan Potter, thank you for being great coworkers, brilliant collaborators and sounding boards, and friends. Thank you to my predecessors, Jen Zellers, Pat Corrigan, and Andrew Sprague for being great mentors and friends. A special thank you to Elanna Arhos. We have had each other's backs every step of the way. I could not imagine completing this degree without you. I am so grateful for our friendship. I would like to also thank our lab assistants for your time and dedication to our research. Especially, Nnennaya Okorie, Kayla Miller, Erica Schmidheiser, Lilly Fuerer, Leah Manchel, Phoebe Balascio, and Madeline Collazo, without your help, I never would have completed this dissertation.

To the BIOMS community and neighboring Physical Activity lab and Neuro Studies group, thank you for making work seem more like fun. Thank you for electing me as BIOMS United Coordinator and providing me the opportunity to serve the graduate community and improve the program experience for future PhD students. Thank you to Katie Hunzinger for sharing this role with me and for being a great friend and colleague.

A special thank you to my research collaborators and friends around the world. Thank you to Dr. Fabian Passini and Dr. Jess Snedeker for introducing me to biomedical engineering and the value of interdisciplinary collaboration. Also, thank you to Fabian, for revolutionizing our elastography processing method and saving me countless hours. Thank you to the members of the ICON 2020 Consensus group for involving me in the global effort to advance reporting of Achilles tendinopathy research.

To my Mom, my education would have ended after high school without your sacrifice and support. You are the hardest working person I know, and I have emulated your endurance for overcoming challenges at every stage of my career. To my brothers, John and Brian, thank you for your love and support and understanding for my many absences from birthdays and family gatherings. John and Emily, thanks for raising two beautiful and brilliant girls who I hope will someday want to attend college where their Uncle works. Finally, thank you to my wife, Sarah. Completion of this degree is a grand accomplishment, but being your husband remains my greatest honor. You have been the salient support system for our family, and it may take a lifetime to fully express my gratitude. Your perseverance and work ethic are my inspiration, and I am convinced there is nothing you cannot do. Thank you for your love, for grounding me, understanding the many long days and missed dinners, and for faking your attention toward my reading aloud of excerpts from manuscript drafts and presentations. Now, on to our next adventure.

Research reported in this dissertation was supported by the National Institute of Arthritis and Musculoskeletal Skin Diseases of the National Institutes of Health under award numbers R01-AR07034-01A1, R21-AR067390 as well as the National Athletic Trainer's Association Research Foundation Doctoral Grant under award number 1920DGP08 and the Eastern Athletic Trainer's Association under award number 001_2021.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Achilles tendinopathy is a pervasive painful condition that impacts the ability to be physically active, occupational productivity, and quality of life.[28,140] Achilles tendinopathy occurs equally in men and women, with highest prevalence occurring in middle-aged adults.[65] The lifetime incidence is estimated to be 50% among runners and 5.9% in the general population.[74] Achilles tendinopathy has historically been considered a sports injury, however 65% of cases in the general population have no association with sports participation.[65] The patient population is diverse, ranging from elite athletes to older adults with metabolic disease.[3,65] Although the hallmark symptoms of pain with loading are shared by all, the general health impairments and alterations in tendon structure vary widely among those afflicted.[99] These impairments can be described on a spectrum summarized by the tendon health model.[99,133] The domains of the tendon health model include symptoms, lower extremity function, tendon structure and mechanical properties, psychological factors, and patient-related factors.[133]

Exercise therapy is the first line of care to address deficits in tendon health,[90,153] however between 20-40% of patients experience continued symptoms at 5-year follow-up.[43,112] Despite previous studies addressing inadequacies of the current one-size-fits-all treatment approach,[124,131] no study has prospectively characterized who are the patients that respond unfavorably to the standard of care. Comprehensive evaluation of each domain of tendon health may be required to identify specific barriers to recovery for patients when with exercise therapy alone. After recognizing

these barriers, precision treatment approaches can be developed to address these individual deficits in tendon health to ensure complete and lasting recovery for all.

This dissertation work leveraged the tendon health model to identify patient subgroups with Achilles tendinopathy and revealed implications of subgroup membership for recovery. In the first aim, three latent subgroups among patients with Achilles tendinopathy (insertional and midportion) in the general population were identified with distinct characteristics and clinical deficits. In the second aim, the reproducibility of the subgroups was confirmed in a cohort with only midportion Achilles tendinopathy and differences were observed in recovery trajectories of symptoms, function, tendon structure, and psychosocial factors following 24 weeks of exercise therapy and activity modification. The adolescent population is another group contributing to the heterogeneity of the patient population, but is often excluded from Achilles tendinopathy studies. Therefore, the final aim of this dissertation determined that adolescents with heel pain can present with isolated Achilles tendon pain, heel pain related to calcaneal apophysitis, or concurrent injury. Additionally, Aim 3 determined that treating adolescents with heel pain with exercise therapy and activity modification for 12 weeks is appropriate and feasible for conducting a larger clinical trial to evaluate treatment effectiveness. Collectively, the findings of this dissertation work could drive a shift in treatment from a one-size-fits-all approach to precision treatment strategies for patients with Achilles tendinopathy and transform clinical perceptions and management strategies for adolescents with heel pain.

PREFACE

At the time of publication of this dissertation document, Aim 1 has been published and is reproduced with permission from the Journal of Orthopaedic and Sports Physical Therapy. I would like to recognize my co-authors and clarify my contribution to this study.

> Hanlon SL, Pohlig RT, Silbernagel KG. Beyond the Diagnosis: Using Patient Characteristics and Domains of Tendon Health to Identify Latent Subgroups of Achilles Tendinopathy. *Journal of Orthopaedic and Sports Physical Therapy*. 2021; 51(9): 440-448. [10.2519/jospt.2021.10271].

All authors planned the study. I performed the mixture modeling analysis under the supervision of Ryan T Pohlig. Ryan T Pohlig performed the statistical analysis for the clinical classification model. All authors contributed to the interpretation of results and the writing of the manuscript. All authors approved the final manuscript

Chapter 1

INTRODUCTION

1.1 Background

The Achilles tendon is the strongest tendon in the human body and is essential to walking, running and jumping.[158] The function of all tendons is to absorb and transfer forces between muscles and bones. The Achilles tendon, specifically, is capable of withstanding loads 6-12 times body weight.[72] Mechanical loading is crucial for maintaining tendon health. Regular physical activity and resistance training improve the Achilles tendon's mechanical properties and capacity to absorb and transfer forces.[26,68,69,88] Conversely, excessive tendon loading or sudden increases in tendon loading, coupled with inadequate time for remodeling, can instead lead to the development of Achilles tendinopathy.

Achilles tendinopathy is an overuse injury characterized by pain, symptoms, and structural alterations in the Achilles tendon, that limit the ability to be physically active.[28,87,118] The incidence of Achilles tendinopathy is 2.35 per 1000 adults and the condition occurs in both athletic and non-athletic individuals.[65] Symptoms often start as subtle pain and morning stiffness[11] with a slow progression to persistent pain with loading and reduced ability to absorb and transfer muscle forces,[10,150] leading to occupational and recreational disability,[74,159] psychological burden,[92] and impaired quality of life.[133] Symptoms are present with physical activities such as walking and running and commonly lie dormant when a person avoids such activities. Resting from

painful activity is therefore often attempted as an initial treatment strategy but this "wait and see" approach is known to be ineffective.[119]

While symptoms are often the first perception of tendon injury, Achilles tendon pain may be preceded by years of abnormal tendon remodeling.[51] Predisposing factors for developing Achilles tendon pain vary across the lifespan making it challenging to adequately evaluate the evidence of proposed risk factors.[105,152] Changes in tendon structure (i.e., tendon thickening) are predictive of symptom development,[38,54,63,93] but this has been an inconsistent indicator in the literature because structural changes have also been observed in asymptomatic tendons.[38,93] Athletic patients often develop symptoms related to changes in training load and inadequate rest between training bouts.[3,62,76] However in the general population, 65% of Achilles tendinopathy cases are not sport-related.[65] Obesity[1] and diabetes mellitus[2] also increase the risk of Achilles tendinopathy. Although several studies have been conducted in the populations most frequently affected by Achilles tendinopathy such as middle-aged and older adults, few studies have investigated whether Achilles tendon pathology occurs in adolescent with heel pain.[16,65] This observed diversity among patients may reflect why rehabilitation is notoriously challenging in clinical practice and symptom recurrence occurs in up to 27% of patients.[41]

1.2 The Domains of Tendon Health

Clinical presentation as well as the general health impairments associated with Achilles tendinopathy can be characterized on a spectrum, with severity ranging widely among patients.[99] The tendon health model collectively describes these impairments associated with Achilles tendinopathy in domains.[133] The tendon health domains include symptoms, tendon structure and mechanical properties, lower

extremity function, psychological factors, and patient-related factors. These align with the health-related core domain outcomes for tendinopathy recently established by international consensus to improve uniformity in tendinopathy research reporting.[151] These health-related core domains include the patient's rating of the overall condition, participation, pain on loading or activity, pain over a specified period of time, function, psychological factors, physical function capacity, disability, and quality of life.[151]

The tendon health model promotes a biopsychosocial approach to clinical evaluation. The impact of Achilles tendinopathy can be measured in symptoms, functional impairments, alterations in tendon structure, and elevated fear of movement or re-injury.[21,23,135] Recovery of symptoms and function may not occur in parallel,[136] therefore comprehensive assessment of each domain of tendon health may be required to ensure no aspect of injury is overlooked throughout the rehabilitation process. Altered tendon structure (greater tendon thickening and lower tendon viscosity) has been associated with poor calf muscle endurance.[23] Similarly, increased tendon thickness and color doppler signal on ultrasound have been associated with greater pain on palpation and self-reported pain with functional activities during treatment.[11] Psychological factors may also to be an important piece of the clinical puzzle. Alghamdi et al[9] recently identified that individuals with low kinesiophobia (fear or movement or re-injury) at initial evaluation presented with less symptoms and reported higher quality of life compared to those with moderate or high kinesiophobia. A study by Chimenti et al[21] suggests kinesiophobia may influence the ability to recover lower extremity function in other musculoskeletal disorders. Patient-related factors, such as sex, obesity, and metabolism may also impact the rehabilitation

process and partly explain why 10-45% of patients have less favorable outcomes following exercise treatment.[85,124,137]

1.3 Uncovering Patient Subgroups Using Mixture Modeling: Shifting Focus From Standardized Care to Precision Treatment Strategies.

An increasingly common objective in rehabilitation research is to identify significant predictors of outcomes in order to enhance treatment effectiveness. This is often done by testing relationships between dependent and independent variables via regression model. In Achilles tendinopathy treatment, effectiveness research has typically compared individual or combined interventions, such as various forms of exercises therapy[47,135,144] and shockwave therapy,[4,122] in order to determine which provides the most benefit for the most patients. Then post-hoc, researchers will attempt to identify individual variables that affect clinical outcome, such as tendon morphology[24] or physical activity level.[124] Conversely, no study has tried to *a priori* identify individual's responsiveness to treatment based on their commonalities among a number of clinical measures. Mixture modeling (or latent profile analysis) is a person-centered statistical method that identifies latent subgroups within a cohort using observed data.[100,106] After identifying these profiles, we then hypothesize that treatment effectiveness may vary based on subgroup membership. This has been shown to be beneficial in rehabilitation research in individuals with low back,[53] resulting in the ability to design and test tailored interventions to benefit the differential needs of individual patients. Mixture modeling offers the advantage of having the ability to identify which patient characteristics collectively might affect clinical outcomes *a priori*, instead of examining variables related to those with known successful outcomes post-hoc. The information learned from this may provide

valuable insight for determining which subgroups show changes in various clinical outcomes over the course of treatment. In context, no previous research has explored whether the 10-45% of patients[85,124,137] who do not recover from Achilles tendinopathy share any commonalties to explain their divergent response to treatment.

Precision treatment strategies refers tailoring treatment based on the individual deficits and characteristics of the patient. Through this approach, all patients benefit equally from respectively different treatment approaches for the same disease or injury. Defining recovery from Achilles tendinopathy cannot occur without first learning what deficits in tendon health are present. In order to understand if there are ways to improve treatment outcomes and ensure complete recovery for patients with Achilles tendinopathy, an essential first step is to understand if all patients are affected the same or are there subgroups that might benefit from precision treatment strategies.

Aim 1: Identify and categorize latent subgroups of patients with Achilles tendinopathy and to compare their measures of tendon health.

Hypothesis 1.1.: More than one subgroup exists among patients diagnosed with Achilles tendinopathy.

Hypothesis 1.2: Significant differences will be found among subgroups' measures of tendon health.

1.4 Exercise Therapy: Strengths and Limitations of the Current Standard of Care

Exercise therapy is the treatment with the highest level of evidence[47,90,153] for Achilles tendinopathy, however, many continue to experience pain and impaired function for many months or years.[85,124,137] The goals of treatment for Achilles tendinopathy pertain to pain resolution, return to activity or pre-injury function, and

prevention of symptom recurrence. Prognosis and recovery are commonly defined by changes in patient-reported symptoms with activity, as measured by the Victorian Institute of Sport Assessment-Achilles (VISA-A).[117,136] The tendon health model suggests a broadened approach to evaluating recovery. Considering recovery of symptoms does not ensure recovery of function,[136] addressing of all aspects of injury may be necessary to ensure complete recovery and prevent recurrence. In other words, no single factor should be determinative of successful recovery and treatment must address all deficits in tendon health to ensure complete and lasting recovery.[46,136]

There is conflicting literature to support whether tendon structure can be modified by treatment.[8,23,66,75] A thickened tendon (tendinosis) is historically associated with chronic degenerative tendinopathy,[28,84] but not all patients with Achilles tendinopathy present with an equivalent degree to structural alteration. Therefore, structural recovery might be a critical, yet overlooked, recovery component for a subgroup of patients with considerable tendon degeneration.[23] Tendon tissue may require up to 72 hours to respond to a heavy bout of mechanical loading.[89] This suggests that changes in tendon structure may occur at a slower rate than symptoms and function and may not be observed within a 12 week time period.[70,154] This dissertation work will add to the existing body of knowledge supporting the importance of structural recovery from Achilles tendinopathy beyond 12 weeks of treatment.

While many patients recover from exercise therapy alone,[43] implementing activity modification using the pain monitoring model[149] is an effective adjunct to exercise therapy for Achilles tendinopathy[135] and is also promising for patellar tendinopathy.[142] This strategy was first popularized for sports-active patients to allow

for continued participation with no detrimental effect on recovery.[135] Pain-guided activity modification may additionally be an effective intervention for individuals with elevated kinesiophobia.[43] Elevated kinesiophobia negatively influences recovery, although the exact mechanism remains unknown.[21,29] The prevalence of kinesiophobia in patients with Achilles tendinopathy has not been established, however it is reported to be present in over 60% of adults with leg pain associated with overuse.[80] Using the pain monitoring model, patients are educated on how to interpret pain as "safe," "acceptable," or "high risk" before Achilles tendon-loading exercises are attempted.[135] Whereas traditional loading programs might not provide any pain education or alternatively, recommend avoidance of any pain altogether. Therefore patients following the pain monitoring model might load their tendons more with treatment and expedite recovery.[137] In this context, exercise therapy and activity modification are the first line of care for patients with Achilles tendinopathy. However, whether complete recovery of all tendon health domains is achievable when treated with exercise therapy and activity modification has yet to be explored.

In order to improve treatment outcomes for all patients with Achilles tendinopathy, it is essential to understand whether there are patient subgroups who respond differently to exercise therapy. By evaluating change over time among patient subgroups, precision treatment strategies can be informed and developed to benefit those who respond less favorably to treatment.

Aim 2: Compare recovery trajectories of latent subgroups for symptoms, tendon structure and mechanical properties, lower extremity function, psychological factors and patient-related factors following 24 weeks of exercise therapy and activity modification.

Hypothesis 2.1.: Subgroups will differ in their change over time in VISA-A scores.

Hypothesis 2.2.: Subgroups will differ in their change over time in heel-rise work.

Hypothesis 2.3.: Subgroups will differ in their change over time in viscosity.

Hypothesis 2.4: Subgroups will differ in their change over time in TSK-17 scores.

Hypothesis 2.5: Subgroups will differ in their change over time in FOAS-QoL scores.

Hypothesis 2.6.: Likelihood of recovery will differ among subgroups at 24 weeks.

1.5 Exploring Tendon Health in Adolescents with Heel Pain

Little is known about the development of Achilles tendon pain and pathology in childhood and adolescence.[96] A potential reason this patient population receives little attention may be the assumption that all skeletally immature children who complain of insidious heel pain with activity have calcaneal apophysitis.[28,82] Diagnosis of calcaneal apophysitis is clinical and mirrors the diagnosis of Achilles tendinopathy. The chief distinction between the diagnoses of Achilles tendinopathy and calcaneal apophysitis is patient age.[28] Since adolescents are assumed skeletally immature, heel pain is commonly thought to be due to repetitive stress on the apophysis (growth plate) and Achilles tendon involvement may not be considered.[82]

The discrepancy for differing injury may be related to imbalances in bone, tendon, and muscle tissue development throughout the pubescent-adolescent years of

life. Habitual participation in sports at young age may lead to imbalanced adaptation in muscle and tendon, resulting in increased stress and strain on the weakest connective tissue.[96] Risk of calcaneal apophyseal injury may increase for a transient time in the prepubescent-adolescent years, when the apophysis is the weakest compared to muscle and tendon strength and stiffness. Risk of Achilles tendon involvement increases with age,[57] and might begin following closure of calcaneal apophysis, when tendon strain is rampantly increased due to developmental increases in muscle forces and longer moment arms, coupled with greater loads placed on the tendon from increasing body mass.[96]

Diagnostic imaging (X-ray) is considered uninformative because the radiographic appearance of the developing calcaneal apophysis appears separated in children with and without heel pain.[113] B-mode ultrasound is a safe alternative and a valuable instrument for visualizing Achilles tendon structural alterations and is the preferred imaging instrument for adults with tendon injuries.[134,155] However, few studies have used B-mode ultrasound imaging when evaluating adolescents with heel pain.[16,55]

It is widely assumed that calcaneal apophysitis spontaneously resolves after skeletal maturity is reached,[77,129] but it remains unknown if there are adolescents transitioning into adulthood with Achilles tendon pathology. This is critical because human tendons develop continually until age 17 and is very limited in adulthood.[50] If tendinopathic changes are occurring in adolescents and are not restored, it is uncertain how this may impact lifelong tendon health.

Aim 3a: Explore whether Achilles tendon injury occurs in adolescents with heel pain.

Hypothesis 3a.1.: Achilles tendon injury (pain and/or changes in structure) is present in adolescents with heel pain.

Hypothesis 3a.2.: Alterations in Achilles tendon mechanical properties will be observed in adolescents with heel pain.

1.6 Advancing Treatment for Adolescents with Heel Pain

In clinical practice, treatment options vary widely for adolescents with heel pain because there is no consensus for best practice.[126] Anecdotal evidence suggests that symptoms resolve once the apophyses have fused, yet patients still experience symptoms, disability, and reduced quality of life lasting several weeks to as long as 1 year and recurrence rates are unknown.[61] A range of treatment approaches are anecdotally supported, ranging from complete immobilization with casting to continued activity.[59,82,110] Only one randomized clinical trial has been conducted using an active treatment approach, finding no difference in outcomes between shoe inserts, physical therapy, and no treatment ("wait and see").[157] However the physical therapy intervention was not described.

Exercise therapy, when appropriately prescribed, can promote positive adaptation in tendon and bone tissue in adults,[68] but this has not been explored in the adolescent population. A primary supplement to exercise therapy is the use of pain-guided activity modification, which has become a cornerstone of successful exercise therapy for Achilles tendinopathy[135] and has been successfully employed for adolescent athletes with patellofemoral pain syndrome.[115] In adult individuals with Achilles tendinopathy, those who were allowed to continue modified activity during treatment experienced similar results to those who were required to avoid all

activity.[135] Because youth are generally very physically active, complete cessation of physical activity can have substantial negative impact on quality life.[125] On the other hand, unmodified full participation may also be harmful and often leads to worsening symptoms and could nullify the benefits of concurrent treatment.[77,114] Activity modification for adolescents with heel pain could be a superior alternative that mitigates the psychosocial and physical consequences of either extreme. There is a need to establish high quality evidence for an effective treatment for this patient population. Before treatment effectiveness can be evaluated, it is necessary to explore the feasibility of conducting a pilot study for adolescents with heel pain.

Aim 3b Evaluate the feasibility of treating adolescents with heel pain with 12 weeks of exercise therapy and activity modification.

Hypothesis 3b.1.: Examine access to potential participants, percentage of participants meeting the inclusion criteria, and monthly recruitment and retention rates.

Hypothesis 3b.2.: Examine the compliance and satisfaction of participants with treatment, activity modification, and training diaries.

Hypothesis 3b.3.: Symptom severity, lower extremity function, and quality of life will improve significantly.

1.7 Summary

Achilles tendinopathy is a common overuse condition that plagues athletes and non-athletes alike of all ages. Appraising recovery for patients with Achilles tendinopathy remains challenging due to the multifactorial impact of the injury. Symptom resolution, return to participation, normalization of tendon structure, and treatment satisfaction are all important, but individually may not ensure complete

recovery for all patients. Therefore no single factor may be determinative of recovery. The findings of this dissertation are vital towards broadening our understanding of how patients are individually impacted by Achilles tendinopathy and provides the first evidence identifying specific patient characteristics that distinguish patients with Achilles tendinopathy from one another across a broad spectrum of variables. This is valuable to interpreting clinical presentation as well as informing patient expectations and treatment decisions. Further, this dissertation aims to establish the clinical implications of subgroup membership by concurrently evaluating recovery among the subgroups over time by changes in symptoms, tendon structure and mechanical properties, lower extremity function, psychological and patient-related factors. For the first time, recovery expectations can be estimated and addressed for each domain of tendon health based on patient subgroup membership. In Aim 3, we expand the research to those under 18 with heel pain who might have Achilles tendon injury. To our knowledge, Aim 3 is the first prospective pilot study to evaluate the feasibility and effectiveness of exercise therapy and pain-guided activity modification for adolescents with heel pain. This is a critical first step in developing evidenced-based treatment for this patient population and sets the stage for a larger clinical trial aimed at establishing treatment effectiveness for adolescents with heel pain.

The implications of this dissertation may lead to improved understanding of why many patients with Achilles tendinopathy do not fully recover or develop recurrent symptoms, as well as provide preliminary evidence for Achilles tendinopathy in the adolescent population. This could drive a shift in clinical management of adolescents with heel pain from passive treatment and activity cessation to active treatment that promotes the physical and mental health benefits of

continued exercise with activity modification. Collectively, the findings of this dissertation have the potential to broaden the available knowledge that supports a shift in treatment from a one-size-fits-all approach to precision treatment strategies for patients with Achilles tendinopathy.

Chapter 2

BEYOND THE DIAGNOSIS: USING THE TENDON HEALTH MODEL AND PATIENT CHARACTERISTICS TO IDENTIFY SUBGROUPS OF ACHILLES TENDINOPATHY

2.1 Introduction

Treatment for Achilles tendinopathy has evolved over the past two decades reflected by a growing understanding of pathophysiology.[89,141,159] Exercise therapy is the current gold standard for treating Achilles tendinopathy, however not all patients achieve full recovery.[6,34,86,90] Up to 40% of patients continue to report poor outcomes following 12 weeks of treatment.[7,34,64,108,112,124,131] Recovery remains poorly defined for tendinopathy which impedes the ability to measure success in rehabilitation.[131] Symptom resolution, return to participation, and normalization of tendon structure are all important, but individually may not ensure complete recovery for all patients.[46,136]

Interindividual differences among patients with Achilles tendinopathy are poorly understood due to insufficient reporting of patient characteristics.[116] Because of this paucity, clinicians have limited evidence to inform their treatment plan or determine a patient's propensity and time needed to achieve recovery. All patients with Achilles Tendinopathy will continue to be treated the same until we as clinicians understand what makes patients different and which factors influence treatment outcomes. If patients could be classified into distinct subgroups by their specific deficits and other related factors, treatment could shift from a one size fits all approach[131] to an individualized treatment strategy. In order to understand if there are

ways to improve treatment strategies for patient-specific recovery, it is important to evaluate if all patients diagnosed with Achilles tendinopathy are affected the same or are there subgroups that might need additional or modified treatment strategies.

Mixture modeling is a method for classifying individuals into heterogeneous subgroups within a population when the groups are not known a priori.[106] This model-based approach focuses on relationships among individuals, and identifies patterns among individuals based on who are more similar and separates those who are less similar. Mixture modeling has helped derive targeted treatment approaches for disorders that are multifaceted in nature (e.g. low back pain).[145] No previous study has applied mixture modeling to Achilles tendinopathy. The purpose of this study was three-fold; first to identify the number of patient subgroups with Achilles tendinopathy, second to describe which patient characteristics and clinical attributes define each subgroup, and third to develop a clinical classification model for identifying subgroup membership.

2.2 Methods and Materials

A cross-sectional study was conducted within two larger longitudinal studies for patients with Achilles tendinopathy. Selection criteria were consistent with the parent studies; we analyzed baseline data from the parent studies.

2.2.1 Participants

Participants were asked to provide informed consent if they were at least 18 years old and had a clinical diagnosis of Achilles tendinopathy (insertional or midportion). The clinical diagnosis was established by 1) pain on palpation at either the calcaneal insertion or the midportion of the Achilles tendon 2) reported pain with

loading 3) reported impaired function (e.g. reduced ability to participate in ADL/work/sport).[83,128] Exclusion criteria included previous Achilles tendon rupture, diagnosis of bursitis only, or another injury that limited their ability to complete the tests. All participants were recruited from local physicians, physical therapy clinics, and advertisements. Data were collected between November 2014 and December 2019. Data extracted from both studies were approved by the Institutional Review Board at the University of Delaware.

2.2.2 Variables

To be as inclusive as possible, 14 variables were selected on the basis of 1) outcome measure in previous tendinopathy studies, 2) clinically meaningful, 3) established as associated with Achilles tendinopathy and 4) collected in the parent studies (Figure 2.1). These selected variables represent five domains of tendon health[133] and promotes a biopsychosocial appraisal of the patient suffering from tendinopathy.

2.2.2.1 Symptoms

The Victorian Institute of Sport Assessment- Achilles[117] (VISA-A) and self-rated pain with hopping evaluated pain and symptoms. The VISA-A is valid and reliable measure of symptom severity in patients with Achilles tendinopathy and is scored 0-100, where a lower score indicates more pain and symptoms. Participants performed 2 trials of 25 single leg hopping. Self-rated pain with hopping was recorded using a numerical pain rating scale[31] from 0 (no pain) -10 (worst pain imaginable).

2.2.2.2 Lower Extremity Function

Jump performance and calf muscle endurance were measured via a single leg countermovement jump (CMJ), drop countermovement jump (Drop CMJ), and a heel-rise endurance test using MuscleLab® measurement system (Ergotest Innovation, Porsgrunn, Norway).[132] Participants needed to jump at least 1cm for MuscleLab® to register a trial. Participants received a zero for height if they were unable to jump ≥1cm for a trial. Participants who declined to attempt a jump for any reason were assigned no value for that trial. Average jump height for the CMJ and Drop CMJ were calculated from up to three attempted trials per test. Total heel-rise work was measured in joules (heel-rise height x repetitions x body mass). Physical activity level during the past week was assessed using the Physical Activity Scale[45] (PAS). The PAS is measured on a scale from 1-6, where 1 indicates hardly any physical activity and >5 indicates vigorous physical activity for several days per week.

2.2.2.3 Patient-related Factors

Body Mass Index (BMI) was calculated from measured height and weight. Participant age and sex were collected and considered clinically relevant as tendon mechanical properties and morphology are different between sexes and change throughout the lifespan.[73,111] Quality of life was measured with the Foot and Ankle Outcome Score – Quality of life[120] (FAOS-QoL) and considered to be a patient-related factor as it is "an individual's subjective evaluation of their overall well-being in the context of their own experiences."[19] A higher score (0-100) indicates a higher quality of life. Self-reported duration of symptoms (number of months) was collected since injury duration is proposed to affect nociception and affects quality of life.[32] Injury

side (unilateral, bilateral) and location (insertional, midportion, both) were also recorded.

2.2.2.4 Psychological Factors

The Tampa Scale of Kinesiophobia (TSK-17) measured fear of movement.[39,80,81] A higher TSK-17 score (17-68) indicates greater fear of movement and a score of ≥37 indicates high kinesiophobia.[39] The Pain Catastrophizing Scale[146] (PCS) measured pain catastrophizing. Participants reflect on past painful experiences and indicate the degree to which they experienced catastrophizing thoughts or feelings. A higher PCS score (0-52) indicates higher degree of pain catastrophizing.

2.2.2.5 Tendon Structure and Mechanical Properties

Achilles tendon structure was assessed using B-mode ultrasound imaging (frequency of 10MHz and depth of 3.5 cm) using a GE Logiq e ultrasound scanner (GE LOGIQ e, GE Healthcare, Chicago, IL). All images were taken with the participant lying prone with the feet hanging off the edge of the table. Measurements included tendon thickness, and cross-sectional area (CSA) at the thickest portion using previously described reliable procedures.[134,161]

Achilles tendon mechanical properties were measured using continuous shear wave elastography (cSWE), which has excellent reliability and validity.[25,26,148] This method is similar to commercial SWE[30], however cSWE uses an external actuator to generate shear waves and allows for extrapolation of two separate viscoelastic properties: shear modulus (i.e. stiffness) and viscosity (rate-dependent stiffness) of the tendon.[25]

2.2.3 Statistical Analysis

Mixture Modeling was used to identify the number of subgroups (best-fitting model) using the 14 variables described above (Figure 2.1). Measures for all analyses were taken from the most symptomatic limb (self-reported). The limb with the lower VISA-A[117] score was identified as "most symptomatic" for participants with bilateral symptoms. Mixture Modeling was performed in Mplus (Muthén and Muthén, version 8.3). Missing data were handled using Mplus with a robust maximum likelihood (ML) estimator. A summary of missing data is presented in Appendix A.

Determining the number of subgroups depends on a number of factors in addition to fit statistics.[42,52,104] Fit statistics included Akaike's Information Criterion[5] (AIC), Bayesian Information Criterion[127] (BIC), and sample-adjusted BIC[127] (ABIC); all of which have been considered among the strongest indicators among the fit statistics of subgroup enumeration.[104] The best fitting model should have the lowest AIC, BIC, and ABIC values.[52] Entropy criterion represents the ability of the model to provide well-separated subgroups; a higher value (0-1) indicates the model has both strong separation between subgroups and strong cohesion within subgroups.[17] The Vuong-Lo-Mendell-Rubin (VLMR), sample-adjusted VLMR, and Bootstrap Likelihood Ratio (BLR) tests were used to compare statistical significance between the current model to one with one less subgroup (e.g. 3 vs. 2).[52] Finally, we ensured that each subgroup included > 5% of the sample[160] and used clinical expertise to interpret meaningful differences among subgroups.

Following subgroup enumeration, all variables were compared across subgroups using ANOVAs for continuous variables and chi-square tests for categorical variables and Tukey's post-hoc test using SPSS (Version 26). Sex, BMI, symptom duration, injury location, and injury side were used for post-hoc comparison

across subgroups. All analyses were 2-sided, where $p < .05$ was considered statistically significant. All results are reported as mean ±SD, unless otherwise stated. To help illustrate the group differences visually across domains, variables were rescaled to z-scores and adjusted so better performance is indicated by higher positive values in Figures 2.2 and 2.3. The clinical classification model (Figure 2.4) was developed post-hoc using the results to provide clinicians with a tool to classify patients using outcome measures that are accessible in clinical practice. Initially a Regression Tree approach was attempted using the variables included in the mixture model, but results were unstable. Instead, a two-step ROC process was employed iteratively to differentiate between subgroups by using cut-scores for each variable that jointly maximized sensitivity and specificity using Youden's Index.[36] For each variable, individuals were scored as having or not having met the criteria.

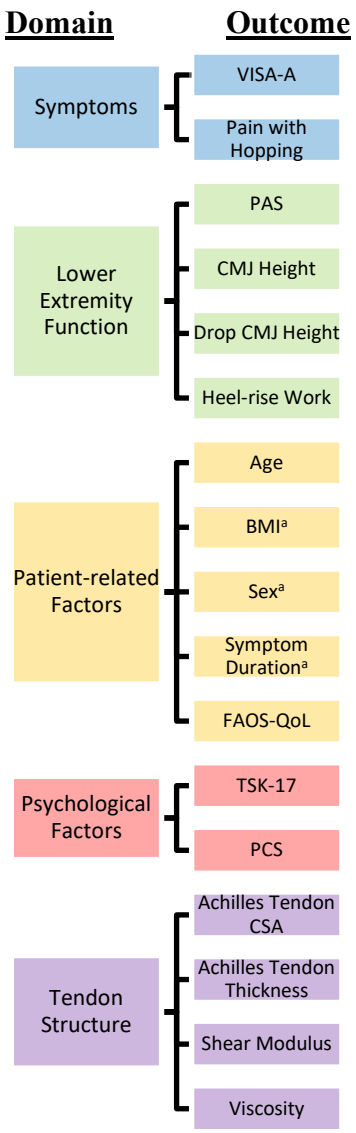


Figure 2.1: Domains and outcomes of tendon health.

Abbreviations: VISA-A, Victorian Institute of Sport Assessment-Achilles; PAS, Physical Activity Scale; CMJ, counter movement jump; BMI, body mass index; FAOS-QoL, Foot and Ankle Outcome Score-Quality of Life; TSK, Tampa Scale of Kinesiophobia; PCS, Pain Catastrophizing Scale; CSA, cross-sectional area.

2.3 Results

The best-fitting model by information criteria (AIC, BIC, aBIC) identified three latent subgroups (Appendix B). The VLMR and aVLMR suggested two subgroups, although three was close to significantly better. The bootstrap version (BLR) was uninformative, and entropy was good for all models. Ultimately, three subgroups were deemed most appropriate. The three patient subgroups were labeled Activity-dominant (n=67), Psychosocial-dominant (n=56), and Structure-dominant (n=22) (Table 2.1) based on their respective distinguishing clinical features (Figure 2.2).

Table 2.1: Comparison of patient characteristics.

	Total Sample n=145[a]	**Activity Dominant n=67 (46%)**[a]	**Psychosocial Dominant n=56 (39%)**[a]	**Structure Dominant n=22 (15%)**[a]	**ANOVA *P-value***	***P*-value** (AD vs. PD)[b]	***P*-value** (AD vs. SD)[b]	***P*-value** (PD vs. SD)[b]
Symptoms								
VISA-A Score	53±21	66±16	40±18	47±19	**< .001**	**< .001**	**< .001**	.254
Pain with Hopping, NPRS	2±4	3±2	3±2	0±3	.485	.663	.799	.510
Lower Extremity Function								
Physical Activity Scale	5±2	5±1	3±2	3±2	**< .001**	**< .001**	**< .001**	.999
CMJ Height, cm	6.4±3.6	8.6±3.0	3.5±1.9	4.2±2.1	**< .001**	**< .001**	**< .001**	.701
Drop CMJ Height, cm	6.6±3.5	8.5±3.3	3.2±2.3	3.6±2.9	**< .001**	**< .001**	**< .001**	.949
Heel-rise Work, J	1470±1209	1832±838	1062±1415	336±937	**< .001**	**< .001**	**< .001**	**.037**
Heel-rise endurance test, repetitions	21±13	28±9	16±14	10±10	**< .001**	**< .001**	**< .001**	.061
Patient-related Factors								
Age, years	51±14	44±13	55±12	62±8.7	**< .001**	**< .001**	**< .001**	**.048**
BMI, kg/m^2	27.6±6.74	24.3±3.8	30.7±7.1	30.7±5.9	**< .001**	**< .001**	**< .001**	.999
Sex, M:F	73:72[c]	37:30[c]	19:37[c]	17:5[c]	**.001**	**.087**	**.042**	**.001**
Duration of Symptoms, months	10.2±25.7	12±25.1	10.3±20.4	8±20.6	.409	.949	.380	.526

Table 2.1. continued.

FAOS-QoL Score	44±19	54±16	32±15	43±14	**< .001**	**< .001**	**0.014**	**.011**
Injury Location	MP:100; I:36; Both:9	MP:48; I:16; Both: 3	MP:36; I:16; Both: 4	MP:16; I:4; Both: 2	.643	.976	.708	.624
Bilateral Symptoms Incidence Rate	67 (46%) [c]	34 (51%) [c]	22 (39%) [c]	11 (50%) [c]	.420	.418	.998	.672
Psychological Factors								
Tampa Scale of Kinesiophobia	38±5	36±5	41±4	38±5	**< .001**	**< .001**	.181	.081
Pain Catastrophizing Scale	5±8	6±8	9±13	5±8	**.002**	**.002**	.942	.065
Tendon Structure								
Achilles Tendon CSA, cm^2	1.0±0.56	0.77±0.3	0.88±0.31	2.06±0.14	**< .001**	.158	**< .001**	**< .001**
Achilles Tendon Thickness, cm	0.78±0.28	0.65±0.2	0.74±0.24	1.22±0.14	**<.001**	.052	**<.001**	**< .001**
Shear Modulus, KPa	97.76±16.55	97.25±16.26	97.47±15.32	100.24±20.9	.791	.998	.781	.821
Viscosity, KPa*s	52.59±12.6	55.6±11.44	52.86±12.26	41.69±12.11	**< .001**	.465	**< .001**	**.003**
FAOS-QoL Score	44±19	54±16	32±15	43±14	**< .001**	**< .001**	**0.014**	**.011**
Injury Location	MP:100; I:36; Both:9	MP:48; I:16; Both: 3	MP:36; I:16; Both: 4	MP:16; I:4; Both: 2	.643	.976	.708	.624
Bilateral Symptoms Incidence Rate	67 (46%) [c]	34 (51%) [c]	22 (39%) [c]	11 (50%) [c]	.420	.418	.998	.672

Table 2.1 continued.

Psychological Factors								
Tampa Scale of Kinesiophobia	38±5	36±5	41±4	38±5	**< .001**	**< .001**	.181	.081
Pain Catastrophizing Scale	5±8	6±8	9±13	5±8	**.002**	**.002**	.942	.065
Tendon Structure								
Achilles Tendon CSA, cm^2	1.0±0.56	0.77±0.3	0.88±0.31	2.06±0.14	**< .001**	.158	**< .001**	**< .001**
Achilles Tendon Thickness, cm	0.78±0.28	0.65±0.2	0.74±0.24	1.22±0.14	**<.001**	.052	**<.001**	**< .001**
Shear Modulus, KPa	97.76±16.55	97.25±16.26	97.47±15.32	100.24±20.9	.791	.998	.781	.821
Viscosity, KPa*s	52.59±12.6	55.6±11.44	52.86±12.26	41.69±12.11	**< .001**	.465	**< .001**	**.003**
Psychological Factors								
Tampa Scale of Kinesiophobia	38±5	36±5	41±4	38±5	**< .001**	**< .001**	.181	.081
Pain Catastrophizing Scale	5±8	6±8	9±13	5±8	**.002**	**.002**	.942	.065
Tendon Structure								
Achilles Tendon CSA, cm^2	1.0±0.56	0.77±0.3	0.88±0.31	2.06±0.14	**< .001**	.158	**< .001**	**< .001**
Achilles Tendon Thickness, cm	0.78±0.28	0.65±0.2	0.74±0.24	1.22±0.14	**<.001**	.052	**<.001**	**< .001**

Table 2.1 Continued.

Shear Modulus, KPa	97.76±16.55	97.25±16.26	97.47±15.32	100.24±20.9	.791	.998	.781	.821
Viscosity, KPa*s	52.59±12.6	55.6±11.44	52.86±12.26	41.69±12.11	**< .001**	.465	**< .001**	**.003**

Abbreviations: AD, Activity Dominant; PD, Psychosocial Dominant; SD, Structure Dominant; VISA-A, Victorian Institute of Sport Assessment-Achilles; NPRS, Numerical Pain Rating Scale; CMJ, Countermovement jump; M:F, Male:Female; NT, not tested; BMI, body mass index; FAOS-QoL, Foot and Ankle Outcome Score-Quality of Life; MP, Midportion; I: Insertional; CSA, cross-sectional area.

[a] Values are presented as Mean±SD. Pain with hopping, Physical Activity Scale, heel-rise work, duration of symptoms, and Pain Catastrophizing Scale are presented as Median±IQR.

[b] Bold values indicate significant post-hoc comparison ($p<0.05$).

[c] Chi Square test was used to compare distribution among subgroups

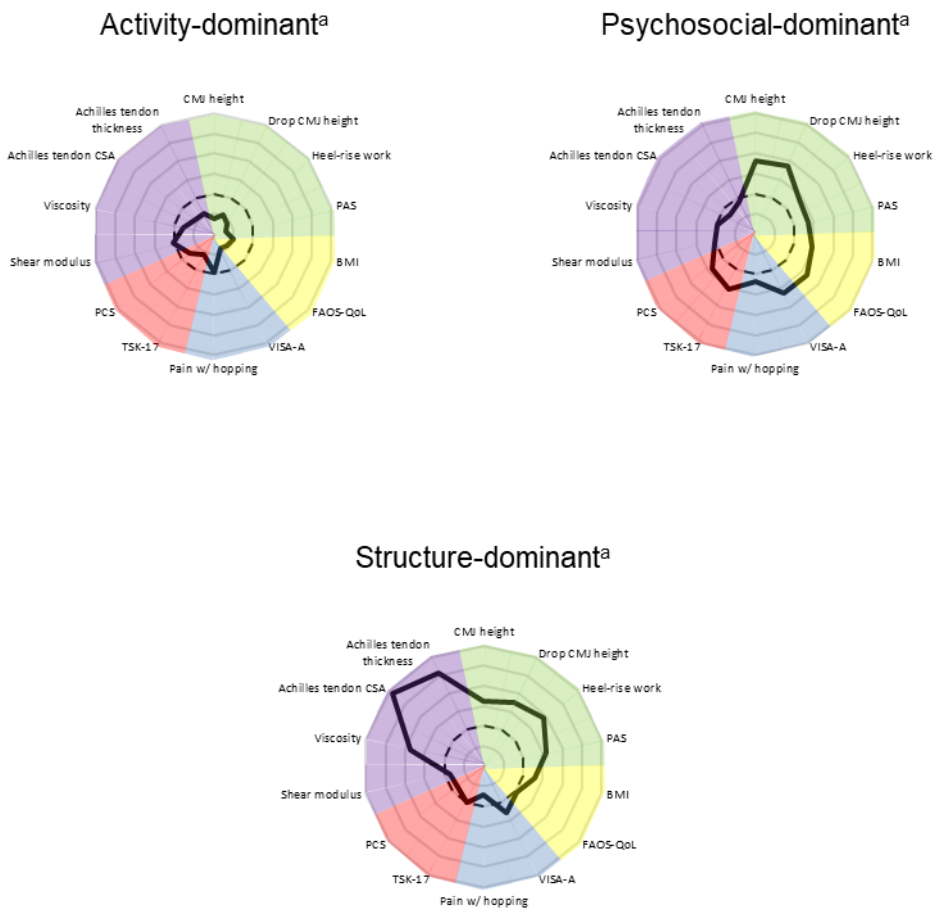


Figure 2.2. Comparison of subgroup performance on outcome measures separated by tendon health domain.

[a] Variables were rescaled by standardizing and adjusted so less distance from center represents less deficit or better performance. Dotted line represents pooled sample mean.

2.3.1 Activity-dominant

Compared to the other subgroups, Activity-dominant reported the highest PAS, VISA-A and FAOS-QOL scores, lowest TSK-17, lowest BMI, and were youngest (Table 2.1). CMJ and Drop CMJ heights were significantly higher, and this subgroup produced nearly twice and five times the heel-rise work compared to Psychosocial-dominant and Structure-dominant, respectively (Table 2.1 and Figure 2.3). Achilles tendon thickness was significantly less than the other subgroups, and CSA and viscosity were significantly better than Structure-dominant.

2.3.2 Psychosocial-dominant

Psychosocial-dominant demonstrated the highest psychological factors (TSK-17, PCS), and lowest FAOS-QoL scores compared to the other subgroups (Table 2.1). This subgroup was older than Activity-dominant and significantly worse, although similar to Structure-dominant, for the following variables: VISA-A, PAS, CMJ and Drop CMJ heights *(*Figures 2.2 and 2.3*)*. Psychosocial-dominant produced over 3 times more heel-rise work than Structure-dominant, but significantly less than Activity-dominant. Achilles tendon thickness, CSA, and viscosity measures were similar to Activity-dominant, but were significantly better than Structure-dominant. This subgroup was predominately obese and 66% female.

2.3.3 Structure-dominant

Structure-dominant demonstrated the largest Achilles tendon thickness and CSA, lowest viscosity, and produced the lowest heel rise work (Table 2.1 and Figure 2.2). This subgroup was the oldest, were predominately obese, and 77% male. Structure-dominant reported similar physical activity levels, but significantly higher quality of life compared to the Psychosocial-dominant.

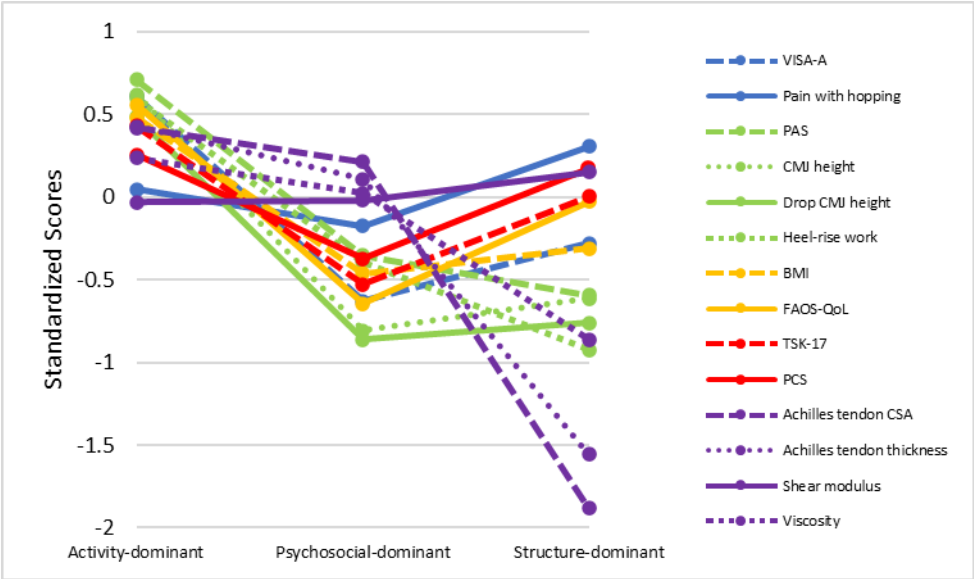


Figure 2.3: Comparison of similar and differing performance on outcome measures and respective tendon domains.

[a] Variables were rescaled by standardizing and adjusted so a higher standardized score indicates less deficit or better performance for each variable.

2.3.4 Clinical Classification

Only variables with a cut-point ROC AUC >.725 (BMI, TSK-17, Age, PAS, FAOS-QoL, Heel-rise work, and VISA-A) were kept in the final model (Figure 2.4). The presence of missing data (Appendix A) caused most combinations of potential predictors to have too few individuals in the Structure-dominant subgroup using ROC curves. Alternatively, multinomial Logistic Regression suggested that CSA > 1.63 cm2 was be used to accurately classify 86% (18/21) of Structure-dominant participants while excluding everyone in the other two subgroups (Figure 2.4). Having 4 or more of the 7 criteria accurately classified individuals 85% of the time (105/123). Using both these rules successfully classified 85% (123/145) of participants (Figure 2.4).

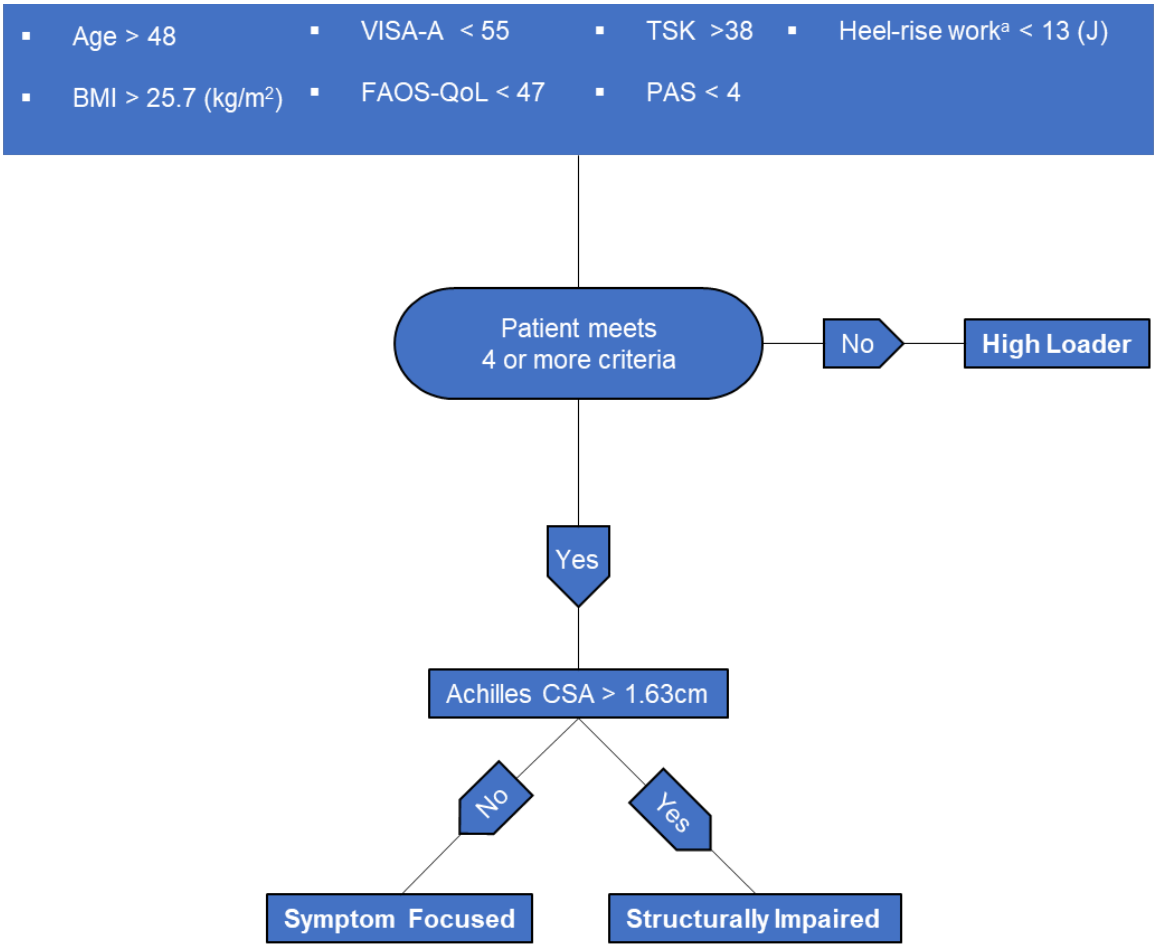


Figure 2.4: Clinical Classification Model.

Abbreviations: BMI, body mass index; VISA-A, Victorian Institute of Sport Assessment-Achilles; FAOS-QoL, Foot and Ankle Outcome Score-Quality of Life; TSK, Tampa Scale of Kinesiophobia; PAS, Physical Activity Scale; CSA, cross-sectional area.
[a] Formula for estimating heel-rise work (J): heel-rise work (J) = 59.44 x reps + BMI(5.87) - 7.3

2.4 Discussion

We identified three subgroups, Activity-dominant, Psychosocial-dominant, and Structure-dominant within the general population of patients with Achilles tendinopathy using statistical modeling. The subgroups were identified by testing

model fit using 14 variables commonly associated with tendinopathy including clinical exam findings, patient-reported outcome measures, ultrasound imaging, patient-related factors, and lower extremity functional tests.

Our latent subgroups share parallels with the theoretical continuum model of tendon pathology, which proposed clinical heterogeneity among patients based on imaging, clinical findings, and histological evidence.[22] Consistently, our results supports the importance of evaluating all domains of tendinopathy that may impact tendon and patient health.[151] While our findings cannot inform treatment recommendations, the distinguishing features of each subgroup reveals three differential patient profiles (Figure 2.2) that may explain the variability observed in both clinical practice and research outcomes.[24,85,122,124] Using the clinical classification model (Figure 2.4), clinicians can prospectively identify a patient's subgroup membership and recognize unique considerations for each subgroup and their potential obstacles to recovery.

Activity-dominant was the majority subgroup. These individuals demonstrated minimal performance impairments, suggesting a higher tendon-load capacity than the other subgroups. This may be because they have less pathological tendons. Athletes with early-onset tendinopathy symptoms have demonstrated slight (25%) increases in tendon CSA with unaltered tendon mechanical properties compared to healthy controls. However, symptom duration was not a distinguishing factor among subgroups. Lower kinesiophobia may explain why Activity-dominant participants reported higher quality of life and high activity levels, or vice versa. If tendon structure dictates physiological capacity, then symptomatic patients with minimal alterations in tendon structure might present with minimal functional impairment.[141]

Future research is needed to explore how Activity-dominant patients respond to treatment. Due to the apparent minimal impact on tendon health, Activity-dominant individuals may represent the majority of patients who achieve good-excellent results following 12 weeks of treatment.[13,109,112,130]

Psychosocial-dominant demonstrated minimal tendon structure and mechanical properties alterations, similar to Activity-dominant, yet this subgroup performed significantly worse on the functional test battery and averaged nearly 20 points lower on VISA-A (Table 2.1). The higher degree of psychological impact reported by Psychosocial-dominant may provide some explanation. Kinesiophobic patients may avoid excessive loading due to fear of pain making their condition worse. Fear-avoidance behaviors are associated with pain intensity[27,91] and could affect loading test performance (premature test cessation or suppressing maximal jump height).[43,79] Future research is needed to determine how psychological factors influence recovery times for patients with Achilles tendinopathy treated with exercise.[85,124] Loading the Achilles tendon through tolerable pain is safe and non-detrimental[135] to recovery. Future research should evaluate if Psychosocial-dominant patients are more reluctant to load their tendon due to kinesiophobia, and explore potential implications for rehabilitation compliance and progress.

Structure-dominant was the minority subgroup. This subgroup had the greatest degree of tendon alteration demonstrated by measures of tendon thickness, CSA, and decreased tendon viscosity (Figure 2.2). Accordingly, 32% of Structure-dominant were unable to perform one heel-rise repetition, which may have indirect effects on other aspects of tendon health. Consistently, Corrigan et al[23] reported greater tendon thickening and lower viscosity was associated with worse calf muscle endurance.

Some of the differences observed between Structure-dominant and the other subgroups might also be due to body mass and age. In this subgroup, 86% were obese (BMI >30) which can increase Achilles tensile load to 6-10 times for every 1lb of excess weight.[1,40,107] From a general health viewpoint, this subgroup's patient-related factors raise concerns for comorbidities (e.g. metabolic disease, sarcopenia, menopause) which could negatively affect tendon healing and lengthen the recovery timeline.[2,124] The extent to which tendon structural changes are reversible in response to non-surgical and surgical treatment remains debated.[8,66] Evidence supports the possibility of recovery of mechanical properties associate with ageing.[102] Animal studies suggest that there is no decline in tendon synthesis capacity with aging, therefore it is possible that detectable changes in tendon structure may require greater length of time than previous studies have captured.[88] Because symptomatic recovery is achievable without functional recovery[136] and we considered Structure-dominant to have the greatest impairments in tendon health. Further research is warranted to determine if this subgroup's propensity for recurrent injury differs compared to the general population. Further study is needed to determine how Structure-dominant patients respond to exercise therapy and if tendon structural adaptations are achievable for these patients.

2.4.1 Limitations and Future Directions

It is possible for patients to fit into more than one subgroup in clinical practice and clinical expertise should not be superseded by any model. The clinical classification model was developed without cross validation using another sample. Therefore, further validation studies are needed. We acknowledge that additional subgroups might exist in youth and elite athletes or other unrepresented cohorts.

Although we tried to be as exhaustive as reasonably possible, we were limited to the variables included in both parent studies. Differences in sex distribution among subgroups was an interesting and unexpected result and merits future research. Future prospective studies are needed to determine how subgroups respond to standardized treatment and to investigate the effectiveness of patient-centered treatment based on tendon health deficits.

2.5 Conclusion

The purpose of this study was to identify unobserved heterogeneity among patients with Achilles tendinopathy. We conclude that Achilles tendinopathy subgroups exist among the general population that are distinct in their patient characteristics and clinical attributes.

Chapter 3

ACHILLES TENDINOPATHY SUBGROUPS REVEAL DISPARITIES IN RECOVERY OF TENDON HEALTH

3.1 Introduction

The persistent symptoms and loss of function[128] caused by Achilles tendinopathy impact quality of life and interferes with social roles and occupational productivity.[140] Achilles tendinopathy occurs equally in men and women, with highest prevalence between age 35-56.[65] Most cases are associated with overuse, with a lifetime incidence of 50% among runners, although 65% of cases in the general population are not sport-related.[65,74] The general health impairments and alterations in tendon structure associated with Achilles tendinopathy can be characterized on a spectrum, with severity ranging widely among patients.[99] Collectively, these impairments can be described across domains of tendon health,[133] consisting of symptoms, tendon structure, lower extremity function, psychological factors, and patient-related factors.

Recently, subgroups were identified within the general population with Achilles tendinopathy (insertional and midportion).[48] These subgroups demonstrated that the impact of Achilles tendinopathy can be statistically characterized by distinct clinical presentations of tendon health: Activity-Dominant patients (highly physically active young-adults with symptoms and minimal-to-no disturbance in all other tendon health domains); Psychosocial-Dominant patients (middle-aged females with severe symptoms, high kinesiophobia (fear of movement) and poor quality of life, with

minimal-to-no tendon damage); Structure-Dominant patients (older males with significant alterations in tendon structure and severe lower extremity function impairment). This cohort also demonstrated the diversity of the patient population by including various ages and activity levels, individuals with bilateral symptoms, comorbidities, and those who have taken statins, fluoroquinolones, or steroid drugs. The next step toward developing targeted treatments for the subgroups is to determine whether the subgroups recover differently over time if they are all provided the same treatment.

A prerequisite challenge to evaluating recovery among the subgroups is that 31% of the original cohort had insertional Achilles tendinopathy.[48] This becomes problematic because insertional and midportion Achilles tendinopathy have differing treatment considerations. Despite exercise therapy having the highest level of evidence for Achilles tendinopathy,[47,121,133,135,153] previous studies report divergent outcomes, with insertional patients having less favorable outcomes.[12,34]

Another challenge to evaluating recovery is the large assortment of available outcome measures used to assess treatment effectiveness for Achilles tendinopathy.[44,151] Defining prognosis and recovery have historically been heavily weighed by patient-reported outcome measures for symptoms and function, as measured by the Victorian Institute of Sport Assessment-Achilles (VISA-A),[58] but symptomatic recovery has been shown to not ensure functional recovery and this might explain the high recurrence rates.[23,136] More recently, alterations in tendon structure and mechanical properties have shown to moderate patient-reported symptoms and function.[46] This supports appraising each tendon health domain is vital to ensuring complete recovery. [23,85]

This study served to accomplish two crucial steps before treatment recommendations can be proposed: first to evaluate the reproducibility of the subgroups through replication in a sample of only midportion Achilles tendinopathy, and second to evaluate whether the subgroups recovered differently within the domains of tendon health when treated with the same treatment protocol.

3.2 Materials and Methods

3.2.1 Participants

To be included, participants needed be 18-65 years old, with a chief complaint of pain located within the midportion (2-6 cm above the calcaneus) of the Achilles tendon, have pain with palpation, and experience pain with loading.[83] Exclusion criteria included previous Achilles tendon rupture, or a diagnosis of only insertional Achilles tendinopathy or bursitis, or any other injury that limited the ability to perform exercises on the injured limb. Participants were recruited through our collaborators at First State Orthopaedics and Delaware Orthopaedic Specialists, University of Delaware physical therapy clinic, and social media advertisements. Baseline data from 61 participants with midportion Achilles tendinopathy were included from the previous cohort.[48]

3.2.2 Study Design

This was a prospective single cohort study conducted within a larger longitudinal study (Clinicaltrials.gov ID: NCT03523325) for participants with midportion Achilles tendinopathy. All participants received standardized treatment of exercise therapy from a licensed physical therapist and completed evaluations every 8 weeks for 24 weeks. Time points of baseline, 8-, 16-, and 24-weeks were used for

analysis. Data were collected between August 2018 and November 2021. This study received approval by the University of Delaware Institutional Review Board (ID:1063764-12)

3.2.3 Exercise Therapy Intervention

All participants received the same comprehensive treatment consisting of Achilles tendon-loading strengthening exercises, pain-guided activity modifications using the pain-monitoring model,[149] and use of training diaries.[133,135] The treatment protocol and criteria for progression are described in detail by Silbernagel et al in a randomized controlled trial.[135] We repeated our data collection every 8 weeks while treatment was ongoing.

All participants were treated by a licensed physical therapist who was trained to provide the treatment intervention. The frequency of supervised treatment visits and progression was determined at the discretion of the treating clinician. Participants were asked to complete training diaries daily, documenting their exercises performed, any physical activity, and symptoms/pain level (morning, highest and lowest). Training diaries were reviewed weekly to monitor and progress treatment. The pain-monitoring model was used to adjust the exercise load and physical activity guided by pain response.[135,149] Load progression comprised of increasing range of motion, repetitions, and adding external load (e.g., backpack, weight vest or weight machine).

3.2.4 Outcome Measures

All outcome measures along with their definition and recovery criterion are summarized in Table 3.1. Patient demographics and medical history were collected at baseline following ICON 2020 recommendations.[116] Consistent with the tendon health

model,[133] recovery at 24 weeks was operationally defined among the domains of tendon health including symptomatic, functional, structural, and psychosocial recovery at 24 weeks. Additionally, differences in recovery trajectories were assessed by determining when subgroups achieved a clinically meaningful change in primary and secondary outcome measures using previously established scores representing a minimal clinically important difference (MCID).

Symptomatic recovery was appraised by the Victorian Institute of Sport Assessment-Achilles (VISA-A)[117] and self-reported pain with hopping. Participants completed two trials of 25 single leg hops[132] (similar cadence to jumping rope) and to rate their Achilles tendon pain with hopping. Participants completed the VISA-A for both limbs. In cases where participants reported bilateral symptoms, the respective limb with a lower VISA-A score was used as the most symptomatic limb for data analysis. In addition the recovery definitions described in Table 3.1, trajectories of symptomatic recovery were also assessed by comparing when each subgroup achieved an MCID of 14 points on VISA-A by 16 weeks.[78]

Lower extremity function was assessed using a functional test battery which has been described in detail by Silbernagel et al.[132] The functional test battery consisted of the countermovement jump (CMJ), drop countermovement jump (Drop CMJ), and the heel-rise endurance test using a MuscleLab® measurement system (Ergotest Innovation, Porsgrunn, Norway).

We assessed Achilles tendon morphology using B-mode ultrasound imaging (linear transducer, frequency of 10 MHz and depth of 3.5 cm) on a LOGIQ e ultrasound scanner (General Electric Company, Boston, MA). All images were taken with the participant lying prone with their feet hanging off the edge of the table.

Measurements included degree of tendon thickening, Achilles tendon thickness and cross-sectional area (CSA) at the thickest portion, using established reliable procedures.[134,162] Tendon thickening was measured as a within-limb estimate of tendon structural alteration using a validated measure, by subtracting the thickness of healthy tendon from the thickest portion of the injured tendon (between Achilles osteotendinous junction and soleus musculotendinous junction).[24] We measured tendon mechanical properties using continuous shear wave elastography (cSWE). cSWE is a valid and stable method for monitoring changes in injured tendon.[25,26] cSWE allows for calculation of two tendon mechanical properties: shear modulus (i.e. stiffness) and viscosity (i.e. rate-dependent stiffness).[26] A SonixMDP Q+ ultrasound scanner (Ultrasonix, Vancouver, Canada) with a L14-5/38 probe, a 128-channel data acquisition unit, and an external actuator which generate shear waves was used to record cSWE data and the methods are described in detail by Cortes et al[26] and Corrigan et al.[25]

We assessed the psychosocial aspects of tendon health through the Foot and Ankle Outcomes Score Quality of Life Subscore (FAOS-QoL),[120] the Tampa Scale of Kinesiophobia (TSK-17),[9,39,80] select subscales from the Patient Reported Outcomes Information Systems-29 (PROMIS 29),[18] and the Global Rating of Change (GROC).[95]

Table 3.1: Summary of outcome measures

Outcome Variable	Evaluation Method	Definition/Description	Recovery Definition
Symptomatic Recovery	VISA-A questionnaire*	• Scored 0-100, lower scores indicate more pain and symptoms[117]	• MCID of 14 points by 16 weeks[78] • Score ≥ 90 points at 24 weeks [136]
	Pain with hopping	• Self-rated Achilles tendon pain with single-leg hopping (25 hops).[132] • Numerical pain rating scale from 0-10 (no pain-worst pain imaginable). • Represents tendon loading tolerance	• ≤ 2/10 pain with hopping • MCID of 2 points[35]
Functional Recovery	Functional test battery consisting of the heel-rise endurance test* and 2 jump tests	• The heel-rise test evaluates calf muscle endurance. Total work is expressed in joules (heel-rise height x repetitions x body mass). [132] • Jump tests include the countermovement jump (CMJ) and drop countermovement jump (Drop CMJ). • Average height measured in cm from three trials for each jump test.[132]	• Limb Symmetry Index (LSI) > 90% at 24 weeks. (most symptomatic limb/least symptomatic limb x100). [136]
Structural Recovery	Tendon morphology: Degree of tendon thickening*, Achilles tendon thickness, and cross-sectional area (CSA)	• Measured using B-mode ultrasound imaging • Tendon thickening in mm describes tendon structural abnormality (difference between healthy tendon thickness and the maximum thickness on the injured tendon). • 2mm thickening or more is pathologic.[75] • Maximum Achilles thickness measured in cm and CSA in cm^2.[134,162]	• LSI values 100 ±10% at 24 weeks for Achilles thickness, CSA, shear modulus, viscosity.
	Tendon mechanical properties: viscosity* and shear modulus	• Viscosity measured in Pa*s and Shear modulus measured in kPa are calculated using continuous Shear Wave Elastography (cSWE) [25,26]	

Table 3.1. continued

Psychosocial Recovery	FAOS-QoL*	• Scored 0-100, with 100 being highest quality of life. [120]	• Score ≥ 90 points at 24 weeks.
	TSK-17*	• Evaluates fear of movement scored 17-68. Higher scores mean more fear; scores ≥37 indicate high kinesiophobia. [9,39,80]	• Score < 37 points at 24 weeks
	PROMIS-29 Subscales	• PROMIS-29 Subscales including Social roles and Activities (PROMIS-SRA), Pain interference with functioning (PROMIS-PI), Anxiety (PROMIS-ANX). T-scores calculated for each, higher scores indicate greater presence of the concept being measured.[18]	• T-scores of 50 ±10 points
	GROC	• Represents change in overall status on a Likert scale ranging -5 - +5 ("very much worse" to "completely recovered"). [95]	• Reported descriptively

Abbreviations: VISA-A, Victorian Institute of Sport Assessment- Achilles; MCID, Minimally Clinically Important Change; TSK-17, Tampa Scale of Kinesiophobia-17 item; FAOS-QoL, Foot and Ankle Outcome Score- Quality of Life; PROMIS-29, Patient Reported Outcomes Measurement Information Systems-29; GROC, Global Rating of Change.
* Primary Outcome Measures

3.2.5 Statistical Analysis

The appropriate number of subgroups were identified using Mixture Modeling as described in Aim 1. We sought to confirm the subgroups described in the previous study by replicating the statistical analysis but only including individuals with midportion Achilles tendinopathy.[48] In the previous study, following subgroup enumeration, differences among subgroups were compared at baseline using one-way Analysis of Variance and χ^2 tests. In the current study, a Linear Mixed Model assessed the changes of the subgroups over time for the following outcomes: VISA-A, heel-rise work LSI, viscosity LSI, degree of tendon thickening, FAOS-QoL and TSK-17. Group and time (baseline, 8-, 16- and 24-weeks) and their interaction were

included as fixed effects. A compound symmetric covariance matrix was used to model the correlation among residuals. Mixed models garner estimates in the presence of missing data without listwise deletion, allowing for participants with incomplete data to be included.[71] To test the assumption of normality and to screen for outliers, residuals were tested using Shapiro-Wilk tests. If the effect of time or group was significant, pairwise comparisons were tested post-hoc using Bonferroni correction.

3.3 Results

One-hundred fourteen participants were included in this study. The best-fitting mixture model (Appendix C) identified four distinct subgroups: Activity-Dominant (n=34), Function-Dominant (n=38), Psychosocial-Dominant (n=27), and Structure-Dominant (n=15) (Figure 3.1).

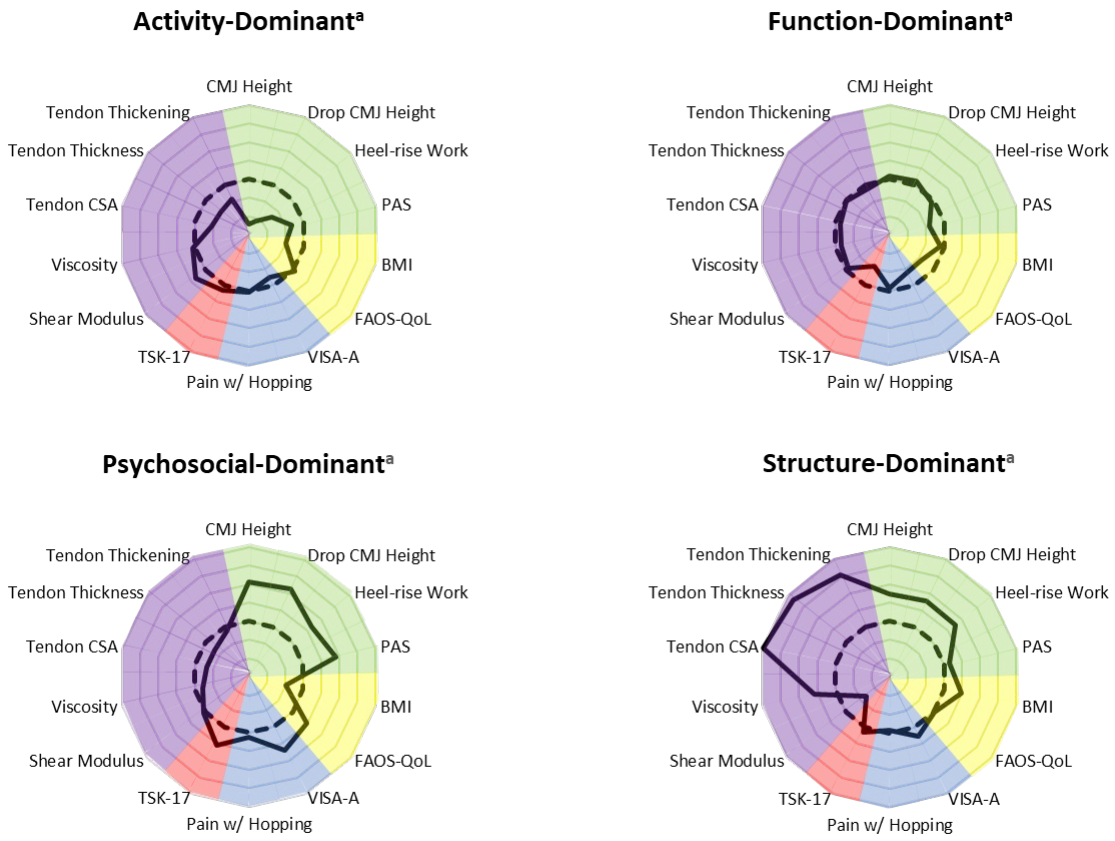


Figure 3.1: Comparison of subgroup baseline characteristics, separated by tendon health domain.

[a] Less distance from center represents less deficit or better performance. The dotted line represents the pooled sample mean.

3.3.1 Baseline Characteristics of Subgroups

Baseline patient characteristics are presented in Table 3.2**.** Activity-Dominant participants were youngest (37 years) compared to the Function-Dominant (50 years), Psychosocial-Dominant (50 years), and Structure-Dominant (58 years) and there was no significant difference in symptom duration among the subgroups. The majority of the Function-Dominant and Activity-Dominant were runners (68.4% and 67.6%,

respectively) compared to 29.6% in the Psychosocial-Dominant and zero runners in the Structure-Dominant subgroups. The Psychosocial-Dominant reported the lowest physical activity. The Function-Dominant consisted of the most participants with bilateral symptoms (52.6%) compared to Activity-Dominant (50%), Psychosocial-Dominant (33.3%), and Structure-Dominant (20%). The Psychosocial-Dominant and Structure-Dominant shared similar anthropometrics (BMI 31.5 and 31.6, respectively), compared to the Activity-Dominant (25.7) and Function-Dominant (28.0). All subgroups, except the Activity-Dominant, contained individuals with a previous history of Achilles tendinopathy (Function-Dominant: 21%; Psychosocial-Dominant: 14.8%; Structure-Dominant: 20%). Differences in marginal means of outcome measures are presented in Appendix D. Significant effects of group were observed among subgroups for all primary and secondary outcomes (Appendix D).

Table 3.2: Summary of subgroup demographics and baseline characteristics.

	Pooled Sample (n=114)	Activity Dominant (n=34, 30%)	Function Dominant (n=38, 33%)	Psychosocial Dominant (n=27, 24%)	Structure Dominant (n=15, 13%)	*P*-value
Age, years	47±12 (45-49)	37±10 (33-41)	50±10 (47-53)	50±11 (45-55)	58±6 (54-61)	**<.001**
Height, cm	171.7±8.6 (170.1-173.3)	174.3±8.2 (171.5-177.2)	170.4±8.5 (167.6-173.2)	167.3±6.4 (164.8-169.9)	176.9±9.0 (171.9-181.9)	**<.001**
Body mass, kg	84.4±19.2 (80.7-88.0)	78.1±11.2 (74.2-82.0)	81.8±24.0 (74.0-89.7)	88.1±16.3 (81.7-94.6)	98.7±17.5 (89.1-108.4)	**<.001**
BMI	28.6±6.1 (27.4-29.7)	25.7±3.2 (24.6-26.7)	28.0±7.3 (25.6-30.4)	31.6±6.0 (29.2-33.9)	31.5±4.9 (28.6-34.2)	**<.001**
Sex, F	57 (50%)	9 (26.5%)	20 (52.6%)	23 (85%)	5 (33%)	**<.001***
Symptom duration, months, median [IQR]	10.2 [29.1]	15.2 [42.4]	23.5 [31.1]	7.1 [31.6]	5.5 [16]	.800
Previous history of Achilles tendinopathy, n (%n)	20 (17.5%)	0	8 (21%)	4 (14.8%)	3 (20%)	.857*
Comorbidities, n (%n)						
Diabetes Mellitus	1 (.8%)	0	0	1 (3.7%)	0	.355*
Rheumatological	2 (1.8%)	0	1 (2.6%)	1 (3.7%)	0	.650*
Thyroid	9 (7.9%)	1 (2.9%)	3 (7.8%)	4 (14.8%)	1 (6.6%)	.398*
Medications, n (%n)						
FQN	7 (6.1%)	2 (5.8 %)	1 (2.6%)	3 (11.1%)	1 (6.6%)	.576*
Steroid	4 (3.5%)	0	1 (2.6%)	3 (11.1%)	0	.091*
Statins	11 (9.6%)	1 (2.9%)	3 (7.8%)	3 (11.1%)	4 (26.7%)	.074*
Identify as a runner, n (%n)	57 (50%)	23 (67.6%)	26 (68.4%)	8 (29.6%)	0	**<.001***
Bilateral symptoms, n (%n)	49 (43%)	17 (50%)	20 (52.6%)	9 (33.3%)	3 (20%)	.060*
Physical Activity Scale, median [IQR]	5 [2] (4-5)	5 [1] (5-5)	5 [1] (5-5)	3 [2] (3-4)	5 [2] (4-5)	**<.001**
VISA-A	51±18 (47-54)	55±15 (49-60)	58±15 (53-62)	38±17 (31-45)	46±20 (35-56)	**<.001**
Heel-rise work LSI	91.9 ±30.2%	102.6 ±18.0%	94.9 ±19.8%	85.0 ±39.5%	71.0 ±44.1	**.005**
Tendon thickening, mm	2.38 ±1.93	1.53 ±1.21	2.11 ±1.57	2.16 ±1.51	5.36 ±2.09	**<.001**

Table 3.2. Continued

Viscosity LSI	98.0 ±34.1%	92.3 ±23.2%	96.4 ±90.1%	112.7 ±49.9%	92.6 ±30.2%	**.158**
FAOS-QoL	40±18 (37-43)	39±18 (33-45)	47±15 (43-52)	31±16 (24-38)	40±22 (37-52)	**.004**
TSK-17	38±5 (37-39)	39±5 (37-41)	35±5 (34-37)	41±5 (39-43)	39±5 (36-42)	**<.001**

Abbreviations: FQN, Fluroquinolone; VISA-A, Victorian Institute of Sport Assessment-Achilles; TSK-17, Tampa Scale of Kinesiophobia; FAOS-QoL, Foot and Ankle Outcomes Score-Quality of Life.
Note: Data are presented as Mean ±SD (95% CI) unless otherwise specified. *Chi-square test.

3.3.2 Change Over Time Among Subgroups

Appendix D reports the marginal means for each time point. There was a significant effect of time and interaction effect (both $p < .001$) for tendon thickening (Figure 3.2D). No significant change in tendon thickening was observed between baseline and 24 weeks in the Activity-Dominant (1.53 ±1.21mm to 1.54 ±0.89mm, p=.320) or Function-Dominant (2.11 ±1.57mm to 2.22 ±1.66mm, p=.853), however the Psychosocial-Dominant had a change in tendon thickening (2.16 ±1.51mm to 2.28 ±1.47mm, p =.032) and the Structure-Dominant had a significant reduction (5.36 ±2.09mm to 3.75 ±1.94mm, p <.001). VISA-A, heel-rise work, FAOS-QoL, and TSK-17 (Figure 3.2A-F) each had a significant main effect of time and no significant interaction effect, indicating no statistical difference in change over time in response to exercise therapy among the subgroups. Marginal means for all secondary outcome measures are summarized in Appendix D. A summary of recovery status at 24 weeks for the subgroups is presented in Table 3.3.

All groups met or exceeded the MCID for VISA-A by 8-weeks except the Structure-Dominant, who did not reach the MCID until 16 weeks (Table 3.3). The intervention yielded different responses for heel-rise work for all subgroups. Heel-rise work improved 5.3 % for Activity-Dominant, 10.4% for Function-Dominant, 12.5% for Psychosocial-Dominant, and 15.8% for Structure-Dominant (Appendix D) between baseline and 24 weeks. Psychosocial recovery was similar across all subgroups (Figure 3.2E-F). By 16 weeks, all subgroups had scored below the TSK-17 cutoff score (37 points) for no kinesiophobia, however he Structure-Dominant reported elevated kinesiophobia at 24 weeks. At 24 weeks there were no differences in FAOS-QoL scores.

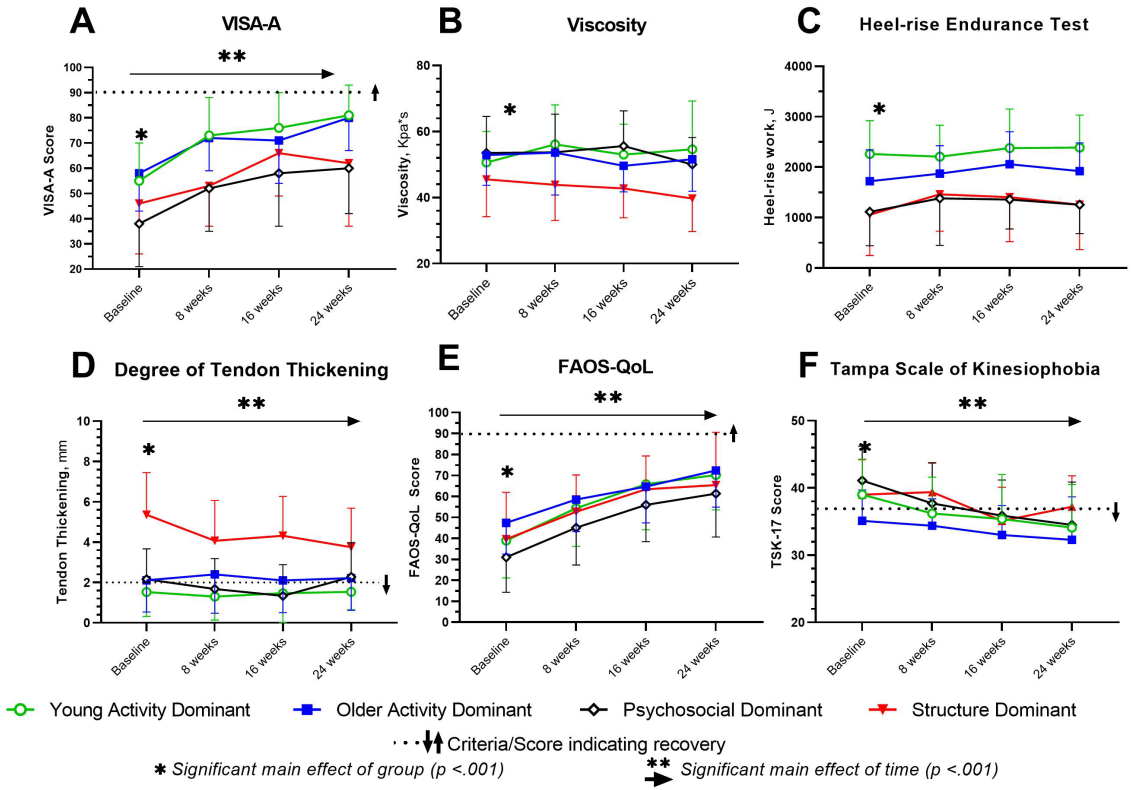


Figure 3.2: Recovery trajectories among subgroups primary outcome measures.

Abbreviations: VISA-A, Victorian Institute of Sport Assessment- Achilles; FAOS-QoL, Foot and Ankle Outcome Score- Quality of Life.

Table 3.3: Recovery Status Within the Domains of Tendon Health at 24-week follow-up.

	Pooled Sample	Activity Dominant	Function Dominant	Psychosocial Dominant	Structure Dominant
Symptomatic Recovery					
VISA-A score*	72 ±20 13/71 (18.3%)	81 ±18 4/17 (23.5%)	80 ±14 7/25 (28.0%)	60 ±18 1/16 (6.3%)	62 ±25 1/13 (7.7%)
Functional Recovery					
Heel-rise work LSI†	95.7 ±29.6% 34/58 (58.6%)	104.1 ±20.9% 9/15 (60%)	105 ±13.8% 13/19 (68.4%)	87.0 ±30.0% 7/11 (63.6%)	76.4 ±48.1 4/11 (36.4%)
CMJ height LSI†	99.9 ±32.9% 17/57 (29.8%)	104.5 ±21.3% 4/15 (26.7%)	105.8 ±25.6% 6/19 (31.6%)	86.4±49.6% 4/11 (36.4%)	99.1±40.1% 2/10 (20%)
Drop CMJ height LSI†	88.1 ±40.6% 18/54 (33.3%)	104.5 ±21.3% 7/15 (46.7%)	95.8 ±25.6% 8/19 (42.1%)	86.4 ±49.7% 0/9 (0%)	99.1 ±40.1% 2/9 (22.2%)
Structural Recovery					
Tendon Thickening (mm)	2.33 ±1.70	1.54 ±0.89	2.22 ±1.66	2.28 ±1.47	3.75 ±1.94
Viscosity LSI‡	97.8 ±22.7% 22/53 (41.5%)‡	99.4 ±25.6% 5/12 (41.7%)	99.4 ±25.6% 8/18 (44.4%)	102.4 ±25.9% 4/12 (33.3%)	87.1 ±18.3% 5/11 (45.5%)
Psychosocial Recovery					
TSK-17 score§	34.1 ±5.6	34.1 ±6.4	32.3 ±6.4	34.5 ±6.4	37.2 ±4.6
FAOS-QoL score‖	68.0 ±9.7	70.2 ±16.6	72.4 ±17.5	61.3 ±20.6	65.4 ±25.2

Abbreviations: CMJ, countermovement jump; TSK-17, Tampa Scale of Kinesiophobia; FAOS-QoL, Foot and Ankle Outcomes Score- Quality of Life.
All values presented as Mean±SD, *n* recovered/*n* (%). Recovery criteria: *VISA-A score >90 points. †LSI >90%, ‡LSI 100 ±10%, §TSK-17 score <37 points, ‖FAOS-QoL score >90 points.

3.4 Discussion

The objectives of this study were to evaluate the reproducibility of the Achilles tendinopathy subgroups through replication in a sample of only midportion Achilles tendinopathy and to evaluate whether the subgroups recovered differently when treated with the same treatment protocol. We successfully confirmed the existence of the previously established[48] Achilles tendinopathy subgroups in the present study and have discovered that these subgroups recover differently within the domains of tendon health following 24 weeks of standardized treatment.

3.4.1 Reproducibility of the Subgroups

We identified four subgroups (Activity-Dominant, Function-Dominant, Psychosocial-Dominant, Structure-Dominant) among patients diagnosed with midportion Achilles tendinopathy in this study that are akin to the subgroups established previously (Appendix E). The previous study[48] included 24.8% insertional, 68.9% midportion Achilles tendinopathy and 6.2% with both diagnoses, however distribution was similar among each subgroup. Therefore the exclusion of insertional Achilles tendinopathy in the previous did not impact subgroup membership. The defining characteristics of the former Activity-Dominant subgroup appears to have been divided into Activity-Dominant and Function Dominant. The most apparent difference between the Function-Dominant compared to the Activity-Dominant was increased participant age, higher BMI, and the presence of functional deficits not observed in the Activity-Dominant. This division also reflects changes in eligibility criterion and recruitment. The current study included younger, athletic participants, resulting in the final model to divide the former Activity Dominant subgroup. In the

present study, inclusion age was limited to 65 years compared to no age limit in the previous study. The patient characteristics that defined the Psychosocial-Dominant and Structure-Dominant were consistent with the previous study.[48] In the present study, the Psychosocial-Dominant reported the worst symptoms and quality of life, highest kinesiophobia, and lowest functional performance of all and were primarily obese (51.9%) and female (85%). The Structure-Dominant were again the minority subgroup, were the oldest, the majority were obese (66.7%) and male (77%) and were defined by having the largest alterations in tendon structure and mechanical properties.

We also evaluated the robustness of the clinical classification model proposed in the previous study[48] and its clinical utility for accurately subgrouping participants against the model in the present study. Using this clinical tool to classify participants, 73.5% of the Activity-Dominant and 65.8% of the Function-Dominant were classified to the former Activity-Dominant subgroup; 81.5% of the Psychosocial-Dominant and 53.3% of the Structure-Dominant were classified to their respective former subgroup. Although this model shows promising stability, future studies are required to investigate external validity prior to subgrouping patients with midportion Achilles tendinopathy in clinical practice.

3.4.2 Informing Precision Treatment Strategies for Subgroups

Identification of the subgroups revealed the longitudinal benefits and consequences to subgroup membership. The majority of participants in our study were classified into Activity- and Function-Dominant. Both shared minimal tendon health deficits with similar recovery trajectories for all tendon health domains. This further demonstrates how some patients may be more inclined to favorable outcomes than those with greater degrees of deficits in tendon health.[85,143] At 24 weeks, remaining

deficits were only observed in VISA-A and FAOS-QoL scores, therefore prescribing exercise therapy and activity modification for at least 24 weeks appears most appropriate for individuals classified as for Function-Dominant while Activity Dominant may require attention to their physical activity behaviors. It is possible that symptoms remained elevated for this subgroup at 24 weeks due to unchanged physical activity levels during the study, as reported by PAS scores. Future research would benefit from use of more objective measures of physical activity, such as step count, to determine whether excessive activity might explain whether these individuals require additional considerations to promote limiting their activities in order to prevent nullifying the benefits of this intervention. The remaining deficits of the Function-Dominant at 24 weeks (symptoms, function, and foot and ankle-related quality of life) prompt future research questions to explore whether this subgroup may further benefit from an adjunct intervention to address functional deficits.

The Psychosocial-Dominant demonstrated improvements in all measures of tendon health but responded less favorably to the intervention overall compared to the Activity- and Function-Dominant. Considering that activity modification using the pain-monitoring model might address fear of pain, it is plausible that this intervention alone may also be appropriate with more time, however the potential benefit of pain-neuroscience education warrants future study for this subgroup.

The Structure-Dominant demonstrated concerns to address beyond symptomatic recovery at 24 weeks, including altered tendon structure and mechanical properties, physical deconditioning, and fear of movement. Interestingly, tendon thickening reduced by 30% in the Structure-Dominant, while the other subgroups experienced minimal changes (Figure 3.2D). This finding evokes a debate in the

literature as to whether tendon structure can improve with treatment.[8,109] Differing proportions of patients who would be classified Structure Dominant may have been included in previous treatment studies, which might explain discrepancies in reporting change[109] or no change[8] in tendon thickness. The Structure-Dominant required an additional 8 weeks to achieve an MCID for VISA-A compared to the others and displayed continued deficits in all domains of tendon health at 24 weeks (Table 3.3). Comparing these subgroup's results to the pooled sample further demonstrates the value in recognizing subgroup membership. Particularly, interpreting the results of the pooled sample alone would potentially miss the divergent outcomes for symptoms and tendon structure observed in the Structure-Dominant. Based on these results, Structure-Dominant individuals did benefit from this intervention, however additional considerations to address tendon healing, such as shockwave therapy, may provide greater benefit along. Future research should also investigate whether individuals in this subgroup have metabolic considerations that could influence recovery.

Collectively, our results demonstrate the clinical validity of the subgroups and provides strong evidence that recovery differs among them. The next step towards precision rehabilitation for patients with Achilles tendinopathy is to improve the understanding of how each subgroup recovers within each domain so that recovery can be achieved for all. Based on our findings, development of individualized treatments for each subgroup is warranted. Our results also affirm that clinicians should advocate expected recovery timelines to require at least 6 months and should educate patients accordingly at initial evaluation irrespective of subgroup membership.

3.4.3 Limitations and Future Directions

Our future work will explore how the Activity-Dominant and Function-Dominant subgroups recover from the current treatment approach, however they may require more than 24 weeks of treatment. We will explore whether the Psychosocial-Dominant respond favorably to supplemental pain neuroscience education with exercise therapy. We will also explore whether the Structure-Dominant respond favorably to addressing factors early in the rehabilitation process related to improving tendon healing and physical activity, and weight management, while also extending recovery expectations beyond 24 weeks. Our interpretation of the results might have been different if the recovery criteria were evaluated differently. We identified heterogeneity among the participants and in their response to treatment, therefore it is reasonable that recovery definitions might need to be scaled appropriately for different subgroups. For example, the magnitude of change over time in VISA-A scores was similar among groups, but lower baseline scores might explain why Psychosocial-Dominant individuals did not meet the predefined criteria for symptomatic recovery, despite GROC scores suggesting that many achieved an acceptable state of their condition. Development of the VISA-A for non-athletic patients or scaling scores to omit questions related to sports participation may be necessary for future studies. If sports participation questions were omitted, a score of 80 points would indicative of symptomatic recovery for more sedentary individuals.[19] Similar scaling should be considered for all outcomes to improved recovery definitions and align closer with satisfactory levels of symptoms, function, and quality of life..

Previous studies have suggested that complete recovery from Achilles tendinopathy may require between 6 months to one year,[135] therefore our interpretation of the results may have been different if outcomes were evaluated at one

year. Our study was also limited to individuals 18-65 years old in the general population and therefore additional subgroups may exist that were underrepresented in this study such as adolescents and elite athletes. The generalizability of the subgroups could be limited due to several factors. The subgroups were formed from the selected 14 outcomes collected in Aim 1, which if interchanged for other outcomes, may yield different results. The cohort from Aims 1 and 2 represent the general population, however 61 participants were included in both studies (Appendix E), therefore replication in a new set of participants should be performed to validate the subgroups. Despite our efforts, those who do not have equitable access to healthcare may have been prevented from participation due to transportation means. Due the COVID-19 pandemic, we were unable to collect clinical measures for enrolled participants between May and July 2020 although participants did continue to complete patient reported outcome measures online.

3.5 Conclusion

The four subgroups with midportion Achilles tendinopathy were confirmed that are akin to the previously established subgroups. Following 24 weeks of exercise therapy and activity modification, recovery trajectories of symptoms, function, tendon structure, and psychosocial factors were different among the subgroups. These findings substantiate the important clinical implications of recognizing subgroup membership for patients at baseline. Members of the Function-Dominant had the highest proportion of achieving symptomatic recovery. Only the Psychosocial-Dominant and Structure-Dominant had remaining functional deficits at 24 weeks. Structural recovery may not be a concern for Activity-Dominant or Function-Dominant patients and more than 24 weeks of treatment may be required for the

Structure-Dominant. Psychosocial improvement was similar for all subgroups. Our results support that recovery considerations should be individually tailored for each subgroup.

Chapter 4

EXERCISE THERAPY AND ACTIVITY MODIFICATION FOR ADOLESCENTS WITH HEEL PAIN: A PILOT AND FEASIBILITY STUDY

4.1 Introduction

Adolescents with insidious posterior heel pain are commonly diagnosed with calcaneal apophysitis.[156] Calcaneal apophysitis is caused by repeated pull and strain at the developing cartilaginous growth plate where the Achilles tendon inserts.[16] The condition affects 3.7 per 1000 adolescents[156] with the highest prevalence in boys age 8-15 and girls 7-13.[98] In adults, the same symptoms are clinically diagnosed as Achilles tendinopathy, which is defined by Achilles tendon pain with loading and loss of function.[128] Little is known regarding involvement of Achilles tendon during adolescence and development of Achilles tendon pain or pathology in adolescents has been minimally studied.[15] As such, calcaneal apophysitis may be the most common diagnosis for heel pain in adolescents because evidence is lacking to support appreciation of Achilles tendon involvement or the tendon structural alterations (tendon thickening, altered mechanical properties) related to Achilles tendon overuse in adults.[33,139]

Calcaneal apophysitis is a clinical diagnosis which relies on the patient history of gradual onset of heel pain with activity and the patient‘s age (<18 years old) relative to skeletal maturity.[76,82] Radiograph are rarely used for confirming the diagnosis because it is considered uninformative due to the appearance of a separated apophyseal plate (sclerosis) seen in all skeletally immature children.[113] The main

distinction between a diagnosis of calcaneal apophysitis or Achilles tendon pain is therefore primarily based on pain location and patient age. Considering chronological age and biological development are not equivalent,[67] it is conceivable that Achilles tendon pathology masquerades as calcaneal apophysitis in some adolescents. The lack of description regarding pain location in studies may also contribute to the historic disregard of Achilles tendon involvement in adolescents.[97] Diagnostic ultrasound is frequently used for confirming tendon pathology in adults,[134,161] however few studies have used ultrasound imaging when evaluating adolescent patients with heel pain.[16,55]

Determining the presence of Achilles tendon pain and/or altered tendon structure in adolescents diagnosed with calcaneal apophysitis is a critical interest considering injury to either structure may prompt different treatment approaches. Irrespective of whether symptoms are from injury to either structure, a range of management recommendations are anecdotally supported for treating all adolescents with heel pain, from complete immobilization, which may inadvertently promote sedentary habits, to continued activity which risks progressing pathology and may nullify any therapeutic intervention.[60,82,110] Only one randomized clinical trial has been conducted using an active treatment, finding no difference in outcomes between shoe inserts, physical therapy, and no treatment ("wait and see"), although little description of the physical therapy intervention was provided.[157] Exercise therapy has the highest evidence for the treatment of Achilles tendinopathy in adults.[68,90,135] Furthermore, exercise therapy, when combined with pain-guided activity modification, is non-detrimental to recovery.[135] Although numerous research studies have examined the efficacy of exercise therapy for Achilles tendon pain in adults, this approach has never been evaluated for adolescents with heel pain.[6,47,122]

Since this active treatment approach has never been evaluated for adolescents, the purpose of this study was to determine the feasibility of treating adolescents with heel pain with 12 weeks of exercise therapy and pain-guided activity modification and to describe the feasibility of recruitment, enrollment, retention, and compliance for the intervention. We also explored whether outcome measures commonly used for Achilles tendinopathy could capture changes in symptoms severity, tendon structure and mechanical properties, muscle-tendon function, and psychosocial factors in response to an intervention consisting of exercise therapy, pain-guided activity modification, and load management. Additionally, we aimed to provide preliminary evidence whether Achilles tendon pain and/or altered tendon structure occurs in the adolescent population.

4.2 Materials and Methods

4.2.1 Study Design

This was a pilot and feasibility study of a single cohort of adolescents with posterior heel pain. This study was approved by the University of Delaware Institutional Review Board (ID:1652996-3) and is registered with clinicaltrials.gov (ID:1652996). Written parental permission and child assent was required for all participants before enrollment. One parent was also invited to consent to participate in the study by completing surveys. Participation was voluntary and participants could withdraw from the study at any time. Receiving other treatment for the injury was discouraged during the study.

Participants were evaluated at baseline and 4-, 8-, and 12-weeks (Figure 4.2). Data collection and supervised treatment occurred on the same day. Participants

completed daily exercises using a standardized treatment protocol (Appendix F) and were instructed to modify their activity as recommended using the pain-monitoring model.[135,149] Additionally, participants were asked to record all activities in a training diary.[43,135,137] Virtual treatment sessions occurred every two weeks following each in-person visit to review the progress between the in-person visits (Figure 4.2). Both in-person and virtual visits included patient education, supervised treatment and instruction, review of training diaries, and home exercise program prescription. If a parent consented to participate, they were asked to complete surveys at both in-person and virtual visits. All supervised treatments and evaluation sessions were completed at the University of Delaware Health Sciences Complex in Newark, DE. The same clinician obtained informed consent and assent, and conducted enrollment, evaluation, and treatment precluding blinding. A physician reviewed all ultrasound imaging and was blinded from participant data except for participant age. All data for this study were recorded and stored using Research Electronic Data Capture (REDCap) (Vanderbilt University, Nashville, TN).[49] The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 checklist was used to ensure our protocol's adherence to standardized reporting.[20]

4.2.2 Participants

Criteria for enrollment are shown in Table 4.1.

Table 4.1: Study inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
1. 7-17 years old 2. Insidious onset of posterior heel pain with running and jumping activities	1. Any other injury that limits the ability to participate in treatment and/or muscle-tendon function testing 2. Any lower extremity surgery or injection within with past 6 months 3. Any underlying predisposing heel pain (spina bifida, inflammatory spondyloarthropathy)

Potential participants were recruited through our collaborators at local orthopedic/podiatry offices, the University of Delaware Physical Therapy Clinic, as well as through local pediatricians, athletic trainers and nurses who work in middle schools and high schools using flyers. Social media advertisements were also used. An online screening questionnaire was accessible for any interested individuals to complete a preliminary eligibility assessment and request to be contacted. After completion of the screening questionnaire, a member of the research team contacted potential participants to clarify responses and schedule an in-person screening and obtain informed consent. Access to potential participants and results of eligibility screening, recruitment sources, and reasoning for ineligibility or declined participation were recorded in REDCap.[49]

Table 4.2. Schedule of enrollment, intervention, and assessments.

		STUDY PERIOD						
	Recruitment	**Enrollment**	**Post-enrollment**					**Close-Out**
Timepoint (week)		**0**	**2**	**4**	**6**	**8**	**10**	**12**
ENROLLMENT:								
Telephone screen	**X**							

Table 4.2. Continued.

In-person screening		**X**						
Informed consent		**X**						
INTERVENTION:								
Injury education		X						
Exercise prescription		X	X	X	X	X	X	
Activity modification instruction		X	X	X	X	X	X	
Training diary review			X	X	X	X	X	
Exercise adherence			X	X	X	X	X	
ASSESSMENTS:								
Demographics		X						
Medical and procedure history		X						
Medication		X						
Sports Participation History		X						
Physical Activity before injury		X						
VISA-A Questionnaire		X	X	X	X	X	X	X
Foot and Ankle Outcome Survey		X	X	X	X	X	X	X
PROMIS Pediatric Physical Activity		X	X	X	X	X	X	X
PROMIS Pediatric Pain Interference		X	X	X	X	X	X	X
PROMIS Pediatric Global Health		X	X	X	X	X	X	X
Fear of Pain Questionnaire- Child		X	X	X	X	X	X	X
Parent Surveys		X	X	X	X	X	X	X
Clinical Examination		X	X	X	X	X	X	X
Muscle-tendon function outcomes		X	X	X	X	X	X	X
Ultrasound imaging outcomes		X		X		X		X
Tendon mechanical properties outcomes		X		X		X		X
Global rating of change		X	X	X	X	X	X	X

Table 4.1. Continued.

Compliance with activity modification			X	X	X	X	X	X
Adverse events			X	X	X	X	X	X
Access to potential participants								X
Enrollment and recruitment rates								X
Safety								X

4.2.3 Clinical Evaluation

Following enrollment, participants completed a past medical history questionnaire related to their current symptoms and any previous lower extremity injuries. Self-reported location of symptoms with activity were documented. Height, weight, shoe size, and ankle dorsiflexion range of motion was recorded at each in-person visit. Ankle range of motion was measured in weight bearing positions with a goniometer in full knee extension and in knee flexion.

A clinical exam was conducted which included a discriminatory palpation exam and special tests. The purpose to the clinical exam was to document the frequency of participants with symptoms focal to the Achilles tendon (henceforth called "Achilles tendon pain"), the calcaneal apophyseal plate (henceforth called "heel pain"), or symptoms from both structures (henceforth called "concurrent injury"). Participants were asked to "rate pain on a scale from 0-10, with 0 being no pain and 10 being the worst pain imaginable" at the Achilles tendon osteotendinous insertion, the medial and lateral aspects of the retrocalcaneal bursa, and squeezing along the midportion of the Achilles tendon (2-6cm proximal to the calcaneus). Special tests included the Heel Squeeze test, Royal London Hospital test, and Arc Sign test.[56,114] The Heel Squeeze test is a pain provocation test in which the examiner squeezes the

medial and lateral aspects of the calcaneus, confirming calcaneal apophysitis.[114] Both the Royal London Hospital test and Arc Sign test are sensitive and specific for diagnosis of midportion Achilles tendinopathy.[56] Distinguishing between Achilles tendon pain, heel pain, or concurrent injury is summarized in Figure 4.1.

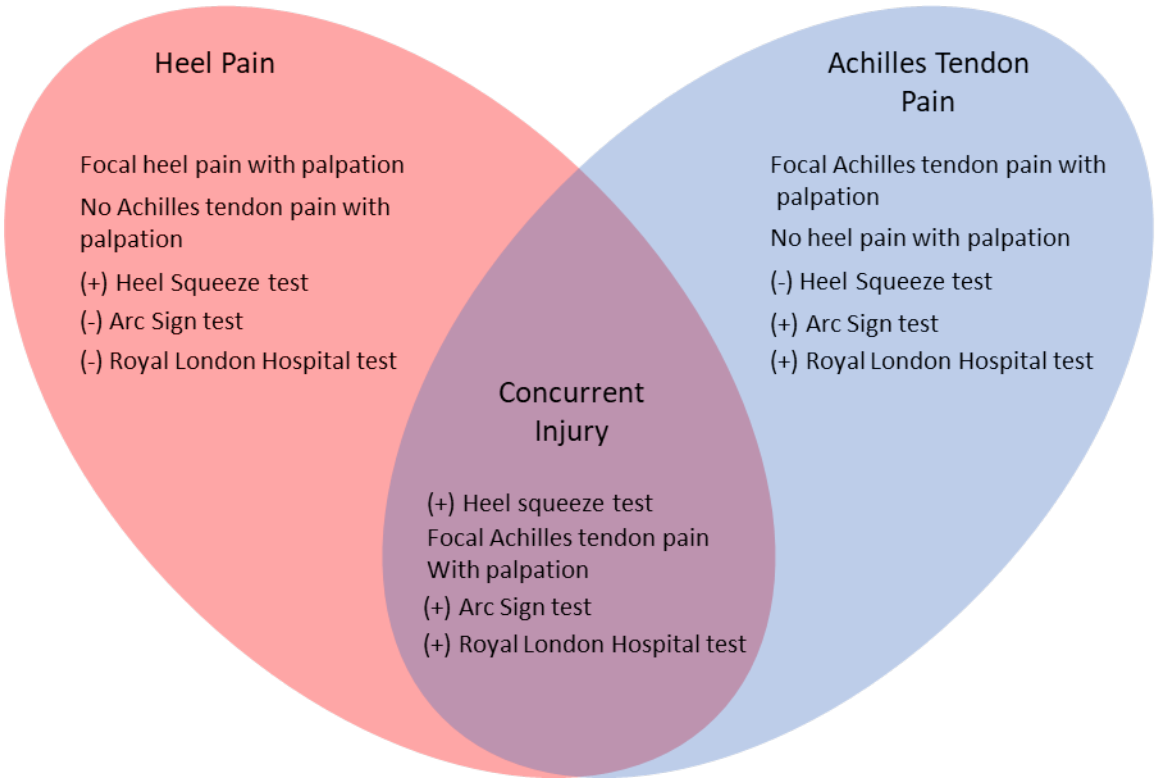


Figure 4.1. Criteria for clinical diagnosis of isolated heel pain, Achilles tendon pain, and concurrent injury.

4.2.4 Ultrasound Examination

B-mode ultrasound was used to record any abnormal findings. The presence or absence of hypoechoic regions in the Achilles tendon, tendon thickening (tendinosis), bursitis, intratendinous calcifications, and neovascularization (intratendinous or at the

growth plate) was recorded. When observable, the appearance of bony fragmentation and the status of the secondary ossification site of the calcaneal apophyseal growth plate (open or closed) was recorded. All findings were reviewed by a physician who holds a Registered in Musculoskeletal (RMSK) sonography certification.

4.2.4.1 Examination of Achilles Tendon Structure

Achilles tendon morphology was measured using the same methods described in Aim 1 and 2. Measurements included maximal Achilles tendon thickness, tendon CSA, and degree of tendon thickening. Additionally, Achilles CSA was measured at 10%, 20%, and 30% length proximal to the calcaneal insertion of the Achilles tendon to identify changes in tendon morphology to account for varying tendon shape during development.[14] Images were measured using Osirix MD imaging software (Pixmeo, Geneva, Switzerland). All images and measurements were reviewed by the same physician.

4.2.4.2 Achilles Tendon Mechanical Properties

Continuous Shear Wave Elastography (cSWE) was used to calculate the Achilles tendon mechanical properties (shear modulus and viscosity), as described in Aim 1. The region of interest was marked at 20% length mark along the free tendon, proximal to the osteotendinous junction. LSI values were calculated for shear modulus and viscosity, as described in Aim 2, to evaluate interlimb differences in tendon mechanical properties.

4.2.5 Patient Reported Outcome Measures

4.2.5.1 Symptom Severity

Symptom severity was measured using the VISA-A, as described in Aim 1, and the Foot and Ankle Outcome Score Symptom subscore (FAOS-Symptom). The FAOS-Symptom is scored from 0-100, where 100 indicates absence of any foot and ankle-related symptoms, stiffness, and pain over a 7-day period.[120] The Patient-Reported Outcomes Measurement Information System (PROMIS) Pediatric Pain Interference Scale measured the extent to which pain interferes with functioning.[147] All included PROMIS subscores use a T-score metric in which 50 is the mean of the relevant reference population and 10 is the standard deviation of that population. Reporting a higher score represents more of the concept being measured (more pain interference).[147] Parents were asked to complete the PROMIS Parent Proxy Pain Intensity and Pain Interference questionnaires as a secondary measure of symptom severity from the parent's perspective.[147]

4.2.5.2 Treatment Satisfaction and Self-reported Improvement

Self-reported treatment satisfaction was measured on a scale of 0-10, ranging from "not satisfied" to "very satisfied." Perceived improvement was measured using a 7-point Likert global rating of change (GROC) scale, ranging from "much worse" to "much improved". The GROC has been used in previous trials with adolescents.[115]

4.2.5.3 Fear-Avoidance Behaviors

The Fear of Pain Questionnaire- Child (FOPQ-C) was used to evaluate fear of pain and avoidance of activities due to pain has been validated for children with chronic pain with good reliability (test-retest: $r = 0.74$) and stability.[138] FOPQ-C

scores range from 0 to 96, with a higher score indicating more fear of pain and activity avoidance. Parents were asked to complete the FOPQ-Parent as a secondary measure of the parent's perspective on their child's fears related to pain and activity.

4.2.5.4 Quality of Life

The PROMIS Pediatric Global Health questionnaire was used to assess self-reported impact of injury on mental and physical health.[37] The FAOS Quality of life (FAOS-QoL) subscore was used to measure foot and ankle-related quality of life, scoring is as described in Aim 1 and 2.[120] Parents were asked to complete the PROMIS Parent Proxy Global Health questionnaire as a secondary measure of the parent's perspective on the participant's mental and physical health.[147]

4.2.5.5 Physical Activity

The PROMIS Pediatric Physical Activity Short Form questionnaire and the Parent Proxy form were used to assess self-reported capability of physical activities over a 7-day period.[147] Parents were asked to complete the PROMIS Parent Proxy Physical Activity form. This was used as a secondary measure of physical activity from the parent's perspective.

4.2.6 Muscle-Tendon Function

The CMJ, drop CMJ, and heel-rise endurance test were used to measure lower extremity function, as described in Aim 1.[132] The FAOS Sports and Recreation (FAOS-Sports) was used to subjectively assess the degree of difficulty with higher level functional activities (sports and recreational activities).[120] The FAOS-Sports is scored from 0-100, where 100 indicates no difficulties with higher level activities.

4.2.7 Feasibility Measures

4.2.7.1 Compliance, Retention, and Safety

Participants were given a training diary to document the exercises performed, other activities, and their symptoms/pain level daily. This training diary has successfully been used in our previous study[135] and clinical practice. Each day, participants were asked to rate their heel/Achilles pain in the morning and the lowest and highest pain experienced that day, record their completed treatment exercises, any other physical activity, and whether they participated in any running or jumping activities. Training diaries were reviewed at each in-person visit. Participants who performed the heel-rise exercises two times or more per week were considered compliant with the exercise treatment program. For each week, the frequency of days participants completed treatment exercises, days the training diary was filled out completely, days of running or jumping activity were performed, and days in compliance with activity modification and pain monitoring were recorded. Any missed follow-up visits, drop-outs, and adverse events were recorded. Any adverse event, occurring during a visit or reported outside of a visit, that potentially affected a participant's ability to participate in the study was recorded.

4.2.8 Treatment Protocol

All participants were treated with a standardized treatment protocol consisting of Achilles tendon-loading strengthening exercises, as described in Aim 2, for 12 weeks (Appendix F). Participants received standardized education and were prescribed activity modification recommendations using the pain-monitoring model, as described in Aim 2.[135] Additionally, participants were provided with an educational handout at baseline as an aid to educate them on appropriate progression to return to full

participation. Exercises were prescribed once per day and the volume and intensity was based on the participant's status using the pain-monitoring model. Progression consisted of increasing the number of repetitions, resistance, speed, and progression from standing on flat ground to standing on a step or incline (if tolerable) when performing the exercises. Participants were instructed to perform the exercises even if they experienced pain and were instructed to stop if the pain became intolerable. The pain-monitoring model was used to adjust the exercise load consistent with previous studies.[135,137] External loading (using a backpack, weighted vest, or weight machine) was incorporated when a participant could complete all bodyweight exercises with minor pain. In phase 2-3, participants were prescribed to complete weighted exercises 2-3 times per week and bodyweight exercises for all other days.

4.2.9 Patient Education

Education for the participant and parent was standardized to address the following topics: (1) understanding of their injury, (2) how to use the pain-monitoring model (Figure 4.3), (3) rationale for treatment, (4) how to use the treatment diary (5) proper exercise instruction, (6) questions from the patient or the parent. Participants received educational information both in-person and in written form (Appendix G.

4.2.10 Statistical Analysis

The results of Aim 3a. were reported descriptively as frequencies of participants having isolated Achilles tendon pain or heel pain, or concurrent injury. Presence or absence of Achilles tendinosis, visible calcaneal fragmentations, a visible open secondary ossification site, bursitis, neovascularization, and calcifications were reported descriptively. The results of Aim 3b were reported descriptively Feasibility

outcomes of recruitment and retention, compliance with activity modification, and patient satisfaction were reported descriptively. Linear Mixed Models were used to evaluate the main effect of time (treatment) on symptom severity, muscle-tendon function, and quality of life from baseline to 4- 8- and 12-weeks. A compound symmetric covariance matrix was used to model the correlation among residuals.

4.3 Results

4.3.1 Recruitment

Potential participants were actively recruited from August 2020 to March 2022. A total of 15 individuals consented to be contacted. Of these, three potential participants were deemed ineligible (Figure 4.2).

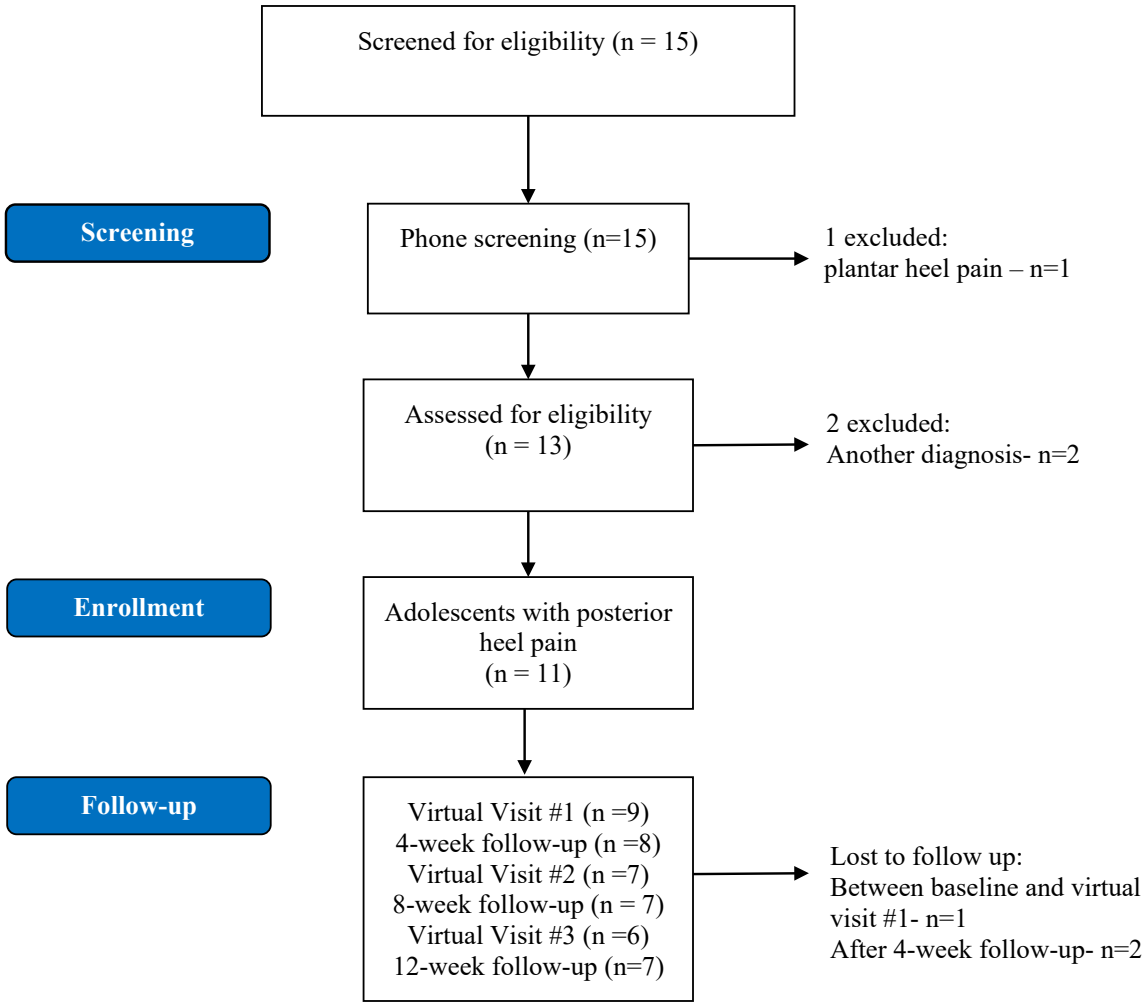


Figure 4.2: Summary of study enrollment.

4.3.2 Participants

Eleven individuals met the inclusion criteria and 10 parents agreed to enroll along with their child. Participant demographics are summarized in Table 4.3.

Table 4.3: Participant demographics and medical history.

Variable	**Mean ±SD (min-max)** ***n* proportion *(%)***
Age, years	11.3 ±2.6 (8-15)
Sex, F	4 (36.4%)
Height, cm	154.2 ±16.1 (128.9 -188.6)
Weight, kg	53.9 ±17.2 (28.6-80.0)
BMI	22.5 ±2.1 (16.7-32.3)
Ethnicity	
Hispanic/Latinx	2/11 (18.2%)
Not Hispanic/Latinx	7/11 (63.6%)
Prefer not to say	2/11 (18.2%)
Race Identity	
Native American/ American Indian/Alaska Native	2/11 (18.2%)
African American/Black	1/11 (9.1%)
Hispanic/Latinx	1/11 (9.1%)
Caucasian/White	6/11 (54.5%)
Prefer not to say	1/11 (9.1%)
Symptom duration*, months	8.4 ±17.4 (0.7- 68.0)
Bilateral symptoms, Y/N	7/11 (54%)
Annual sports participation	
0-3 months or 1 sport season	1/11 (9.1%)
3-6 months or 2 sport seasons	1/11 (9.1%)
6-9 months or 3 sports seasons	1/11 (9.1%)
> 9 months or year-round sports	8/11 (72.7%)
Previous history of heel pain, Y/N	1/11 (9.1)
Activity changes due to symptoms, Y/N	8/11 (72.7%)
Comorbidities	
Diabetes	0/11 (0%)
Thyroid	0/11 (0%)
Scoliosis	2/11 (18.2%)

*Symptom duration reported as Median±IQR.

4.3.3 Feasibility Outcomes

4.3.3.1 Treatment Compliance, Retention, and Safety

Compliance with treatment, and compliance with activity modification are summarized in Table 4.4. One participant was lost to follow-up after their baseline evaluation and failed to attend their first virtual visit. Another participant was lost to follow-up who missed their first virtual visit and did not attend their 4-week evaluation, however they did complete their 4-week questionnaires prior to cancelling their evaluation and did not reschedule. One participant was lost to follow-up after their 4-week evaluation stating the study commitment was too difficult to attend in-person appointments while navigating challenges related to the COVID-19 pandemic causing school closures. There were two adverse events during the course of the study. One participant sustained a lateral ankle sprain while participating in a baseball game and was prescribed complete rest by their primary care physician for 20 days and no additional treatment. This occurred between the 8-week evaluation and final virtual visit. This participant was able to complete the study. Another participant incurred a contusion on their foot (less symptomatic side) during a soccer game one week after enrollment in the study and was unable to fully bear weight for several days. Following pain resolution, they did continue with their exercises and no study timepoints were lost.

Table 4.4: Participants compliance with treatment and activity modification.

Outcome	**Mean (SD)** **Median (IQR)**
Proportion of participants compliant with treatment (%)	91.3 (28.4) 100 (0)
Days compliant with activity modification per week (days/week)	5.1 (2.6) 7.0 (4.2)
Days participating in running/jumping activities per week (days/week)	5.6 (0.9) 5.8 (1.0)

4.3.4 Summary of Ultrasound Examination Findings

Ultrasound examination findings are summarized in Figure 4.3. Upon clinical evaluation, four participants (all unilateral) presented with signs and symptoms of isolated Achilles tendon symptoms, one of which presented with concurrent symptoms on the contralateral limb; eight participants (4 bilateral) presented with signs and symptoms suggesting concurrent injury, and two participants (both bilateral) presented with isolated calcaneal apophysitis.

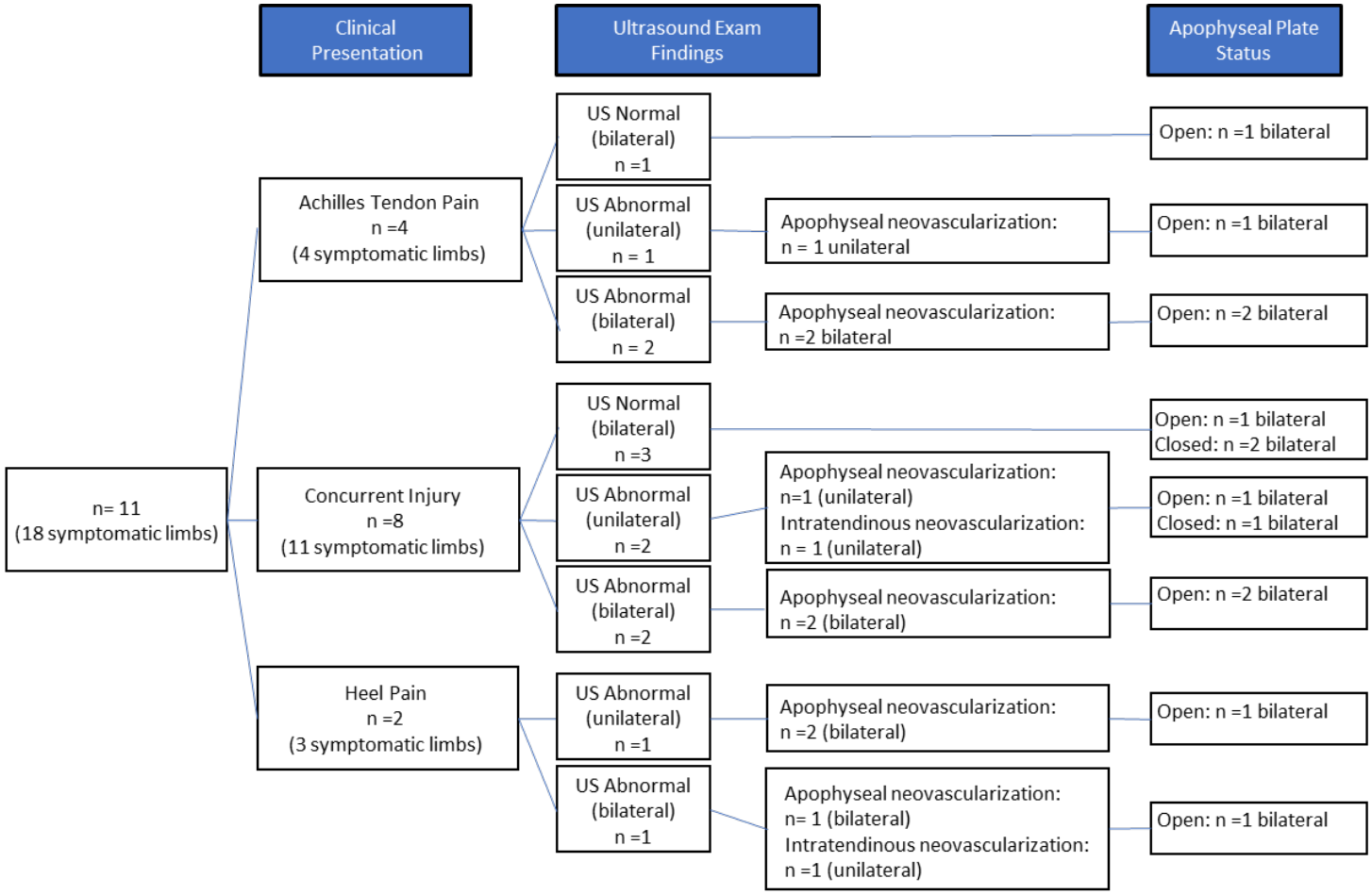


Figure 4.3: Summary of ultrasound examination findings.

4.3.5 Responsiveness to Clinical Outcomes

Marginal means and pairwise comparisons for all clinical outcomes are summarized in Table 4.5. There were significant improvements in observed in VISA-A scores, pain with hopping, heel-rise work, FAOS-QoL scores, FAOS-Sports scores, and FOPQ-Child scores between baseline and 12 weeks. No other statistically significant change over time was noted among clinical outcomes. GROC scores suggested the treatment improved the overall status of all participants at 12 weeks. All participants reported very high satisfaction with treatment at each time point (Figure 4.4).

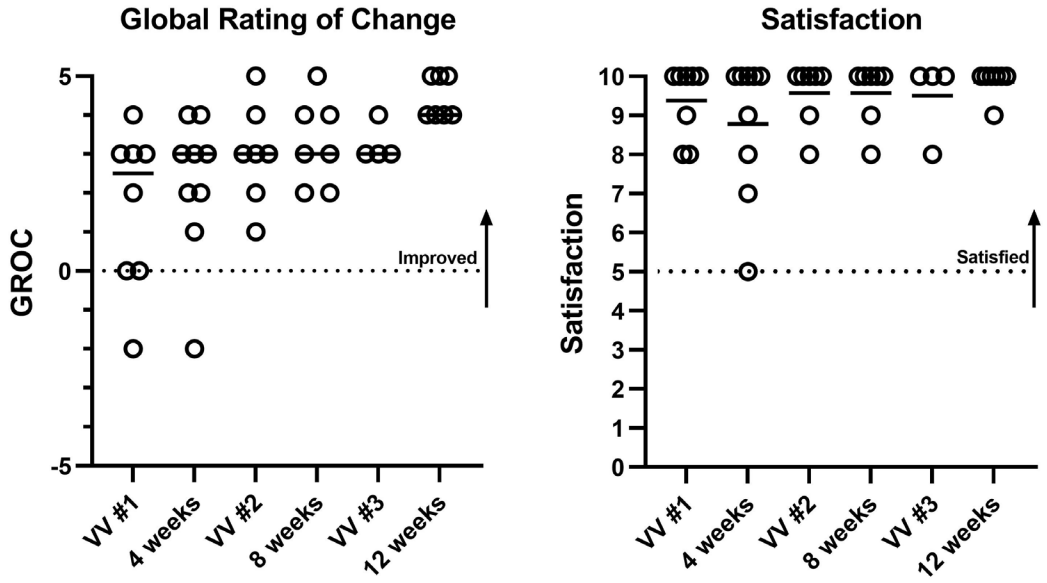


Figure 4.4. Summary of Global Rating of Change (GROC) scores and satisfaction with treatment.

Abbreviations: VV, virtual visit.

Table 4.5. Marginal means and pairwise comparisons of participant clinical outcomes

	Baseline	4 weeks[a]	8 weeks[b]	12 weeks[a]	p-values				
	M (SE)	M (SE)	M (SE)	M (SE)	Base to 4 weeks	Base to 8 weeks	4 to 8 weeks	8 to 12 weeks	Base to 12 weeks
VISA-A	63.0 (4.7)	65.2 (5.2)	80.1 (5.7)	81.6 (5.7)	1.00	.057	.150	1.00	**.031**
Palpation pain- Achilles Midportion, NPRS	4.6 (0.9)	2.7 (1.0)	2.0 (1.0)	0.1 (1.0)	NT	NT	NT	NT	NT
Palpation pain, Achilles Insertion, NPRS	2.6 (0.6)	1.4 (0.7)	0.9 (0.7)	0.1 (0.7)	NT	NT	NT	NT	NT
PROMIS- Peds- Pain Interference, t-score	53.6 (2.7)	52.2 (2.8.)	48.2 (2.9)	49.3 (2.9)	1.00	.089	.400	1.00	.291
Pain with Hopping, NPRS	2.3 (0.6)	1.1 (0.7)	1.2 (0.7)	0.0 (0.7)	.710	.996	1.00	.665	**.028**
FAOS- Symptoms	73.1 (4.1)	78.0 (4.5)	84.6 (5.0)	87.1 (5.0)	1.00	.285	1.00	1.00	.106
CMJ Height, cm	8.0 (1.0)	8.6 (1.1)	9.1 (1.1)	9.0 (1.1)	1.00	.774	1.00	1.00	1.00
Drop CMJ Height, cm	8.4 (1.1)	8.6 (1.2)	8.4 (1.2)	9.2 (1.2)	1.00	1.00	1.00	1.00	1.00
Heel-rise work, J	924.1 (251.8)	1188.4 (267.3)	1529.8 (267.3)	1461.5 (267.3)	.820	**.011**	.363	1.00	**.029**
Heel-rise work LSI	87.7 (10.2)	96.0 (11.1)	117.4 (11.1)	99.7 (11.1)	NT	NT	NT	NT	NT

Table 4.5 continued

PROMIS-Peds-GH, t-score	41.3 (2.4)	36.9 (2.7)	42.5 (3.0)	41.8 (3.0)	1.00	1.00	1.00	1.00	1.00
FAOS-QoL	56.3 (5.4)	56.9 (5.4)	66.9 (6.4)	77.6 (6.4)	1.00	.650	.838	.763	**.016**
FOPQ-Child	25.5 (4.3)	19.3 (5.8)	16.3 (4.7)	11.3 (4.7)	.423	.102	1.00	1.00	**.004**
FAOS- Sports	66.4 (5.5)	64.5 (6.1)	77.3 (6.8)	91.6 (6.8)	1.00	1.00	.880	.764	**.026**
PROMIS-Peds-Physical Activity	54.0 (2.4)	53.9 (2.6)	58.7 (3.0)	57.4 (3.0)	1.00	1.00	1.00	1.00	1.00
Achilles Tendon Thickness, cm	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)	NT	NT	NT	NT	NT
Degree of Tendon Thickening, mm	2.1 (0.1)	2.1 (0.1)	2.1 (0.1)	2.1 (0.1)	NT	NT	NT	NT	NT
Achilles tendon CSA (10% length), cm^2	0.7 (0.1)	0.6 (0.1)	0.7 (0.1)	0.7 (0.1)	NT	NT	NT	NT	NT
Achilles tendon CSA LSI (10% length)	100.5 (4.1)	96.5 (5.4)	96.5 (5.1)	99.5 (5.1)	NT	NT	NT	NT	NT
Achilles tendon CSA (20% length), cm^2	0.6 (0.1)	0.6 (0.1)	0.6 (0.1)	0.6 (0.1)	NT	NT	NT	NT	NT
Achilles tendon CSA LSI (20% length)	97.3 (3.6)	100.0 (4.3)	97.7 (4.3)	99.6 (4.3)	NT	NT	NT	NT	NT
Achilles tendon CSA	0.5 (0.1)	0.5 (0.1)	0.6 (0.1)	0.6 (0.1)	NT	NT	NT	NT	NT

(30% length), cm^2									
Achilles tendon CSA LSI (30% length)	99.3 (2.4)	95.8 (3.2)	100.3 (3.0)	99.6 (3.0)	NT	NT	NT	NT	NT
Shear Modulus, KPa	98.5 (5.0)	102.1 (5.6)	91.6 (6.1)	96.1 (5.6)	1.00	1.00	1.00	1.00	1.00
Shear Modulus LSI	98.0 (6.9)	89.3 (7.9)	100.5 (8.5)	104.2 (7.8)	1.00	1.00	1.00	1.00	.097
Viscosity, KPa***s**	52.8 (6.5)	53.8 (3.8)	53.9 (4.0)	51.9 (3.8)	1.00	1.00	1.00	1.00	1.00
Viscosity LSI	109.3 (7.0)	104.7 (8.0)	101.2 (8.6)	106.8 (8.0)	1.00	1.00	1.00	1.00	1.00

Abbreviations: NPRS, Numerical Pain Rating Scale; VISA-A, Victorian Institute of Sport Assessment-Achilles; PROMIS; Patient Reported Outcome Measurement Systems; FAOS, Foot and Ankle Outcomes Score; CMJ, Countermovement, QoL, Quality of Life; FOPQ, Fear of Pain Questionnaire; CSA, Cross-sectional area; LSI, Limb Symmetry Index.

[a] *n*=7 for all measures at 4 weeks and 12 weeks

[b] *n*=8 for all patient reported outcomes at 8 weeks. *n=7* for all clinical measures.

.

4.3.6 Parent Perceptions

There was a significant reduction in pain interference observed by parents based on PROMIS- pain interference parent proxy t-scores. There was no significant main effect of time for any other parent proxy survey. Marginal means and pairwise comparisons for parent proxy surveys are summarized in Table 4.6.

Table 4.6. Summary of marginal means and pairwise comparisons of parent proxy surveys

Outcome	Baseline	4 weeks	8 weeks	12 weeks	p-values				
	M (SE)	M (SE)	M (SE)	M (SE)	Base to 4 weeks	Base to 8 weeks	4 to 8 weeks	8 to 12 weeks	Base to 12 weeks
PROMIS-Pain Interference, Parent Proxy, t-score	55.7 (1.6)	54.6 (1.6)	51.8 (1.7)	50.8 (1.7)	1.00	.230	1.00	1.00	**.037**
PROMIS-Physical Activity, Parent Proxy, t-score	52.4 (2.2)	53.6 (2.3)	57.9 (2.6)	54.7 (2.6)	1.00	1.00	1.00	1.00	1.00
PROMIS-Global Health, Parent Proxy, t-score	46.8 (1.8)	48.4 (1.9)	49.8 (2.0)	50.3 (2.0)	1.00	1.00	1.00	1.00	1.00
FOPQ- Parent score	23.0 (4.3)	25.4 (4.4)	11.2 (4.8)	17.1 (4.8)	1.00	.285	.080	1.00	1.00

Abbreviations: PROMIS; Patient Reported Outcome Measurement Systems; FOPQ, Fear of Pain Questionnaire; Base, Baseline.

4.4 Discussion

The aims of this study were to establish preliminary evidence whether Achilles tendon pain and/or structural alterations exist in the adolescent population and to determine the feasibility of treating adolescents with heel pain with 12 weeks of exercise therapy and pain-guided activity modification and to report on recruitment, enrollment, retention, and compliance associated with the treatment intervention. Additionally, we aimed to evaluate whether outcome measures commonly used for Achilles tendinopathy could capture changes in symptoms severity, tendon structure and mechanical properties, muscle-tendon function, and psychosocial factors in response to the treatment intervention. Based on our findings, Achilles tendon pain was present in isolation and concurrently in adolescents with heel pain. We determined that exercise therapy and activity modification is appropriate intervention, and a future clinical trial is justified using similar methods.

A total of 15 potential participants were screened and 11 individuals were enrolled. Retention was challenging, with four participants lost to follow up by the first in-person follow-up visit. Among the remaining seven, only one virtual visit was missed. Compliance with treatment was excellent (91.3%), however compliance with activity modifications was more variable (about 5 days/ week compliant). A common theme was also noted among the enrolled participants portraying high fidelity for sports participation and physical activity. Noncompliance with activity modification was frequently associated with multiple day sport tournaments (reported in training diaries). As suggested by baseline PROMIS-Pediatric Physical Activity t-scores (Table 4.5), all participants were physically active and the majority (8/11) participated in sports year-round (Table 4.3).

4.4.1 Compliance, Recruitment, and Retention in the COVID-19 Pandemic

It's important to note that our results were influenced by the COVID-19 pandemic. The rate of recruitment was sporadic throughout the recruitment window. A summary of recruitment by month is depicted in Appendix H. We began recruiting in the same month that schools reopened during the COVID-19 pandemic. Eight months passed before the first potential participants contacted the study team in March 2021. Recruitment spiked between March and June 2021, which was consistent with the timing of one available COVID-19 vaccine becoming available and FDA approved for children aged 12 and older (May 2021). Our most successful recruitment strategy (in order) was flyers (n=7) around the community, followed by word-of-mouth referral (n=4), referral from local healthcare providers (n=2), social media (n=1), and search engine advertising (n=1). To determine the effectiveness of the treatment intervention in a future clinical trial, we would need to recruit a minimum of 48 participants to be adequately powered to detect a minimally clinically important difference between 6.5 and 14 points[78,94] (based on observed mean change in VISA-A (18.6 points), with a medium effect size (partial η^2 =0.06), alpha set to 0.05 and 80% power). Based on our recruitment rate from the first recruit to the following 12 months, it would take approximately 2 years to recruit all participants. Recruitment rates are expected to be increased in a future clinical trial. In the state of Delaware, alone, there are 84 middle schools and 26 high-schools serving over 28,500 youth athletes.[103] According to the Delaware Department of Public Health, 64.2% of all state residents age 12-17 have received at least one dose of the COVID-19 vaccine as of March 2022.[101]

4.4.2 Barriers and Facilitators to Study Implementation

Although the reported incidence rate of calcaneal apophysitis[156] is larger than Achilles tendinopathy,[65] it is probable that the younger population are more reluctant to seek medical attention or report their symptoms to their parent until symptoms are severe enough to cause limping. This is supported by reports of pressures from parents, coaches, and potential college recruitment attributing to 42% of adolescent athletes stating they have hidden or minimized injury during a game so they can continue playing sports.[123]

Another challenge to study implementation was the study design requiring completion of home exercises. The later stages of the treatment protocol required external loads for the exercises ranging from 35lb to over 100lbs. The youngest participant in the study (8 years old) could perform 55lb seated calf raises by week 4. Therefore, considerations for access to weight training equipment will be important for planning a future clinical trial.

4.4.3 Responsiveness to Clinical Outcomes

It was of interest to determine whether the proposed outcome measures were sensitive to change over time during the intervention to ensure all aspects of injury are appraised in a future nonrandomized clinical trial. Significant differences were observed between baseline and 12 weeks for VISA-A scores and pain with hopping, heel-rise work, FAOS-Sport and FAOS-QoL subscores, FOPQ-Child and FOPQ-Parent scores, and PROMIS-Pain Interference Parent Proxy t-scores, indicating an appreciable improvement in symptoms, muscle-tendon function, foot and ankle-related capability and quality of life, and fear of pain. Jump measures (CMJ and Drop CMJ) appeared to be uninformative for measuring change, although baseline

evaluation may be useful for assessing interlimb deficits. The PROMIS subscores (global health and physical activity) may also be uninformative in a future study, considering t-scores at all time points suggested normal levels of each construct compared to the reference population. All participants were highly satisfied with the intervention and using the GROC was useful for maintaining treatment alliance with participants. There were no interlimb differences found in any measures of tendon structure or mechanical properties. The small sample size may have influenced these findings. The lack change in tendon structure and mechanical properties over time was expected, as these measures are reported to require several months to observe change in adults with Achilles tendinopathy.[23]

4.4.4 Achilles Tendon Involvement in Adolescents

While this study was not adequately powered to form robust conclusions, nine of the 11 participants presented at baseline with Achilles tendon pain and symptoms consistent with presentation of Achilles tendinopathy in adults (either isolated or concurrent with heel pain). Among the participants with Achilles tendon pain, intratendinous neovascularization was found for one participant. There were no other structural alterations observed via ultrasound exam. This provides preliminary evidence to support Achilles tendon involvement being a part of differential diagnosis in patients younger than 18 years old. Our findings support the need for further study to determine prevalence of Achilles tendon pain in the adolescent population.

4.4.5 Future Research

A future clinical trial is justified based on the results of this pilot and feasibility study. Future work should investigate whether individuals with isolated calcaneal

apophysitis respond differently to this treatment intervention compared to those with Achilles tendon involvement to determine if both injuries respond similarly to treatment or differing treatment approaches are warranted. Removal of surveys at virtual visits should be considered for a future trial. The purpose of the additional surveys was to evaluate the earliest meaningful change in patient-reported outcome measures. However, no appreciable change was observed by between in-person and virtual visits, and this may also reduce the potential for survey fatigue. The parent proxy surveys may be unnecessary in a future clinical trial, as scores were similar between the child and parent.

4.4.6 Limitations

The feasibility outcomes of this study were impacted by the COVID-19 pandemic. Recruitment began in August 2020, at which time all states within reasonable driving distance to our research facilities were declared in a state of emergency with stay-at-home orders. We observed the highest interest in our study shortly after the COVID-19 vaccine began rollout in the state of Delaware. Due to the small sample size, the observed responsiveness for clinical measures should be interpreted with caution. The same evaluator carried out all treatment sessions, which may have introduced bias for data collections. Since this was a pilot and feasibility study, it was not possible to keep the evaluator blinded. Another limitation was the use of paper training diaries. For any participant who ceased all communication, we were unable to access training diaries beyond their last visit. From an implementation standpoint, adolescent participants may also be more compliant with completing training diaries if they were app-based and would allow the researcher to set reminders. Attention to participant retention may benefit a future trial. Specifically for

parents with multiple children in sports and those with time conflicts with school and work schedules. Future work would also benefit from collaboration with experts in pediatric research to ensure the patient education and interpretation of pain are appropriate for the adolescent population.

4.5 Conclusion

Exercise therapy and activity modification appears to be an appropriate intervention for Adolescents with heel pain. Although the proposed outcome measures appear appropriate, a randomized controlled trial with a larger sample is needed to assess the effectiveness of this intervention. These preliminary findings suggest that Achilles tendon involvement is present in adolescents with heel pain.

Chapter 5

CONCLUSION

Achilles tendinopathy causes pain and symptoms affecting the ability to be physically active.[128] This impacts quality of life and interferes with social roles and occupational productivity.[140] Achilles tendinopathy occurs equally in men and women[65] with unknown prevalence in adolescents.[82] Most cases are associated with overuse, with a lifetime incidence of 50% among runners and 5.9% in the general population[74] and 65% of cases in the general population having no association with sports participation.[65] The general health impairments and alterations in tendon structure associated with Achilles tendinopathy can be characterized on a spectrum, with severity ranging widely among patients.[99] Collectively, these impairments associated with Achilles tendinopathy can be described across domains of tendon health,[133] consisting of symptoms, lower extremity function, tendon structure and mechanical properties, psychological factors, and patient-related factors. Exercise therapy has the highest level of evidence for treatment of Achilles tendinopathy.[85,124,137] However many do not recover[7,34,86,90] and symptom recurrence is common (27%).[41] Therefore, the objectives of this dissertation were to identify patient subgroups among the general population diagnosed with Achilles tendinopathy, to determine whether the subgroups respond differently to exercise therapy, and to determine whether exercise therapy is a feasible intervention for the adolescent population with heel pain. The impact of this work can inform new precision treatment strategies to improve outcomes for all patients who suffer from Achilles tendon pain.

5.1 Aim 1: Identify and categorize latent subgroups among patients with Achilles tendinopathy and compare their tendon health measures.

The purpose of this aim was to identify latent subgroups among the general population diagnosed with Achilles tendinopathy and to compare respective clinical findings and patient characteristics. A holistic understanding of how Achilles tendinopathy differentially affects patients and their tendon health is lacking and limits the ability to develop precision treatment strategies. Using mixture modeling, a person-centered statistical method that recovers hidden groups from observed data, may be a first step toward identifying subgroups among individuals with Achilles tendinopathy.[106] This approach is most appropriate for categorizing patients when the subgroups are not known *a priori* and people sharing the same diagnosis are widely diverse. Specifically, using the tendon health model to identify subgroups among patients with Achilles tendinopathy is a biopsychosocial approach to identify what patient characteristics and clinical findings distinguish patients from one another. In order to understand if there are ways to improve treatment outcomes and ensure complete recovery, it is important to understand if all patients diagnosed with Achilles tendinopathy are affected the same or are there subgroups that might need additional or modified treatment strategies.

5.1.1 Hypothesis 1.1: More than one subgroup exists among patients diagnosed with Achilles tendinopathy.

This hypothesis was supported. We identified three latent subgroups, Activity-dominant, Psychosocial-dominant, and Structure-dominant within the general population of patients with Achilles tendinopathy.

5.1.2 Hypothesis 1.2: Significant differences will be found among subgroups' measures of tendon health.

This hypothesis was supported. Activity-dominant demonstrated minimal impairments in tendon health. Psychosocial-dominant demonstrated minimal tendon structure and mechanical properties alterations, similar to Activity-dominant, yet this subgroup performed significantly worse on the functional test battery and had the most severe psychological factors. Structure-dominant had the greatest degree of tendon alteration demonstrated by measures of tendon thickness, CSA, and decreased tendon viscosity.

5.2 Aim 2: Compare recovery trajectories of latent subgroups for symptoms, tendon structure and mechanical properties, lower extremity function, psychological factors and patient-related factors following 24 weeks of exercise therapy and activity modification.

The purpose of this study was to determine how Achilles tendinopathy subgroups respond to standardized treatment in all aspects of tendon health over 24 weeks by comparing recovery trajectories for symptoms, function, tendon structure, and psychosocial factors. Exercise therapy is considered the current gold standard for treatment of Achilles tendinopathy,[90] however 10-45% of patients do not respond favorably and many continue to experience pain and impaired function for many months or years.[85,124,137] This variable response demonstrates an outstanding need to develop a patient-centered approach to management of Achilles tendinopathy. One key barrier to improved management is that recovery remains poorly defined for Achilles tendinopathy.[131] Symptom resolution, return to participation, or normalization of tendon structure are all important, but individually may not ensure complete recovery for all patients.[46,136] Considering symptomatic recovery does not ensure full functional recovery,[136] each domain of tendon health may require differing amounts of

time and possibly different treatment approaches to ensure complete recovery of tendon health. Improved treatment outcomes can be achieved if all aspects of injury affecting the patient are identified and addressed. Identifying how latent subgroups among patients respond to exercise therapy could elucidate who are the best candidates for the current treatment protocol, and who might need modified or additional interventions.

5.2.1 Hypothesis 2.1.: Subgroups will differ in their change over time in VISA-A scores.

This hypothesis was supported. The Structure-Dominant achieved the VISA-A MCID at 16-week follow up, while all other subgroups achieved the MCID at 8-week follow-up. At 24 weeks, the Function-Dominant had the highest proportion of individuals to achieve symptomatic recovery.

5.2.2 Hypothesis 2.2.: Subgroups will differ in their change over time in heel-rise work.

This hypothesis was partially supported. There was no significant effect of time for heel-rise work. The Activity- and Function-Dominant subgroups demonstrated no deficits in heel-rise work at baseline and no significant change over 24 weeks. Psychosocial-Dominant and Structure-Dominant individuals improved 12.5% and 15.8% over 24 weeks, respectively.

5.2.3 Hypothesis 2.3.: Subgroups will differ in their change over time in viscosity.

This hypothesis was not supported. There was a significant effect of group, indicating differences in baseline viscosity measures. There was no significant effect of time for viscosity.

5.2.4 Hypothesis 2.4: Subgroups will differ in their change over time in TSK-17 scores.

This hypothesis was partially supported. There was a significant effect of group and time, indicating significant differences in baseline TSK-17 scores and similar improvement over time. At 24 weeks, Structural-dominant patients reported elevated kinesiophobia compared to the other subgroups.

5.2.5 Hypothesis 2.5: Subgroups will differ in their change over time in FAOS-QoL scores.

This hypothesis was partially supported. There was a significant effect of group and time, indicating different baseline FAOS-QoL scores and similar improvement over time among the subgroups.

5.2.6 Hypothesis 2.6.: Likelihood of recovery will differ among subgroups at 24 weeks.

This hypothesis was partially supported. Function-Dominant individuals had the highest proportion (28%) to achieve symptomatic recovery. Structure-Dominant individuals had the smallest proportion (36.4%) to achieve functional recovery and were the only subgroup to not achieve structural recovery. All subgroups achieved psychosocial recovery. No subgroup achieved complete recovery of tendon health at 24 weeks.

5.3 Aim 3: Evaluate whether Achilles tendon injury occurs in adolescents with heel pain (Aim 3a) and to evaluate the feasibility of treating adolescents with heel pain with 12 weeks of exercise therapy and activity modification (Aim 3b).

The purpose of this study was to determine the feasibility of recruitment, enrollment, retention, and compliance for prescribing exercise therapy and pain-guided activity modification over 12 weeks for adolescents with heel pain. We

explored whether outcome measures commonly used for Achilles tendinopathy were able to capture changes in symptoms severity, tendon structure and mechanical properties, muscle-tendon function, and quality of life in response to an intervention consisting of exercise therapy, pain-guided activity modification, and load management. Additionally, we provided preliminary evidence whether Achilles tendon pain or pathology exists in the adolescent population. Calcaneal apophysitis is a clinical diagnosis which relies on the patient history of gradual onset of heel pain with activity and the patient‘s age (<18 years old).[76,82] In adults age 18 and older, the same injury mechanism is clinically diagnosed as Achilles tendinopathy which is defined by Achilles tendon pain with loading and loss of function.[128] Achilles tendon involvement is understudied in the adolescent population and is therefore rarely considered until adulthood.[33,139] Determining the presence of Achilles tendon pain and/or altered tendon structure in adolescents diagnosed with calcaneal apophysitis is a critical concern since this affects prognosis and may warrant different treatment approaches. Although numerous research studies have examined treatment efficacy of Achilles tendon pain in adults, only one randomized controlled trial has been published in the past decade on treatment for heel pain in the adolescent population.[157]

5.3.1 Hypothesis 3a.1.: Achilles tendon pain and pathology occurs in adolescents with heel pain.

This hypothesis was partially supported. Among the 11 participants enrolled, nine (81.8%) presented with isolated (4 participants) or concurrent Achilles tendon pain. Among those with Achilles tendon or concurrent injury, one participant presented with neovascularization at the Achilles tendon insertion. No participants

presented with tendinosis, hypoechoic presentation, or appreciable increase in tendon thickness or CSA compared to the uninvolved limb upon ultrasound examination.

5.3.2 Hypothesis 3a.2.: Alterations in Achilles tendon mechanical properties will be observed in adolescents with heel pain

This hypothesis was not supported. LSI values indicated normal symmetry between limbs for shear modulus (98.0 (6.9 KPa)) and viscosity (109.3 (7.0 KPa*s)).

5.3.3 Hypothesis 3b.1.: Examine access to potential participants, percentage of participants meeting the inclusion criteria, and monthly recruitment and retention rates.

Over the span of the recruitment period, 15 potential participants requested to be enrolled. Of these 15 potential participants, 11 met the eligibility criteria and were enrolled. Among the 11 enrolled, seven participants completed the study. The highest monthly recruitment rate was 4 participants per month.

5.3.4 Hypothesis 3b.2.: Examine the compliance and satisfaction of participants with treatment, activity modification, and training diaries.

Compliance with treatment was high, with 91.3% of participants considered compliant. On average, participants were compliant with activity modification 5.6 days per week. Treatment satisfaction was excellent at all time points.

5.3.5 Hypothesis 3b.3.: Symptom severity, lower extremity function, and quality of life will improve significantly.

Due to limitations in sample size, effect of time was analyzed for the cohort to determine whether any change occurred in the selected outcomes. VISA-A scores significantly improved between baseline and 12 weeks (mean difference =18.6 points). Lower extremity function improved for Heel-rise work improved between baseline

and 8 weeks (mean difference 537.4 J). No change was observed in CMJ and Drop CMJ jump heights. Foot and ankle-related quality of life significantly improved as measured by the FAOS-QoL between baseline and 12 weeks

5.4 Limitations

In Aims 1 and 2, the variables selected to represent tendon health were limited to those selected for the studies a priori, therefore it is important to note that use of different outcome measures representing tendon health might have produced different results regarding subgroup distribution. Furthermore, there may be other domains of tendon health that have not yet been explored, such as metabolic factors. Finally, further improvements may be observed among the individuals in Aim 2 because the participants are a part of a larger clinical trial evaluating recovery over one year. The primary limitation of Aim 3 work was the small sample size. Recruitment and retention were negatively affected by the COVID-19 pandemic. As a result, it is expected that recruitment will be higher in a future clinical trial.

5.5 Conclusions and Clinical Significance

Recovery from Achilles tendinopathy has been impeded by a lack of appreciation for the various biopsychosocial components of the disease. The condition does not affect all individuals equally, and recovery has been historically defined by pain and symptoms.[131] The first aim of this dissertation demonstrated that there are distinct subgroups among patients diagnosed with Achilles tendinopathy. These subgroups differ in their degree of clinical deficits as well as in sex distribution, body anthropometrics, and psychosocial factors. In the second aim, the subgroups did not experience the same recovery trajectories in terms of symptoms, function, tendon

structure, and psychosocial factors. Together Aims 1 and 2 affirm there is a critical need to develop precision treatment strategies based on subgroup membership. Finally, the third aim investigated a potentially overlooked subgroup in the adolescent population. This study revealed that there are adolescents who develop Achille tendon pain and symptoms consistent with Achilles tendinopathy in the absence of signs and symptoms of calcaneal apophysitis. Furthermore, this study built a practical framework for a successful future clinical trial to investigate the effects of exercise therapy and activity modification for adolescents with Achilles tendon and/or heel pain. This may revolutionize active treatment for adolescents with heel pain, with the potential to mitigate any potential long-term consequence of injury during the years of growth and development.

5.6 Future Directions

The findings from this dissertation have motivated the next steps in precision treatment strategies for patients with Achilles tendinopathy across the lifespan. The discovery of the patient subgroups and the associated differences in recovery have revealed the need for additional or adjunctive treatment for some patient groups who would otherwise not respond to standard treatment alone. To determine how to ensure complete and lasting recovery for all individuals, precision treatment strategies should be designed and tested against the standard of care for the subgroups. The results of Aim 3 justify conducting a future clinical trial using similar methods to determine the effectiveness of exercise therapy and activity modification for adolescents. This has potential to shift clinical practice in the treatment of adolescents with heel pain. More broadly, the results of Aim 3 suggest questioning the lower age limit for clinical trials to include individuals under 18 years old with Achilles tendon pain.

REFERENCES

1. Abate M, Oliva F, Schiavone C, Salini V. Achilles tendinopathy in amateur runners: Role of adiposity (Tendinopathies and obesity). *Muscles Ligaments Tendons J*. 2012;2(1):44-48.

2. Abate M, Salini V, Schiavone C. Achilles tendinopathy in elderly subjects with type II diabetes: the role of sport activities. *Aging Clin Exp Res*. 2016;28(2):355-358. doi:10.1007/s40520-015-0391-7

3. Abate M, Schiavone C, Salini V, Andia I. Occurrence of tendon pathologies in metabolic disorders. *Rheumatol (United Kingdom)*. 2013;52(4):599-608. doi:10.1093/rheumatology/kes395

4. Abdelkader NA, Helmy MNK, Fayaz NA, Saweeres ESB. Short- and Intermediate-Term Results of Extracorporeal Shockwave Therapy for Noninsertional Achilles Tendinopathy. *Foot Ankle Int*. 2021;42(6):788-797. doi:10.1177/1071100720982613

5. Akaike H. Factor analysis and AIC. *Psychometrika*. 1987;52:317-332. doi:10.1007/BF02294359

6. Alfredson H, Cook J. A treatment algorithm for managing Achilles tendinopathy: New treatment options. *Br J Sports Med*. 2007;41(4):211-216. doi:10.1136/bjsm.2007.035543

7. Alfredson H, Pietilä T, Jonsson P, Lorentzon R. Heavy-load eccentric calf muscle training for the treatment of chronic achilles tendinosis. *Am J Sports Med*. 1998;26(3):360-366. doi:10.1177/03635465980260030301

8. Alfredson H, Zeisig E, Fahlström M. No normalisation of the tendon structure and thickness after intratendinous surgery for chronic painful midportion Achilles tendinosis. *Br J Sports Med*. 2009;43(12):948-949. doi:10.1136/bjsm.2008.050955

9. Alghamdi NH, Pohlig RT, Lundberg M, Silbernagel KG. The Impact of the Degree of Kinesiophobia on Recovery in Patients With Achilles Tendinopathy. *Phys Ther*. 2021;101(11):1-9. doi:10.1093/ptj/pzab178

10. Arya S, Kulig K. Tendinopathy alters mechanical and material properties of the Achilles tendon. *J Appl Physiol*. 2010;108(3):670-675. doi:10.1152/japplphysiol.00259.2009

11. Bakkegaard M, Johannsen FE, Højgaard B, Langberg H. Ultrasonography as a prognostic and objective parameter in Achilles tendinopathy: A prospective observational study. *Eur J Radiol*. 2015;84(3):458-462. doi:10.1016/j.ejrad.2014.11.028

12. Bernstein DN, Anderson MR, Baumhauer JF, et al. A Comparative Analysis of Clinical Outcomes in Noninsertional Versus Insertional Tendinopathy Using PROMIS. *Foot Ankle Spec*. 2018;XX(X):193864001880666. doi:10.1177/1938640018806662

13. Beyer R, Kongsgaard M, Hougs Kjær B, Øhlenschlæger T, Kjær M, Magnusson SP. Heavy slow resistance versus eccentric training as treatment for achilles tendinopathy: A randomized controlled trial. *Am J Sports Med*. 2015;43(7):1704-1711. doi:10.1177/0363546515584760

14. Bohm S, Mersmann F, Schroll A, Mäkitalo N, Arampatzis A. Insufficient accuracy of the ultrasound-based determination of Achilles tendon cross-sectional area. *J Biomech*. 2016;49(13):2932-2937. doi:10.1016/j.jbiomech.2016.07.002

15. Cassel M, Baur H, Hirschmüller A, Carlsohn A, Fröhlich K, Mayer F. Prevalence of Achilles and patellar tendinopathy and their association to intratendinous changes in adolescent athletes. *Scand J Med Sci Sport*. 2015;25(3):e310-e318. doi:10.1111/sms.12318

16. Cassel M, Risch L, Intziegianni K, et al. Incidence of Achilles and Patellar Tendinopathy in Adolescent Elite Athletes. *Int J Sports Med*. 2018;39(09):726-732. doi:10.1055/a-0633-9098

17. Celeux G, Soromenho G. An Entropy Criterion for Assessing the Number of Clusters in a Mixture Model. *J Classif*. 1996;13:195-212. doi:10.1016/S0167-8655(98)00144-5

18. Cella D, Riley W, Stone A, et al. The patient-reported outcomes measurement information system (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. *J Clin Epidemiol*. 2010;63(11):1179-1194. doi:10.1016/j.jclinepi.2010.04.011

19. Ceravolo ML, Gaida JE, Keegan RJ. Quality-of-Life in Achilles Tendinopathy : An Exploratory Study. *Clin J Sport Med*. 2018;00(00):1-8.

doi:10.1097/JSM.0000000000000636

20. Chan AW, Tetzlaff JM, Altman DG, et al. Spirit 2013 statement: Defining standard protocol items for clinical trials. *Chinese J Evidence-Based Med*. 2013;13(12):1501-1507. doi:10.7507/1672-2531.20130256

21. Chimenti RL, Pacha MS, Glass NA, et al. Elevated Kinesiophobia Is Associated with Reduced Recovery from Lower Extremity Musculoskeletal Injuries in Military and Civilian Cohorts. *Phys Ther*. Published online 2021:1-10. doi:10.1093/ptj/pzab262

22. Cook JL, Purdam CR. Is tendon pathology a continuum? A pathology model to explain the clinical presentation of load-induced tendinopathy. *Br J Sports Med*. 2009;43(6):409-416. doi:10.1136/bjsm.2008.051193

23. Corrigan P, Cortes DH, Pohlig RT, Grävare Silbernagel K. Tendon Morphology and Mechanical Properties Are Associated With the Recovery of Symptoms and Function in Patients With Achilles Tendinopathy. *Orthop J Sport Med*. 2020;8(4). doi:10.1177/2325967120917271

24. Corrigan P, Cortes DH, Pontiggia L, Silbernagel KG. the Degree of Tendinosis Is Related To Symptom Severity and Physical Activity Levels in Patients With Midportion Achilles Tendinopathy. *Int J Sports Phys Ther*. 2018;13(2):196-207. doi:10.26603/ijspt20180196

25. Corrigan P, Zellers JA, Balascio P, Silbernagel KG, Cortes DH. Quantification of Mechanical Properties in Healthy Achilles Tendon Using Continuous Shear Wave Elastography: A Reliability and Validation Study. *Ultrasound Med Biol*. 2019;45(7):1574-1585. doi:10.1016/j.ultrasmedbio.2019.03.015

26. Cortes DH, Suydam SM, Silbernagel KG, Buchanan TS, Elliott DM. Continuous Shear Wave Elastography: A New Method to Measure Viscoelastic Properties of Tendons in Vivo. *Ultrasound Med Biol*. 2015;41(6):1518-1529. doi:10.1016/j.ultrasmedbio.2015.02.001

27. Debenham JR, Malliaras P, Stace R, Littlewood C, Mallows AJ. Cognitive and contextual factors to optimise clinical outcomes in tendinopathy. *Br J Sports Med*. 2017;52(13):822-823. doi:10.1136/bjsports-2017-098064

28. van Dijk CN, van Sterkenburg MN, Wiegerinck JI, Karlsson J, Maffulli N. Terminology for Achilles tendon related disorders. *Knee Surgery, Sport Traumatol Arthrosc*. 2011;19(5):835-841. doi:10.1007/s00167-010-1374-z

29. DiMatteo MR, Lepper HS, Croghan TW. Depression Is a Risk Factor for

Noncompliance With Medical Treatment. *Arch Intern Med*. 2000;160(14):2101-2107. doi:10.1001/archinte.160.14.2101

30. Dirrichs T, Quack V, Gatz M, Tingart M, Kuhl CK, Schrading S. Shear Wave Elastography (SWE) for the Evaluation of Patients with Tendinopathies. *Acad Radiol*. 2016;23(10):1204-1213. doi:10.1016/j.acra.2016.05.012

31. Downie WW, Leatham PA, Rhind VM, Wright V, Branco JA, Anderson JA. Studies with pain rating scales. *Ann Rheum Dis*. 1978;37(4):378-381. doi:10.1136/ard.37.4.378

32. Edwards RR, Ness TJ, Weigent DA, Fillingim RB. Individual differences in diffuse noxious inhibitory controls (DNIC): Association with clinical variables. *Pain*. 2003;106(3):427-437. doi:10.1016/j.pain.2003.09.005

33. Elengard T, Grävare-Silbernagel K, Karlsson J. Aspects of treatment for posterior heel pain in young athletes. *Open Access J Sport Med*. 2010;1:223-232. doi:10.2147/oajsm.s15413

34. Fahlström M, Jonsson P, Lorentzon R, Alfredson H. Chronic Achilles tendon pain treated with eccentric calf-muscle training. *Knee Surgery, Sport Traumatol Arthrosc*. 2003;11(5):327-333. doi:10.1007/s00167-003-0418-z

35. Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94(2):149-158. doi:10.1016/S0304-3959(01)00349-9

36. Fluss R, Faraggi D, Reiser B. Estimation of the Youden Index and its associated cutoff point. *Biometrical J*. 2005;47(4):458-472. doi:10.1002/bimj.200410135

37. Forrest CB, Bevans KB, Pratiwadi R, et al. Development of the PROMIS® pediatric global health (PGH-7) measure. *Qual Life Res*. 2014;23(4):1221-1231. doi:10.1007/s11136-013-0581-8

38. Fredberg U, Bolvig L. Significance of ultrasonographically detected asymptomatic tendinosis in the patellar and Achilles tendons of elite soccer players: A longitudinal study. *Am J Sports Med*. 2002;30(4):488-491. doi:10.1177/03635465020300040701

39. French DJ, France CR, Vigneau F, French JA, Evans TR. Fear of movement/(re)injury in chronic pain: A psychometric assessment of the original English version of the Tampa scale for kinesiophobia (TSK). *Pain*. 2007;127(1):42-51. doi:10.1016/j.pain.2006.07.016

40. Gaida JE, Cook JL. Risk Factors for overuse tendinopathy. *Australas Musculoskelet Med*. 2008;13(2):60-65.

41. Gajhede-Knudsen M, Ekstrand J, Magnusson H, Maffulli N. Recurrence of Achilles tendon injuries in elite male football players is more common after early return to play: an 11-year follow-up of the UEFA Champions League injury study. *Br J Sports Med*. 2013;47:763-768. doi:10.1136/bjsports-2013-092271

42. Geiser C. *Data Analysis with Mplus*. Guilford Press; 2013.

43. Grävare Silbernagel K, Brorsson A, Lundberg M, et al. The majority of patients with Achilles tendinopathy recover fully when treated with exercise alone: A 5-year follow-up. *Am J Sports Med*. 2011;39(3):607-613. doi:10.1177/0363546510384789

44. Grävare Silbernagel K, Malliaras P, de Vos R-J, et al. ICON 2020—International Scientific Tendinopathy Symposium Consensus: A Systematic Review of Outcome Measures Reported in Clinical Trials of Achilles Tendinopathy. *Sport Med*. 2021;(0123456789). doi:10.1007/s40279-021-01588-6

45. GRIMBY G. Physical Activity and Muscle Training in the Elderly. *Acta Med Scand*. 1986;220(S711):233-237. doi:10.1111/j.0954-6820.1986.tb08956.x

46. Habets B, van den Broek AG, Huisstede BMA, Backx FJG, van Cingel REH. Return to Sport in Athletes with Midportion Achilles Tendinopathy: A Qualitative Systematic Review Regarding Definitions and Criteria. *Sport Med*. 2018;48(3):705-723. doi:10.1007/s40279-017-0833-9

47. Habets B, van Cingel REH, Backx FJG, van Elten HJ, Zuithoff P, Huisstede BMA. No Difference in Clinical Effects When Comparing Alfredson Eccentric and Silbernagel Combined Concentric-Eccentric Loading in Achilles Tendinopathy: A Randomized Controlled Trial. *Orthop J Sport Med*. 2021;9(10):1-10. doi:10.1177/23259671211031254

48. Hanlon SL, Pohlig RT, Silbernagel KG. Beyond the Diagnosis: Using Patient Characteristics and Domains of Tendon Health to Identify Latent Subgroups of Achilles Tendinopathy. *J Orthop Sport Phys Ther*. 2021;51(9):440-448. doi:10.2519/jospt.2021.10271

49. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J*

Biomed Inform. 2009;42(2):377-381. doi:10.1016/j.jbi.2008.08.010

50. Heinemeier KM, Schjerling P, Heinemeier J, Magnusson SP, Kjaer M. Lack of tissue renewal in human adult Achilles tendon is revealed by nuclear bomb 14C. *FASEB J*. 2013;27(5):2074-2079. doi:10.1096/fj.12-225599

51. Heinemeier KM, Schjerling P, Øhlenschlæger TF, Eismark C, Olsen J, Kjær M. Carbon-14 bomb pulse dating shows that tendinopathy is preceded by years of abnormally high collagen turnover. *FASEB J*. 2018;32(9):4763-4775. doi:10.1096/fj.201701569R

52. Henson JM, Reise SP, Kim KH. Detecting mixtures from structural model differences using latent variable mixture modeling: A comparison of relative model fit statistics. *Struct Equ Model*. 2007;14(2):202-226. doi:10.1080/10705510709336744

53. Hicks GE, Pohlig RT, Coyle PC, et al. Classification of Geriatric Low Back Pain Based on Hip Characteristics with a 12-Month Longitudinal Exploration of Clinical Outcomes: Findings from Delaware Spine Studies. *Phys Ther*. 2021;101(12):1-10. doi:10.1093/ptj/pzab227

54. Hirschmüller A, Frey V, Konstantinidis L, et al. Prognostic value of achilles tendon doppler sonography in asymptomatic runners. *Med Sci Sports Exerc*. 2012;44(2):199-205. doi:10.1249/MSS.0b013e31822b7318

55. Hosgören B, Köktener A, Dilmen G. Ultrasonography of the Calcaneus in Sever's Disease. *Indian Pediatr*. 2005;42:801-803.

56. Hutchison AM, Evans R, Bodger O, et al. What is the best clinical test for achilles tendinopathy? *Foot Ankle Surg*. 2013;19(2):112-117. doi:10.1016/j.fas.2012.12.006

57. Intziegianni K, Cassel M, Rauf S, et al. Influence of Age and Pathology on Achilles Tendon Properties During a Single-leg Jump. *Int J Sports Med*. 2016;37(12):973-978. doi:10.1055/s-0042-108198

58. Iversen JV, Bartels EM, Langberg H. The victorian institute of sports assessment - achilles questionnaire (visa-a) - a reliable tool for measuring achilles tendinopathy. *Int J Sports Phys Ther*. 2012;7(1):76-84. http://www.ncbi.nlm.nih.gov/pubmed/22319681%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3273883

59. James AM, Williams CM, Haines TP. Effectiveness of footwear and foot orthoses for calcaneal apophysitis: A 12-month factorial randomised trial. *Br J*

Sports Med. 2016;50(20):1268-1275. doi:10.1136/bjsports-2015-094986

60. James AM, Williams CM, Haines TP. Effectiveness of interventions in reducing pain and maintaining physical activity in children and adolescents with calcaneal apophysitis (sever's disease): A systematic review. *J Foot Ankle Res*. 2013;6(1):1-11. doi:10.1186/1757-1146-6-16

61. James AM, Williams CM, Haines TP. Health related quality of life of children with calcaneal apophysitis: Child & parent perceptions. *Health Qual Life Outcomes*. 2016;14(1):1-7. doi:10.1186/s12955-016-0497-4

62. Järvinen TAH, Kannus P, Maffulli N, Khan KM. Achilles tendon disorders: Etiology and epidemiology. *Foot Ankle Clin*. 2005;10(2):255-266. doi:10.1016/j.fcl.2005.01.013

63. Jhingan S, Perry M, O'Driscoll G, et al. Thicker Achilles tendons are a risk factor to develop Achilles tendinopathy in elite professional soccer players. *Muscles Ligaments Tendons J*. 2011;1(2):51-56.

64. Johannsen F, Jensen S, Wetke E. 10-year follow-up after standardised treatment for Achilles tendinopathy. *BMJ Open Sport Exerc Med*. 2018;4(1):e000415. doi:10.1136/bmjsem-2018-000415

65. De Jonge S, Van Den Berg C, De Vos RJ, et al. Incidence of midportion Achilles tendinopathy in the general population. *Br J Sports Med*. 2011;45(13):1026-1028. doi:10.1136/bjsports-2011-090342

66. De Jonge S, Tol JL, Weir A, Waarsing JH, Verhaar JAN, De Vos RJ. The tendon structure returns to asymptomatic values in nonoperatively treated achilles tendinopathy but is not associated with symptoms. *Am J Sports Med*. 2015;43(12):2950-2958. doi:10.1177/0363546515605077

67. Jylhävä J, Pedersen NL, Hägg S. Biological Age Predictors. *EBioMedicine*. 2017;21:29-36. doi:10.1016/j.ebiom.2017.03.046

68. Khan KM, Scott A. Mechanotherapy: How physical therapists' prescription of exercise promotes tissue repair. *Br J Sports Med*. 2009;43(4):247-252. doi:10.1136/bjsm.2008.054239

69. Kjaer M, Kjær M. Role of Extracellular Matrix in Adaptation of Tendon and Skeletal Muscle to Mechanical Loading. *Physiol Rev*. 2004;84(2):649-698. doi:10.1152/physrev.00031.2003

70. Kjær M, Langberg H, Heinemeier K, et al. From mechanical loading to

collagen synthesis, structural changes and function in human tendon. *Scand J Med Sci Sport*. 2009;19(4):500-510. doi:10.1111/j.1600-0838.2009.00986.x

71. Koch K-R. Mixed models. In: ; 1990:109-121. doi:10.1007/BFb0048712

72. Komi P V., Fukashiro S, Järvinen M. Biomechanical Loading of Achilles Tendon During Normal Locomotion. *Clin Sports Med*. 1992;11(3):521-531. doi:10.1016/S0278-5919(20)30506-8

73. Kubo K, Kanehisa H, Fukunaga T. Gender differences in the viscoelastic properties of tendon structures. *Eur J Appl Physiol*. 2003;88(6):520-526. doi:10.1007/s00421-002-0744-8

74. Kujala UMM, Sarna S, Kaprio J. Cumulative incidence of achilles tendon rupture and tendinopathy in male former elite athletes. *Clin J Sport Med*. 2005;15(3):133-135. doi:10.1097/01.jsm.0000165347.55638.23

75. Kulig K, Chang YJ, Winiarski S, Bashford GR. Ultrasound-Based Tendon Micromorphology Predicts Mechanical Characteristics of Degenerated Tendons. *Ultrasound Med Biol*. 2016;42(3):664-673. doi:10.1016/j.ultrasmedbio.2015.11.013

76. Kvist M. Achilles tendon injuries in athletes. *Ann Chir Gynaecol*. 1991;80(2):188-201. doi:10.2165/00007256-199418030-00004

77. Kvist MH, Heinonem OJ. Calcaneal apophysitis (Sever's disease) — a common cause of heel pain in young athletes. *Scand J Med Sci Sports*. 1991;1(4):235-238. doi:10.1111/j.1600-0838.1991.tb00303.x

78. Lagas IF, van der Vlist AC, van Oosterom RF, et al. Victorian Institute of Sport Assessment-Achilles (VISA-A) Questionnaire—Minimal Clinically Important Difference for Active People With Midportion Achilles Tendinopathy: A Prospective Cohort Study. *J Orthop Sport Phys Ther*. 2021;51(10):510-516. doi:10.2519/jospt.2021.10040

79. Leeuw M, Goossens MEJB, Linton SJ, Crombez G, Boersma K, Vlaeyen JWS. The fear-avoidance model of musculoskeletal pain: Current state of scientific evidence. *J Behav Med*. 2007;30(1):77-94. doi:10.1007/s10865-006-9085-0

80. Lundberg M, Styf J. Kinesiophobia among physiological overusers with musculoskeletal pain. *Eur J Pain*. 2009;13(6):655-659. doi:10.1016/j.ejpain.2008.08.004

81. Lundberg MKE, Styf J, Carlsson SG. A psychometric evaluation of the Tampa

Scale for Kinesiophobia - From a physiotherapeutic perspective. *Physiother Theory Pract*. 2004;20(2):121-133. doi:10.1080/09593980490453002

82. Madden C, Mellion M B. Sever's disease and other causes of heel pain in adolescents. *Am Fam Physician*. 1996;54(6):1995-2000.

83. Maffulli N, Kenward MG, Testa V, Capasso G, Regine R, King JB. Clinical diagnosis of Achilles tendinopathy with tendinosis. *Clin J Sport Med*. 2003;13(1):11-15. doi:10.1097/00042752-200301000-00003

84. Maffulli N, Khan KM, Puddu G. Overuse tendon conditions: Time to change a confusing terminology. *Arthroscopy*. 1998;14(8):840-843. doi:10.1016/S0749-8063(98)70021-0

85. Maffulli N, Walley G, Sayana M, Longo UG, Denaro V. Eccentric calf muscle training in athletic patients with Achilles tendinopathy. *Disabil Rehabil*. 2008;30(20-22):1677-1684. doi:10.1080/09638280701786427

86. Mafi N, Lorentzon R, Alfredson H. Superior short-term results with eccentric calf muscle training compared to concentric training in a randomized prospective multicenter study on patients with chronic Achilles tendinosis. *Knee Surgery, Sport Traumatol Arthrosc*. 2001;9(1):42-47. doi:10.1007/s001670000148

87. Magnan B, Bondi M, Pierantoni S, Samaila E. The pathogenesis of Achilles tendinopathy: A systematic review. *Foot Ankle Surg*. 2014;20(3):154-159. doi:10.1016/j.fas.2014.02.010

88. Magnusson P, Kjaer M. The impact of loading, unloading, ageing and injury on the human tendon. *J Physiol*. 2018;0:1-16. doi:10.1113/JP275450

89. Magnusson SP, Langberg H, Kjaer M. The pathogenesis of tendinopathy: Balancing the response to loading. *Nat Rev Rheumatol*. 2010;6:262-268. doi:10.1038/nrrheum.2010.43

90. Martin RL, Chimenti R, Cuddeford T, et al. Achilles Pain, Stiffness, and Muscle Power Deficits: Midportion Achilles Tendinopathy Revision 2018. *J Orthop Sport Phys Ther*. 2018;48(5):A1-A38. doi:10.2519/jospt.2018.0302

91. Martinez-Calderon J, Jensen MP, Morales-Asencio JM, Luque-Suarez A. Pain Catastrophizing and Function in Individuals with Chronic Musculoskeletal Pain. *Clin J Pain*. 2019;35(3):279-293. doi:10.1097/AJP.0000000000000676

92. Mc Auliffe S, Synott A, O'Sullivan K, et al. Beyond the tendon: Experiences

and perceptions of people with persistent Achilles tendinopathy. *Musculoskelet Sci Pract*. 2017;29:108-114. doi:10.1016/j.msksp.2017.03.009

93. McAuliffe S, McCreesh K, Culloty F, Purtill H, O'Sullivan K. Can ultrasound imaging predict the development of Achilles and patellar tendinopathy? A systematic review and meta-analysis. *Br J Sports Med*. 2016;50(24):1516-1523. doi:10.1136/bjsports-2016-096288

94. McCormack J, Underwood F, Slaven E, Cappaert T. the Minimum Clinically Important Difference on the Visa-a and Lefs for Patients With Insertional Achilles Tendinopathy. *Int J Sports Phys Ther*. 2015;10(5):639-644. http://www.ncbi.nlm.nih.gov/pubmed/26491614%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4595917

95. McCormack JR, Underwood FB, Slaven EJ, Cappaert TA. Eccentric Exercise Versus Eccentric Exercise and Soft Tissue Treatment (Astym) in the Management of Insertional Achilles Tendinopathy: A Randomized Controlled Trial. *Sports Health*. 2016;8(3):230-237. doi:10.1177/1941738116631498

96. Mersmann F, Bohm S, Arampatzis A. Imbalances in the development of muscle and tendon as risk factor for tendinopathies in youth athletes: A review of current evidence and concepts of prevention. *Front Physiol*. 2017;8(DEC):1-18. doi:10.3389/fphys.2017.00987

97. Micheli LJ, Fehlandt AF. Overuse Injuries to Tendons and Apophyses in Children and Adolescents. *Clin Sports Med*. 1992;11(4):713-726.

98. Micheli LJ, Ireland ML. Prevention and management of calcaneal apophysitis in children: An overuse syndrome. *J Pediatr Orthop*. 1987;7(1):34-38. doi:10.1097/01241398-198701000-00007

99. Millar NL, Silbernagel KG, Thorborg K, et al. Tendinopathy. *Nat Rev Dis Prim*. 2021;7(1). doi:10.1038/s41572-020-00234-1

100. Muthén BO, Muthén LK. Integrating person-centered and variable-centered analyses: Growth mixture modeling with latent trajectory classes. *Alcohol Clin Exp Res*. 2000;24(6):882-891. doi:10.1111/j.1530-0277.2000.tb02070.x

101. My Healthy Community: Delaware Environmental Public Health Tracking Network. Published 2022. Accessed February 4, 2022. https://myhealthycommunity.dhss.delaware.gov/locations/state/vaccine-tracker

102. Narici M V., Maffulli N, Maganaris CN. Ageing of human muscles and tendons. *Disabil Rehabil*. 2008;30(20-22):1548-1554.

doi:10.1080/09638280701831058

103. National Federation of State High School Associations. 2018-19 High School Athletics Participation Survey. *2018-2019 NFHS Handb*. Published online 2019:55-69. doi:Accessed June 9, 2014

104. Nylund KL, Asparouhov T, Muthén BO. Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study. *Struct Equ Model*. 2007;14(4):535-569. doi:10.1080/10705510701575396

105. O'Neill S, Watson PJ, Barry S. a Delphi Study of Risk Factors for Achilles Tendinopathy- Opinions of World Tendon Experts. *Int J Sports Phys Ther*. 2016;11(5):684-697. http://www.ncbi.nlm.nih.gov/pubmed/27757281%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC5046962

106. Oberski DL. Mixture Models: Latent Profile and Latent Class Analysis. In: *Modern Statistical Methods for HCI*. ; 2016:275-287. doi:10.1007/978-3-319-26633-6_12

107. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Heal Organ - Tech Rep Ser*. 2000;894(i-xii):1-253.

108. Öhberg L, Alfredson H. Effects on neovascularisation behind the good results with eccentric training in chronic mid-portion Achilles tendinosis? *Knee Surgery, Sport Traumatol Arthrosc*. 2004;12(5):465-470. doi:10.1007/s00167-004-0494-8

109. Öhberg L, Lorentzon R, Alfredson H. Eccentric training in patients with chronic Achilles tendinosis: Normalised tendon structure and decreased thickness at follow up. *Br J Sports Med*. 2004;38(1):8-11. doi:10.1136/bjsm.2001.000284

110. Perhamre S, Janson S, Norlin R, Klässbo M. Sever's injury: Treatment with insoles provides effective pain relief. *Scand J Med Sci Sport*. 2011;21(6):819-823. doi:10.1111/j.1600-0838.2010.01051.x

111. Peter Magnusson S, Hansen M, Langberg H, et al. The adaptability of tendon to loading differs in men and women. In: *International Journal of Experimental Pathology*. Vol 88. ; 2007:237-240. doi:10.1111/j.1365-2613.2007.00551.x

112. Van Der Plas A, De Jonge S, De Vos RJ, et al. A 5-year follow-up study of Alfredson's heel-drop exercise programme in chronic midportion Achilles

tendinopathy. *Br J Sports Med*. 2012;46(3):214-218. doi:10.1136/bjsports-2011-090035

113. Rachel JN, Williams JB, Sawyer JR, Warner WC, Kelly DM. Is radiographic evaluation necessary in children with a clinical diagnosis of calcaneal apophysitis (sever disease)? *J Pediatr Orthop*. 2011;31(5):548-550. doi:10.1097/BPO.0b013e318219905c

114. Ramponi DR, Baker C. Sever's Disease (Calcaneal Apophysitis). *Adv Emerg Nurs J*. 2019;41(1):10-14. doi:10.1097/TME.0000000000000219

115. Rathleff MS, Graven-Nielsen T, Hölmich P, et al. Activity Modification and Load Management of Adolescents With Patellofemoral Pain: A Prospective Intervention Study Including 151 Adolescents. *Am J Sports Med*. 2019;47(7):1629-1637. doi:10.1177/0363546519843915

116. Rio EK, Mc Auliffe S, Kuipers I, et al. ICON PART-T 2019–International Scientific Tendinopathy Symposium Consensus: recommended standards for reporting participant characteristics in tendinopathy research (PART-T). *Br J Sports Med*. 2020;54(11):627-630. doi:10.1136/bjsports-2019-100957

117. Robinson JM, Cook JL, Purdam C, et al. The VISA-A questionnaire : a valid and reliable index of the clinical severity of Achilles tendinopathy The VISA-A questionnaire : a valid and reliable index of the clinical severity of Achilles tendinopathy. *Sport Med*. 2001;35(5):335-341. doi:10.1136/bjsm.35.5.335

118. Rolf C, Movin T. Etiology, histopathology, and outcome of surgery in achillodynia. *Foot Ankle Int*. 1997;18(9):565-569. doi:10.1177/107110079701800906

119. Rompe JD, Nafe B, Furia JP, Maffulli N. Eccentric loading, shock-wave treatment, or a wait- and-see policy for tendinopathy of the main body of tendo Achillis: A randomized controlled trial. *Am J Sports Med*. 2007;35(3):374-383. doi:10.1177/0363546506295940

120. Roos EM, Brandsson S, Karlsson J. Validation of the Foot and Ankle Outcome Score for Ankle Ligament Reconstruction. *Foot Ankle Int*. 2001;22(10):788-794. doi:10.1007/s11420-015-9466-4

121. Roos EM, Engström M, Lagerquist A, Söderberg B. Clinical improvement after 6 weeks of eccentric exercise in patients with mid-portion Achilles tendinopathy- a randomized trial with 1-year follow-up. *Scand J Med Sci Sports*. 2004;14:286-295. doi:10.1111/j.1600-0838.2004.00378.x

122. Rowe V, Hemmings S, Barton C, Malliaras P, Maffulli N, Morrissey D. Conservative Management of Midportion Achilles Tendinopathy. *Sport Med*. 2012;42(11):941-967. doi:10.2165/11635410-000000000-00000

123. SafeKids Worldwide: Changing the Culture of Youth Sports Report. Published 2014. http://www.pysc.org/resources/documents/ChangingtheCultureofYouthSports.pdf

124. Sayana MK, Maffulli N. Eccentric calf muscle training in non-athletic patients with Achilles tendinopathy. *J Sci Med Sport*. 2007;10:52-58. doi:10.1016/j.jsams.2006.05.008

125. Scharfbillig RW, Jones S, Scutter S. Sever's disease-Does it effect quality of life? *Foot*. 2009;19(1):36-43. doi:10.1016/j.foot.2008.07.004

126. Scharfbillig RW, Jones S, Scutter SD. Sever's disease: What does the literature really tell us? *J Am Podiatr Med Assoc*. 2008;98(3):212-223. doi:10.7547/0980212

127. Schwarz G. Estimating the Dimension of a Model. *Ann Stat*. 1978;6:461-464. doi:10.1214/aos/1176344136

128. Scott A, Squier K, Alfredson H, et al. ICON 2019: International Scientific Tendinopathy Symposium Consensus: Clinical Terminology. *Br J Sports Med*. 2020;54:260-262. doi:10.1136/bjsports-2019-100885

129. Sever J. Apophysitis of the os calcis. *N Y Med J*. 1912;95:1025–1029.

130. Shalabi A, Kristoffersen-Wilberg M, Svensson L, Aspelin P, Movin T. Eccentric training of the gastrocnemius-soleus complex ion chronic achilles tendinopathy results in decreased tendon volume and intratendinous signal as evaluated by MRI. *Am J Sports Med*. 2004;32(5):1286-1296. doi:10.1177/0363546504263148

131. Silbernagel KG. Does One Size Fit All When It Comes to Exercise Treatment for Achilles Tendinopathy? *J Orthop Sport Phys Ther*. 2014;44(2):42-44. doi:10.2519/jospt.2014.0103

132. Silbernagel KG, Gustavsson A, Thomeé R, Karlsson J. Evaluation of lower leg function in patients with Achilles tendinopathy. *Knee Surgery, Sport Traumatol Arthrosc*. 2006;14(11):1207-1217. doi:10.1007/s00167-006-0150-6

133. Silbernagel KG, Hanlon S, Sprague A. Current Clinical Concepts: Conservative

Management of Achilles Tendinopathy. *J Athl Train*. 2020;55(5):438-447. doi:10.4085/1062-6050-356-19

134. Silbernagel KG, Shelley K, Powell S, Varrecchia S. Extended field of view ultrasound imaging to evaluate achilles tendon length and thickness: A reliability and validity study. *Muscles Ligaments Tendons J*. 2016;6(1):104-110. doi:10.11138/mltj/2016.6.1.104

135. Silbernagel KG, Thomeé R, Eriksson BI, Karlsson J. Continued sports activity, using a pain-monitoring model, during rehabilitation in patients with achilles tendinopathy: A randomized controlled study. *Am J Sports Med*. 2007;35(6):897-906. doi:10.1177/0363546506298279

136. Silbernagel KG, Thomeé R, Eriksson BI, Karlsson J. Full symptomatic recovery does not ensure full recovery of muscle-tendon function in patients with Achilles tendinopathy. *Br J Sports Med*. 2007;41(4):276-280. doi:10.1136/bjsm.2006.033464

137. Silbernagel KG, Thomeé R, Thomeé P, et al. Eccentric overload training for patients with chronic Achilles tendon pain - a randomised controlled study with reliability testing of the evaluation methods. *Scand J Med Sci Sport*. 2001;11(4):197-206. doi:10.1034/j.1600-0838.2001.110402.x

138. Simons LE, Sieberg CB, Carpino E, Logan D, Berde C. The Fear of Pain Questionnaire (FOPQ): Assessment of pain-related fear among children and adolescents with chronic pain. *J Pain*. 2011;12(6):677-686. doi:10.1016/j.jpain.2010.12.008

139. Simpson M, Rio E, Cook J. At What Age Do Children and Adolescents Develop Lower Limb Tendon Pathology or Tendinopathy? A Systematic Review and Meta-analysis. *Sport Med*. 2016;46(4):545-557. doi:10.1007/s40279-015-0438-0

140. Sleeswijk Visser TSO, van der Vlist AC, van Oosterom RF, van Veldhoven P, Verhaar JAN, de Vos R-J. Impact of chronic Achilles tendinopathy on health-related quality of life, work performance, healthcare utilisation and costs. *BMJ Open Sport Exerc Med*. 2021;7(1):e001023. doi:10.1136/bmjsem-2020-001023

141. Snedeker JG, Foolen J. Tendon injury and repair – A perspective on the basic mechanisms of tendon disease and future clinical therapy. *Acta Biomater*. 2017;63:18-36. doi:10.1016/j.actbio.2017.08.032

142. Sprague AL, Couppé C, Pohlig RT, Snyder-Mackler L, Silbernagel KG. Pain-guided activity modification during treatment for patellar tendinopathy: a

feasibility and pilot randomized clinical trial. *Pilot Feasibility Stud*. 2021;7(1):1-17. doi:10.1186/s40814-021-00792-5

143. Stergioulas A, Stergioula M, Aarskog R, Lopes-Martins RAB, Bjordal JM. Effects of low-level laser therapy and eccentric exercises in the treatment of recreational athletes with chronic achilles tendinopathy. *Am J Sports Med*. 2008;36(5):881-887. doi:10.1177/0363546507312165

144. Stevens M, Tan CW. Effectiveness of the alfredson protocol compared with a lower repetition-volume protocol for midportion achilles tendinopathy: A randomized controlled trial. *J Orthop Sports Phys Ther*. 2014;44(2):59-67. doi:10.2519/jospt.2014.4720

145. Stynes S, Konstantinou K, Ogollah R, Hay EM, Dunn KM. Novel approach to characterising individuals with low back-related leg pain: Cluster identification with latent class analysis and 12-month follow-up. *Pain*. 2018;159(4):728-738. doi:10.1097/j.pain.0000000000001147

146. Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and Validation. *Psychol Assess*. 1995;7(4):524-532. doi:10.1037/1040-3590.7.4.524

147. Suryavanshi JR, Goto R, Jivanelli B, et al. Age-Appropriate Pediatric Sports Patient-Reported Outcome Measures and Their Psychometric Properties: A Systematic Review. *Am J Sports Med*. 2019;47(13):3270-3276. doi:10.1177/0363546518818822

148. Suydam SM, Soulas EM, Elliott DM, Gravare Silbernagel K, Buchanan TS, Cortes DH. Viscoelastic properties of healthy achilles tendon are independent of isometric plantar flexion strength and cross-sectional area. *J Orthop Res*. 2015;33(6):926-931. doi:10.1002/jor.22878

149. Thomeé R. A comprehensive treatment approach for patellofemoral pain syndrome in young women. *Phys Ther*. Published online 1997. doi:10.1093/ptj/77.12.1690

150. Tran PHT, Malmgaard-Clausen NM, Puggaard RS, et al. Early development of tendinopathy in humans: Sequence of pathological changes in structure and tissue turnover signaling. *FASEB J*. 2020;34(1):776-788. doi:10.1096/fj.201901309R

151. Vicenzino B, De Vos RJ, Alfredson H, et al. ICON 2019 - International Scientific Tendinopathy Symposium Consensus: There are nine core health-related domains for tendinopathy (CORE DOMAINS): Delphi study of

healthcare professionals and patients. *Br J Sports Med*. Published online 2019:1-8. doi:10.1136/bjsports-2019-100894

152. Van Der Vlist AC, Breda SJ, Oei EHG, Verhaar JAN, De Vos RJ. Clinical risk factors for Achilles tendinopathy: a systematic review. *Br J Sports Med*. 2019;(C):1-11. doi:10.1136/bjsports-2018-099991

153. van der Vlist AC, Winters M, Weir A, et al. Which treatment is most effective for patients with Achilles tendinopathy? A living systematic review with network meta-analysis of 29 randomised controlled trials. *Br J Sports Med*. 2021;55(5):249-256. doi:10.1136/bjsports-2019-101872

154. de Vos RJ, Heijboer MP, Weinans H, Verhaar JAN, van Schie HTM. Tendon structure's lack of relation to clinical outcome after eccentric exercises in chronic midportion Achilles tendinopathy. *J Sport Rehabil*. 2012;21(1):34-43. doi:10.1123/jsr.21.1.34

155. De Vos RJ, Weir A, Cobben LPJJ, Tol JL. The value of power doppler ultrasonography in achilles tendinopathy: A prospective study. *Am J Sports Med*. 2007;35(10):1696-1701. doi:10.1177/0363546507303116

156. Wiegerinck JI, Yntema C, Brouwer HJ, Struijs PAA. Incidence of calcaneal apophysitis in the general population. *Eur J Pediatr*. 2014;173(5):677-679. doi:10.1007/s00431-013-2219-9

157. Wiegerinck JI, Zwiers R, Sierevelt IN, van Weert HCPM, van Dijk CN, Struijs PAA. Treatment of Calcaneal Apophysitis: Wait and See Versus Orthotic Device Versus Physical Therapy: A Pragmatic Therapeutic Randomized Clinical Trial. *J Pediatr Orthop*. 2016;36(2):152-157. doi:10.1097/bpo.0000000000000417

158. Wren T, Yerby S, Beaupre G, Carter D. Mechanical properties of the human Achilles tendon. *Clin Biomech*. 2001;16:245-251. doi:10.1016/j.clinbiomech.2011.02.011

159. Xu Y, Murrell GAC. The basic science of tendinopathy. *Clin Orthop Relat Res*. 2008;466(7):1528-1538. doi:10.1007/s11999-008-0286-4

160. Yang CC. Evaluating latent class analysis models in qualitative phenotype identification. *Comput Stat Data Anal*. 2006;50(4):1090-1104. doi:10.1016/j.csda.2004.11.004

161. Zellers JA, Bley BC, Pohlig RT, Alghamdi NH. Frequency of pathology on diagnostic ultrasound and relationship to patient demographics in individuals

with insertional Achilles tendinopathy. *Int J Sports Phys Ther*. 2019;14(5):1-9. doi:10.26603/ijspt201901

162. Zellers JA, Cortes DH, Pohlig RT, Silbernagel KG. Tendon morphology and mechanical properties assessed by ultrasound show change early in recovery and potential prognostic ability for 6 month outcomes. *Knee Surgery, Sport Traumatol Arthrosc*. 2019;27(9):2831-2839. doi:10.1016/j.physbeh.2017.03.040

Appendix A

SUMMARY OF MISSING DATA IN AIM 1

Variable	N	Total Missing (count)	Missing from Activity-dominant (count)	Missing from Psychosocial-dominant (count)	Missing from Structure-dominant (count)
BMI	144	1	0	1	0
CMJ Jump	109	36	7	19	10
Tendon CSA	143	2	1	0	1
Drop CMJ Jump	90	55	10	30	15
FAOS-QoL	144	1	1	0	0
Pain with Hopping	77	68	21	32	15
Heel-rise Work	139	6	1	3	2
Physical Activity Scale	144	1	1	0	0
Pain Catastrophizing Scale	142	3	2	1	0
Shear Modulus	125	20	6	10	4
Symptom Duration	138	7	4	2	1
Tendon Thickness	144	1	1	0	0
Tampa Scale of Kinesiophobia	134	11	3	4	4
VISA-A	138	7	2	1	4
Viscosity	125	20	6	10	4
Age	145	0	0	0	0
Sex	145	0	0	0	0

Appendix B

SUMMARY OF FIT STATISTICS INDICATING A 3-SUBGROUP MODEL IS BEST-FITTING IN AIM 1

Fit Statistic	*2-subgroup model*	*3-subgroup model*	*4-subgroup model*
AIC	12736.371	**11736.4**	12586.82
BIC	12873.3	**11909.05**	12819.01
ABIC	12727.74	**11725.516**	12572.19
Entropy	0.916	**0.899**	0.889
VLMR Test	$p < 0.001$	**$p = 0.16$**	$p = 0.63$
AVLMR Test	$p < 0.001$	**$p = 0.16$**	$p = 0.62$
BLR Test	$p < 0.001$	**$p < 0.001$**	$p < 0.001$

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; ABIC, Sample-adjusted Bayesian Information Criteria; VLMR, Vuong-Lo-Mendell Rubin; AVLMR, Sample-adjusted Vuong-Lo-Mendell Rubin; BLR, Bootstrap Likelihood Ratio.

Appendix C

SUMMARY OF FIT STATISTICS INDICATING A 4-SUBGROUP MODEL IS BEST-FITTING IN AIM 2

Fit Statistic	*2-subgroup model*	*3-subgroup model*	*4-subgroup model*	*5-subrgroup model*
AIC	9824.187	9734.258	**9661.881**	9616.175
BIC	9941.843	9898.958	**9861.624**	9856.961
ABIC	9805.935	9709.639	**9630.895**	9578.822
Entropy	0.874	0.887	**0.911**	0.931
VLMR Test	p = 0.11	p = 0.24	**p = 0.86**	p = 0.09
AVLMR Test	p = 0.11	p = 0.25	**p = 0.86**	p = 0.09
BLR Test	p <0.001	p <0.001	**p <0.001**	p <0.001
Subgroup membership size	1: n = 54 2: n = 60	1: n = 40 2: n = 44 3: n = 30	1: n = 38 2: n = 34 3: n =27 4: n = 15	1: n = 24 2: n = 32 3: n = 15 4: n =38 5: n = 5

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; ABIC, Sample-adjusted Bayesian Information Criteria; VLMR, Vuong-Lo-Mendell Rubin; AVLMR, Sample-adjusted Vuong-Lo-Mendell Rubin; BLR, Bootstrap Likelihood Ratio.

Appendix D

MARGINAL MEANS AND MAIN EFFECTS FROM AIM 2

Outcome Measures	Activity Dominant	Function Dominant	Psychosocial Dominant	Structural Dominant	Group		Time		Group × Time	
					F	*p*	F	*p*	F	*p*
Primary Outcome Measures										
VISA-A										
Baseline	55 ±15	58 ±15	38 ±17	46 ±20						
8 weeks	73 ±15	72 ±13	52 ±17	53 ±16	14.718	**<.001**	55.090	**<.001**	1.247	2.67
16 weeks	76 ±14	71 ±17	58 ±20	66 ±17						
24 weeks	81 ±12	80 ±13	60 ±18	62 ±25						
Heel-Rise Work LSI										
Baseline	102.6 ±18.0	94.9 ±19.8	85.0 ±39.5	71.0 ±44.1						
8 weeks	102.2 ±13.0	100.4 ±13.0	90.7 ±39.9	89.1 ±40.8	NT	NT	NT	NT	NT	NT
16 weeks	106.2 ±25.5	104.8 ±14.3	99.8 ±26.8	89.7 ±46.6						
24 weeks	104.0 ±20.9	105.4 ±13.8	87.0 ±30.0	76.4 ±48.1						
Degree of tendon Thickening, mm										
Baseline	1.53 ±1.21	2.11 ±1.57	2.16 ±1.51	5.36 ±2.09						
8 weeks	1.30 ±1.16	2.40 ±1.92	1.68 ±1.61	4.07 ±2.05	22.002	**<.001**	6.824	**<.001**	3.224	**.001**
16 weeks	1.47 ±1.46	2.10 ±1.60	1.34 ±1.55	4.32 ±1.95						
24 weeks	1.54 ±0.89	2.22 ±1.66	2.28 ±1.47	3.75 ±1.94						

Viscosity LSI										
Baseline	92.3 ±23.2	96.4 ±90.1	112.7 ±49.9	92.6 ±30.2						
8 weeks	108.6 ±32.9	99.3 ±108.6	107.6 ±33.2	85.7 ±20.5	NT	NT	NT	NT	NT	NT
16 weeks	87.2 ±14.3	90.1 ±18.9	107.3 ±27.5	85.8 ±25.2						
24 weeks	101.0 ±23.0	93.0 ±20.0	102.4 ±25.9	87.1 ±18.3						
FAOS-QoL										
Baseline	39.0 ±17.9	47.4 ±14.9	31.0 ±16.7	39.6 ±22.4						
8 weeks	54.4 ±18.2	58.5 ±15.3	45.1 ±17.8	52.7 ±17.5	3.881	**.011**	79.357	**<.001**	.675	.731
16 weeks	65.8 ±21.7	64.7 ±17.3	56.0 ±17.6	63.4 ±15.9						
24 weeks	70.2 ±16.6	72.4 ±17.5	61.3 ±20.6	65.4 ±25.2						
TSK-17										
Baseline	39.0 ±5.3	35.1 ±4.6	41.1 ±5.1	39.0 ±5.2						
8 weeks	36.2 ±5.4	34.4 ±4.0	37.7 ±6.0	39.4 ±4.4	5.503	**<.001**	22.080	**<.001**	1.739	.081
16 weeks	35.4 ±6.6	33.0 ±4.4	35.9 ±5.3	35.1 ±5.0						
24 weeks	34.1 ±6.4	32.3 ±6.4	34.5 ±6.4	37.2 ±4.6						
Secondary Outcome Measures										
Hopping Pain, NPRS										
Baseline	3.1 ±2.5	2.9 ± 2.4	3.3 ±2.3	2.8 ±2.9						
8 weeks	2.0 ±2.0	2.0 ±2.3	2.4 ±2.0	1.9 ±2.4	2.025	.115	19.443	**<.001**	.923	**.**506
16 weeks	1.4 ±1.9	1.4 ±1.7	1.8 ±2.1	.5 ±0.9						
24 weeks	0.7 ±0.9	0.9 ±1.4	2.7 ±2.6	1.4 ±2.5						
Heel-rise Work, J										
Baseline	2260 ±662	1721 ±624	1115 ±675	1057 ±810						
8 weeks	2209 ±624	1873 ±552	1382 ±934	1416 ±728	14.477	**<.001**	7.769	**<.001**	1.752	.079
16 weeks	2378 ±775	2059 ±643	1375 ±583	1405 ±881						
24 weeks	2387 ±562	1921±562	1254 ±574	1255 ±891						
CMJ Height, cm										
Baseline	10.9 ±2.1	6.2 ±1.5	2.7 ±1.4	3.8 ±1.8						
8 weeks	10.7 ±2.1	5.6 ±1.9	3.3 ±1.8	4.1 ±2.5	106.439	**<.001**	2.525	.059	.941	.491
16 weeks	11.5 ±2.3	6.1 ±1.8	3.7 ±1.7	4.8 ±2.5						
24 weeks	11.1 ±2.9	5.7 ±2.5	2.4 ±1.5	4.6 ±3.0						
Drop CMJ Height, cm										
Baseline	10.5 ±2.4	5.7 ±1.7	1.7 ±1.7	3.1 ±2.7						
8 weeks	9.9 ±2.1	5.7 ±2.5	2.8 ±2.5	4.0 ±3.2	77.831	**<.001**	5.118	**.002**	1.544	.135
16 weeks	10.5±2.4	6.0 ±1.9	3.9 ±2.3	5.6 ±3.8						
24 weeks	10.1 ±2.3	5.8 ±2.5	1.8 ±1.7	4.6 ±3.0						

Physical Activity Scale										
Baseline	5 ±1	5 ±1	3 ±1	4 ±1	NT	NT	NT	NT	NT	NT
8 weeks	4 ±1	5 ±1	4 ±1	4 ±1						
16 weeks	5 ±1	5 ±1	3 ±1	4 ±1						
24 weeks	5 ±1	5 ±1	3 ±1	4 ±1						
Achilles Thickness, cm										
Baseline	0.62 ±.15	0.74 ±.19	0.66 ±.16	1.19 ±.13	40.083	**<.001**	1.904	.130	.617	.782
8 weeks	0.59 ±.15	0.74 ±.21	0.65 ±.19	1.18 ±.15						
16 weeks	0.62 ±.18	0.72 ±.18	0.64 ±.21	1.19 ±.17						
24 weeks	0.61 ±.14	0.72 ±.21	0.67 ±.18	1.14 ±.16						
Achilles CSA, cm^2										
Baseline	0.72 ±.21	0.85 ±.26	0.77 ±.26	1.72 ±.32	73.051	**<.001**	2.494	.061	.643	.760
8 weeks	0.66 ±.20	0.87 ±.33	0.72 ±.24	1.76 ±.46						
16 weeks	0.73 ±.24	0.92 ±.34	0.79 ±.30	1.90 ±.52						
24 weeks	0.68 ±.21	0.86 ±.30	0.82 ±.27	1.77 ±.38						
Viscosity, KPa*s*										
Baseline	50.6 ±9.4	52.9 ±9.2	53.5 ±11.1	45.5 ±11.3	6.368	**<.001**	.662	.576	.821	.598
8 weeks	56.1 ±12.0	53.6 ±12.8	53.7 ±11.6	43.9 ±10.8						
16 weeks	53.0 ±9.2	49.6 ±7.9	55.6 ±10.7	42.8 ±8.9						
24 weeks	54.6 ±14.7	51.6 ±9.7	50.0 ±8.2	39.7 ±10.0						
Shear Modulus, KPa										
Baseline	92.7 ±22.1	101.0 ±17.8	99.5 ±16.8	113.9 ±22.4	3.972	**.010**	2.926	**.035**	.560	.829
8 weeks	98.9±16.6	97.3±19.0	92.0 ±21.7	107.9 ±24.2						
16 weeks	106.6±20.1	108.8 ±22.7	103.1 ±25.4	115.1 ±18.4						
24 weeks	95.4 ±14.0	100.6 ±21.3	96.4 ±27.7	114.5 ±17.6						
PROMIS Social Roles & Activities, t-score										
Baseline	56.0 ±6.6	57.5 ±7.7	49.8 ±8.9	56.0 ±9.5	3.692	**.014**	9.814	**<.001**	1.303	.235
8 weeks	57.4 ±6.4	60.0 ±7.4	53.0 ±7.5	57.2 ±6.9						
16 weeks	59.0 ±5.7	59.9 ±5.7	55.2 ±6.1	58.9 ±6.1						
24 weeks	61.5 ±5.3	59.7 ±6.3	58.1 ±8.0	58.3 ±7.0						

PROMIS Pain Interference, t-score										
Baseline	52.7 ±6.9	51.7 ±6.6	58.8 ±6.9	54.3 ±8.3	10.728	**<.001**	36.803	**<.001**	.232	.990
8 weeks	47.0 ±5.4	47.0 ±5.5	52.8 ±6.0	50.1 ±6.0						
16 weeks	46.7 ±5.3	46.7 ±5.3	52.9 ±8.1	48.3 ±7.1						
24 weeks	43.7 ±4.9	44.4 ±5.1	51.1 ±6.8	47.7 ±7.2						
PROMIS Anxiety, t-score										
Baseline	46.5 ±7.8	45.6 ±7.2	48.8 ±10.3	45.5 ±7.2	.396	.756	1.456	.227	.669	.737
8 weeks	44.8 ±6.8	45.5 ±6.9	46.8 ±7.9	44.6 ±6.8						
16 weeks	45.3 ±6.6	43.7 ±5.7	46.9 ±10.9	43.7 ±6.9						
24 weeks	43.4 ±6.5	45.0 ±6.1	44.0 ±7.3	45.0 ±8.0						
GROC										
8 weeks	2.0 ±1.0	1.7 ±1.3	1.8 ±1.4	2.3 ±1.1	1.004	.394	1.780	.153	2.486	**.011**
16 weeks	2.5 ±1.6	2.2 ±1.6	2.1 ±1.6	1.7 ±1.5						
24 weeks	3.8 ±2.1	3.1 ±1.3	2.5 ±1.1	2.9 ±1.3						
CMJ Height LSI										
Baseline	104.7 ±16.1	102.4 ±26.2	88.3 ±44.0	90.7 ±43.2	NT	NT	NT	NT	NT	NT
8 weeks	122.4 ±59.7	102.9 ±30.3	91.8 ±38.0	95.0 ±42.7						
16 weeks	104.0 ±20.4	102.3 ±37.1	97.6 ±36.9	98.6 ±31.7						
24 weeks	104.6 ±21.3	105.8 ±25.6	86.4 ±49.7	99.1 ±40.1						
Drop CMJ Height LSI										
Baseline	101.9 ±16.1	87.6 ±27.1	71.2 ±83.5	70.7 ±44.2	NT	NT	NT	NT	NT	NT
8 weeks	97.5 ±30.1	85.5 ±37.6	76.4 ±58.7	99.9 ±98.3						
16 weeks	103.3 ±27.7	102.3 ±34.9	93.4 ±47.6	83.0 ±44.4						
24 weeks	92.8 ±35.9	102.4 ±27.1	70.3 ±62.4	74.4 ±42.5						
Shear Modulus LSI										
Baseline	98.7 ±26.1	104.7 ±25.9	105.8 ±19.6	113.2 ±38.9	NT	NT	NT	NT	NT	NT
8 weeks	104.0 ±27.4	97.6 ±24.9	94.1 ±25.3	106.2 ±24.8						
16 weeks	115.7 ±24.6	108.3 ±22.9	109.4 ±32.5	109.2 ±33.1						
24 weeks	92.6 ±16.0	97.4 ±18.4	94.1 ±16.7	115.7 ±35.8						
Achilles Thickness LSI										
Baseline	106.3 ±16.4	120.7 ±33.2	125.0 ±33.6	175.4 ±58.8	NT	NT	NT	NT	NT	NT
8 weeks	109.7 ±20.4	120.3 ±31.3	116.3 ±26.0	178.2 ±64.0						
16 weeks	108.1 ±16.5	121.2 ±30.8	113.9 ±34.2	171.9 ±60.2						
24 weeks	106.0 ±13.1	116.1 ±27.0	124.1 ±33.2	170.8 ±66.9						

Achilles CSA LSI										
Baseline	109.5 ±18.7	117.6 ±33.8	129.9 ±39.1	209.3 ±77.1	NT	NT	NT	NT	NT	NT
8 weeks	108.3 ±22.0	125.6 ±44.6	114.5 ±40.8	218.7 ±104.9						
16 weeks	112.3 ±22.7	133.8 ±48.0	129.0 ±41.9	234.1 ±126.8						
24 weeks	103.3 ±23.9	123.3 ±41.0	139.6 ±47.9	216.1 ±121.1						

Abbreviations: VISA-A, Victorian Institute of Sport Assessment-Achilles; LSI, Limb Symmetry Index; FAOS-QoL, Foot and Ankle Outcomes Score-Quality of Life, TSK-17, Tampa Scale of Kinesiophobia 17-item; CMJ, countermovement jump; CSA, cross-sectional area; PROMIS, Patient Reported Outcome Measurement System, GROC, Global Rating of Change.
Note: All values presented as Mean±SD.

Appendix E

REALLOCATION OF SUBGROUP MEMBERSHIP FROM AIM 1 TO AIM 2

	AIM 1 Subgroup Membership (n =61)	**AIM 2 Subgroup Membership**			
		Activity Dominant	**Function Dominant**	**Psychosocial Dominant**	**Structure Dominant**
Activity Dominant	30	14	16	0	0
Psychosocial Dominant	24	1	4	16	3
Structure Dominant	7	0	0	0	7

Appendix F

TREATMENT PROTOCOL FROM USED IN AIM 3

Phase 1: Weeks 1 to 2

Patient Status

Pain and difficulty with all activities, difficulty performing 10 one-legged heel rises

Loading Intensity

Progress loading up to 100% body weight with slow controlled motion. If needed, begin with aquatic therapy, bodyweight support, or isometric plantar flexion

Goals

Start to exercise and understanding nature of the injury and how to use the pain-monitoring model

Treatment Program

- Pain-monitoring model information and advice on exercise activity
- Circulation exercise (moving foot up/down)
- Two-legged heel rises standing on the floor (3 x 10-15 repetitions)
- One-legged heel rises standing on the floor (3 x 10 repetitions)
- Eccentric heel rises standing on the floor (3 x 10 repetitions)
- Sitting heel rises (3 x 10 repetitions)

Phase 2: Weeks 2 to 5

If pain increases by more than 2 points when exercising while standing on edge of step, then perform exercises on a flat surface

Patient Status

Pain with exercise, morning stiffness, pain when performing heel rises

Loading Intensity

External loading should be introduced once patients can complete the bodyweight treatment program without difficulty.

Goals

Improve strength

Treatment Program

- Two-legged heel rises standing on edge of a step (3 x 15 repetitions)
- One-legged heel rises standing on edge of a step (3 x 15 repetitions)
- Eccentric heel rises standing on edge of a step (3 x 15 repetitions)
- Sitting heel rises (3 x 15 repetitions)
- Quick rebounding heel rises (3 x 20 repetitions)

Phase 3: Weeks 3 to 12

If pain increases by more than 2 points when exercising while standing on edge of step, then perform exercises on a flat surface

Patient Status

Tolerates the recovery phase exercise program well, no pain at the distal tendon insertion, possibly decreased or increased morning stiffness

Loading Intensity

Continue to progress external resistance and speed of movement based on patient tolerance

Goals

Heavier strength training

Treatment Program

Perform exercises every day and with heavier load 2 to 3 times per week:

- One-legged heel rises standing on edge of step with added weight (3 x 15 repetitions)
- Eccentric heel rises standing on edge of step with added weight (3 x 15 repetitions)
- Sitting heel rises (3 x 15 repetitions)
- Quick rebounding heel rises (3 x 20 repetitions)

Appendix G

PATIENT EDUCATION HANDOUT

AMP Study

Why your heels hurt

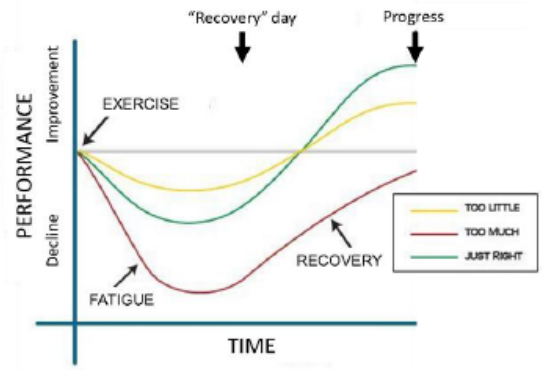
Between age 8-15 for boys and 7-13 for girls, your bones begin to grow very fast. While you are growing, your muscles and tendons that attach to your heel bones are also getting bigger and stronger. Your Achilles tendon can pull with more force than your heel bone can tolerate, and this can cause pain with running and jumping. Your heel may start to feel stiff and painful, especially with running and jumping activities. Normally, this pain can disappear after a break from activity but in some cases the pain can last much longer. The pain may be getting worse when you have increased your physical activities and not have had enough rest for the body to recover. It is also common that the pain varies and sometimes without an obvious reason.

Avoid stretching

Historically, your heel pain was referred to as "growing pains." A traditional treatment for heel pain is to stretch your muscles to keep up with your growing skeleton. Stretching is most helpful for shortened or tight muscles and may not be helpful for your heel pain. Because your heel bone is developing, stretching may only create more stress at your heel instead of helping your calf muscle tightness. We do not recommend stretching your calves to improve your heel pain.

Exercise Smarter, Not Harder

For the first 4-8 weeks of treatment we may recommend you limit activities that aggravate your heel pain. Training hard every day can make your injury worse, instead you should exercise hard every 3 days, with light or moderate days in between. This will ensure you get all the benefits of exercise and



are fully recovered before your next hard exercise day. We will help you set up a specific plan for your exercises and training.

When can you return to sports?

Returning to sports depends on your abilities, not time. You only progress to the next step on the Activity Ladder when you have no increased heel pain during or the next morning after the activity.

When you are able to perform exercises on Step 3 with no pain above a 5/10 you can start participating in sports again. Do not go right into a full game, or you may overload your heels and risk your progress. Below is the guide you will follow to steadily increase your activity level while controlling your heel pain and allowing full recovery between heavy loading days.

You should start by participating in the team warm-up, followed by 15 minutes of team drills/practice. Each week, you can increase the amount of time training by 5-10 minutes, but you must still follow the pain monitoring rules. When you can handle a full week of full training, you can return to full activity/sports games again.

Tracking your progress

Record all of your exercises, sets, repetitions, and resistance in the training diary. If you do any other activities, such as sports, hiking, jogging, etc. you can enter this as well. It is very important to keep track of your heel pain too. Enter a number for pain (0-10 pain scale above) when you first wake up, the worst pain you felt that day, and at the end of the day.

OBJECTIVES OF THE INTERVENTION

Step 1

- Adjust training/exercise to improve recovery and heel pain
- Learn how to perform slow, controlled bodyweight exercises
- Learn to use your pain as a guide (Pain Monitoring Model)
- Avoid stretching

Step 2

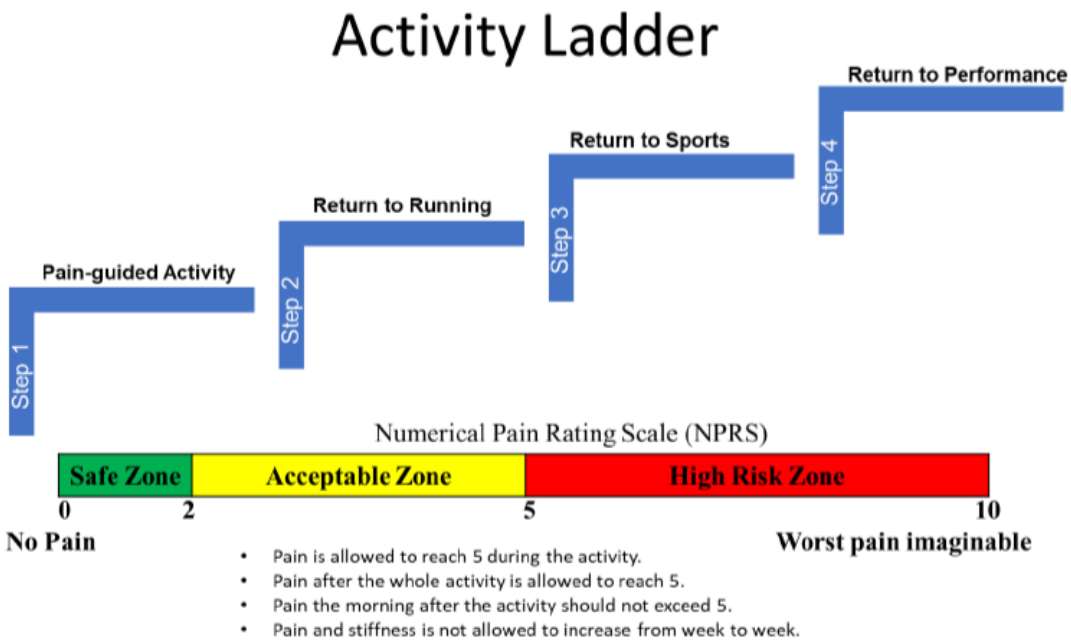
- Sports-specific exercises
- Learn how to plan out training weeks based on heavy, moderate, and light exercise days
- Return to team warm-up activities/drills

Step 3

- Improve lower body strength and stamina
- Learning advanced jumping exercises
- Return to sports competition

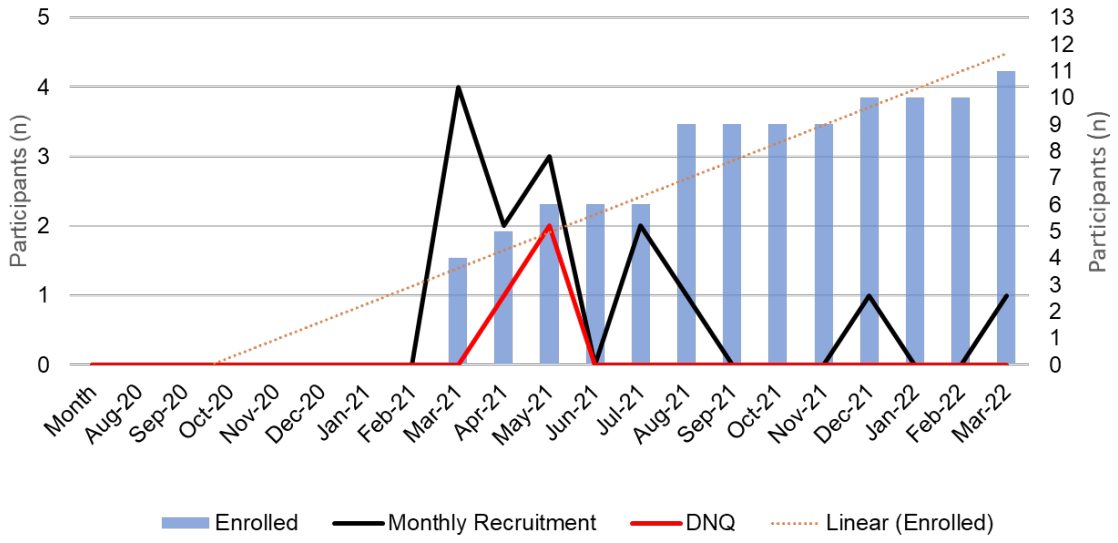
Step 4

- Return to full activity and performance
- Continue to spread heavy exercise to every 3 days with recovery


Activity Ladder
Pain-guided Activity
Step 1
Return to Running
Step 2
Return to Sports
Step 3
Return to Performance
Step 4
Numerical Pain Rating Scale (NPRS)
Safe Zone
Acceptable Zone
High Risk Zone
0
2
5
10
No Pain
Worst pain imaginable
• Pain is allowed to reach 5 during the activity.
• Pain after the whole activity is allowed to reach 5.
• Pain the morning after the activity should not exceed 5.
• Pain and stiffness is not allowed to increase from week to week.

Appendix H

SUMMARY OF RECRUITMENT BY MONTH FROM AIM 3



Appendix I

IRB APPROVAL FOR AIMS 1 AND 2

Institutional Review Board
210H Hullihen Hall
Newark, DE 19716
Phone: 302-831-2137
Fax: 302-831-2828

DATE:	July 1, 2021
TO:	Karin Silbernagel, PT, PhD, ATC
FROM:	University of Delaware IRB
STUDY TITLE:	[1090153-22] Achilles Tendinopathy, Treatment with eXercise Comparing Men and Women
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
APPROVAL DATE:	July 1, 2021
EXPIRATION DATE:	July 17, 2022
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(4,6,7)*

Thank you for your Continuing Review/Progress Report submission to the University of Delaware Institutional Review Board (UD IRB). The UD IRB has reviewed and APPROVED the proposed research and submitted documents via Expedited Review in compliance with the pertinent federal regulations.

As the Principal Investigator for this study, you are responsible for and agree that:

- All research must be conducted in accordance with the protocol and all other study forms as approved in this submission. Any revisions to the approved study procedures or documents must be reviewed and approved by the IRB prior to their implementation. Please use the UD amendment form to request the review of any changes to approved study procedures or documents.
- Informed consent is a process that must allow prospective participants sufficient opportunity to discuss and consider whether to participate. IRB-approved and stamped consent documents must be used when enrolling participants and a written copy shall be given to the person signing the informed consent form.
- Unanticipated problems, serious adverse events involving risk to participants, and all non-compliance issues must be reported to this office in a timely fashion according with the UD requirements for reportable events. All sponsor reporting requirements must also be followed.

Oversight of this study by the UD IRB REQUIRES the submission of a CONTINUING REVIEW seeking the renewal of this IRB approval, which will expire on July 17, 2022. A continuing review/progress report form and up-to-date copies of the protocol form and all other approved study materials must be submitted to the UD IRB at least 45 days prior to the expiration date to allow for the required IRB review of that report.

If you have any questions, please contact the UD IRB Office at (302) 831-2137 or via email at hsrb-research@udel.edu. Please include the study title and reference number in all correspondence with this office.

Appendix J

IRB APPROVAL FOR AIM 3

Institutional Review Board
210H Hullihen Hall
Newark, DE 19716
Phone: 302-831-2137
Fax: 302-831-2828

DATE:	September 15, 2021
TO:	Shawn Hanlon, MS, BS
FROM:	University of Delaware IRB
STUDY TITLE:	[1652996-4] Activity Modification and Load Management for Adolescents with Heel Pain
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
APPROVAL DATE:	September 16, 2021
EXPIRATION DATE:	September 15, 2022
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(9)*

Thank you for your Continuing Review/Progress Report submission to the University of Delaware Institutional Review Board (UD IRB). The UD IRB has reviewed and APPROVED the proposed research and submitted documents via Expedited Review in compliance with the pertinent federal regulations.

As the Principal Investigator for this study, you are responsible for and agree that:

- All research must be conducted in accordance with the protocol and all other study forms as approved in this submission. Any revisions to the approved study procedures or documents must be reviewed and approved by the IRB prior to their implementation. Please use the UD amendment form to request the review of any changes to approved study procedures or documents.
- Informed consent is a process that must allow prospective participants sufficient opportunity to discuss and consider whether to participate. IRB-approved and stamped consent documents must be used when enrolling participants and a written copy shall be given to the person signing the informed consent form.
- Unanticipated problems, serious adverse events involving risk to participants, and all non-compliance issues must be reported to this office in a timely fashion according with the UD requirements for reportable events. All sponsor reporting requirements must also be followed.

Oversight of this study by the UD IRB REQUIRES the submission of a CONTINUING REVIEW seeking the renewal of this IRB approval, which will expire on September 15, 2022. A continuing review/progress report form and up-to-date copies of the protocol form and all other approved study materials must be submitted to the UD IRB at least 45 days prior to the expiration date to allow for the required IRB review of that report.

If you have any questions, please contact the UD IRB Office at (302) 831-2137 or via email at hsrb-research@udel.edu. Please include the study title and reference number in all correspondence with this office.